Gemeinsamer Bundesausschuss

Zusammenfassende Dokumentation

über eine Feststellung im Verfahren der anwendungsbegleitenden Datenerhebung und von Auswertungen nach § 35a Absatz 3b des Fünften Buches Sozialgesetzbuch (SGB V):
Onasemnogen-Abeparvovec (spinale Muskelatrophie) – Vorlage von Studienprotokoll und Statistischem Analyseplan

Vom 20. Januar 2022

Inhalt

A. Tragende Gründe und Beschluss

1. Rechtsgrundlage

Nach § 35a Absatz 3b Satz 1 SGB V kann der Gemeinsame Bundesausschuss (G-BA) bei den folgenden Arzneimitteln vom pharmazeutischen Unternehmer innerhalb einer angemessenen Frist die Vorlage anwendungsbegleitender Datenerhebungen und Auswertungen zum Zweck der Nutzenbewertung fordern:

1. bei Arzneimitteln, deren Inverkehrbringen nach dem Verfahren des Artikels 14 Absatz 8 der Verordnung (EG) Nr. 726/2004 des Europäischen Parlaments und des Rates vom 31. März 2004 zur Festlegung von Gemeinschaftsverfahren für die Genehmigung und Überwachung von Human- und Tierarzneimitteln und zur Errichtung einer Europäischen Arzneimittel-Agentur (ABl. L 136 vom 30.4.2004, S. 1), die zuletzt durch die Verordnung 162 Verfahrensordnung Stand: 16. Dezember 2020 (EU) 2019/5 (ABl. L 4 vom 7.1.2019, S. 24) geändert worden ist, genehmigt wurde oder für die nach Artikel 14-a der Verordnung (EG) Nr. 726/2004 eine Zulassung erteilt wurde, sowie
2. bei Arzneimitteln, die zur Behandlung eines seltenen Leidens nach der Verordnung Nr. 141/2000 zugelassen sind.

2. Eckpunkte der Entscheidung

In seiner Sitzung am 4. Februar 2021 hat der G-BA die Forderung einer anwendungsbegleitenden Datenerhebung und von Auswertungen für den Wirkstoff Onasemnogen-Abeparvovec gemäß § 35a Absatz 3b Satz 1 SGB V beschlossen.

Der G-BA hat in seiner Sitzung am 4. Februar 2021 ebenfalls beschlossen, dass die Versorgungsbefugnis nach § 35a Absatz 3b Satz 2 SGB V für den Wirkstoff Onasemnogen-Abeparvovec auf solche Leistungserbringer beschränkt wird, die an der geforderten anwendungsbegleitenden Datenerhebung mitwirken. Mit Beschluss des G-BA vom 5. Mai 2021 wurde das Inkrafttreten des Beschlusses über die Beschränkung der Versorgungsbefugnis vom 4. Februar 2021 konkretisiert: Die im Beschluss geregelte Beschränkung der Versorgungsbefugnis auf solche Leistungserbringer, die an der geforderten anwendungsbegleitenden Datenerhebung mitwirken, entfaltet ihre Wirkung erst ab der Bestätigung des vom pharmazeutischen Unternehmer vorgelegten Studienprotokolls und des statistischen Analyseplans (SAP) und Veröffentlichung der Bestätigung auf den Internetseiten des G-BA.

Zur Prüfung, ob die Anforderungen des G-BA an die anwendungsgleitende Datenerhebung und an Auswertungen umgesetzt worden sind, hat der pharmazeutische Unternehmer dem G-BA mit Schreiben vom 11. August 2021 fristgerecht Entwürfe für ein Studienprotokoll sowie einen SAP übermittelt. Die Unterlagen wurden vom G-BA unter Einbindung des Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) geprüft.

Aufgrund umfangreichen Anpassungsbedarfes wurde dem pharmazeutischen Unternehmer seitens des G-BA mit Schreiben vom 28. September 2021 eine entsprechende Überarbeitung des Studienprotokolls und des SAP aufgegeben. Der pharmazeutische Unternehmer hat dem G-BA daraufhin die überarbeiteten Studienunterlagen mit Schreiben vom 21. November innerhalb der angesetzten Frist

übermittelt. Unter Einbindung des IQWiG wurde im Anschluss eine erneute Prüfung der Unterlagen vom G BA vorgenommen.

Die erneute Prüfung hat ergeben, dass der pharmazeutische Unternehmer das Studienprotokoll und den SAP auf Basis der Anforderungen des G-BA, die ihm mit Schreiben vom 28. September 2021 übermittelt wurden, überarbeitet hat. Einige Angaben in dem überarbeiteten Studienprotokoll (Version: 2.02, November 18, 2021) und SAP (Version: 2.02, November 18, 2021) werden jedoch als nicht sachgerecht und/oder unvollständig eingestuft und müssen nach Einschätzung des G-BA in einer weiteren Revision behoben werden.

Mit dem vorliegenden Feststellungsbeschluss werden das Studienprotokoll (Version: 2.02, November 18, 2021) und der SAP (Version: 2.02, November 18, 2021) daher unter der Auflage bestätigt, dass der pharmazeutische Unternehmer verpflichtet wird, die im Beschluss aufgelisteten, verbleibenden und weiterhin für erforderlich gehaltenen Anpassungen am Studienprotokoll und SAP vorzunehmen.

Im Beschluss werden die verbleibenden Mängel am Studienprotokoll (Version: 2.02, November 18, 2021) und SAP (Version: 2.02, November 18, 2021) im Detail beschrieben und der jeweilige Anpassungsbedarf mit entsprechender Begründung benannt.

Der G-BA behält sich bei Nichtbeachtung der Auflagen vor, die Daten aus der Studie für die anwendungsbegleitende Datenerhebung bei der späteren Nutzenbewertung nach § 35a SGB V zum Wirkstoff Onasemnogen Abeparvovec unter Verweis auf methodische Mängel der Erhebung zurückzuweisen oder anderweitige Sanktionen an die Nichtumsetzung der Auflagen zu knüpfen.

Mit Inkrafttreten des vorliegenden Feststellungsbeschlusses ist mit der Durchführung der mit Beschluss vom 4. Februar 2021 (BAnz AT 19.04.2021 B3) geforderten anwendungsbegleitenden Datenerhebung und von Auswertungen für den Wirkstoff Onasemnogen-Abeparvovec in der Behandlung der spinalen Muskelatrophie zu beginnen.

Mit diesem Startzeitpunkt entfaltet auch erst der Beschluss vom 4. Februar 2021 (BAnz AT 26.02.2021 B3), zuletzt geändert am 6. Mai 2021 (BAnz AT 01.06.2021 B4) zur Beschränkung der Versorgungsbefugnis nach § 35a Absatz 3b Satz 2 SGB V auf solche Leistungserbringer, die an der geforderten anwendungsbegleitenden Datenerhebung zum Wirkstoff Onasemnogen Abeparvovec mitwirken, seine Wirkung. Auch wenn die Veröffentlichung der Bestätigung des Studienprotokolls und des statistischen Analyseplans unter Auflagen mit Veröffentlichung dieses Feststellungsbeschlusses realisiert wird, erfolgt die Bestätigung des Studienprotokolls und des statistischen Analyseplans unter Auflagen erst mit Inkrafttreten dieses Beschlusses am 1. Februar 2022. Insofern entfaltet auch der Beschluss zur Beschränkung der Versorgungsbefugnis erst zu diesem Datum seine Wirkung.

Zusätzlich zu den als Auflagen verpflichtend umzusetzenden Anpassungen spricht der G-BA nachfolgend genannte Empfehlungen für eine darüberhinausgehende Anpassung des Studienprotokolls und des statistischen Analyseplans aus, um die Datenqualität und Aussagekraft zu verbessern:

1. Seitens des G-BA wird eine Verwendung von Daten aus weiteren Registern (beispielsweise RESTORE) unter Berücksichtigung der Angaben im Beschluss des G-BA zur Forderung der anwendungsbegleitenden Datenerhebung (AbD) für

Onasemnogen-Abeparvovec, ausdrücklich befürwortet. Die Einbindung weiterer Register wird unter Berücksichtigung der genannten Anforderungen an die Datenquelle im Beschluss zur Forderung der AbD für Onasemnogen-Abeparvovec vom 4. Februar 2021 ermöglicht. Voraussetzungen für die Einbindung von Ergebnissen internationaler Register wurden darüber hinaus bereits im Konzept des IQWiG[1] für die AbD beschrieben und die Möglichkeit einer entsprechenden Anpassung des RESTORE-Registers im Fachaustausch am 23.11.2020 diskutiert. Der G-BA empfiehlt, die im Beschluss zur Forderung der AbD beschriebenen Anforderungen zur Einbindung weiterer Register im Studienprotokoll aufzuführen und die notwendigen Bezüge zu den jeweiligen Ausführungen im Studienprotokoll zur AbD, z. B. zur Source Data Verification, herzustellen. Studienprotokoll und SAP zur Datenerhebung im SMArtCARE-Register könnten dann Ausgangspunkt für die Einbindung weiterer internationaler Register einschließlich des RESTORE-Registers sein.

2. Eine Fallzahlplanung erscheint nur unter Berücksichtigung einer verschobenen Nullhypothese methodisch sachgerecht. Der G-BA empfiehlt eine grobe Fallzahlabschätzung für den Zeitraum 36 Monate mit einer Power von 80 % durchzuführen.
3. Der G-BA empfiehlt ausdrücklich, die Anwendung einer methodisch plausiblen verschobenen Hypothesengrenze (unter Berücksichtigung der Angaben in der Ausarbeitung von Konzepten zur Generierung versorgungsnaher Daten[2] und eines Konzeptes für eine anwendungsbegleitende Datenerhebung und Auswertung für den Wirkstoff Onasemnogen-Abeparvovec[1] des IQWiG) bei der Auswertung der Daten im Studienprotokoll und SAP zu ergänzen. Sollte dies nicht der Fall sein, würde bei den Prüfungen auf Vergeblichkeit und in der späteren Nutzenbewertung bei der Interpretation der Ergebnisse seitens des G-BA der Ansatz einer verschobenen Hypothesengrenze auf Basis der Präsentation der Ergebnisse in Form von Effektschätzungen mit Konfidenzintervallen zur Anwendung kommen.
4. In der überarbeiteten Version des SAP wird ergänzt, dass beim Auftreten von fehlenden Daten eine multiple Imputation vorgenommen wird und wie mit unplausiblen Daten umgegangen werden soll. Der G-BA empfiehlt, dass die Angaben zu fehlenden Werten ausreichend detailliert sind und insbesondere der Umfang der fehlenden Daten, Gründe für die fehlenden Daten und Anteile fehlender Daten beschrieben werden.
5. Angaben zur Anzahl von Patienten, die die Behandlung wechseln, einschließlich der jeweils vorliegenden Zeiten unter den verschiedenen Behandlungen, sollten Bestandteil der regelmäßig dem G-BA vorzulegenden Angaben zum Verlauf der AbD sein. Der pharmazeutische Unternehmer beabsichtigt gemäß Studienprotokoll, zu den unterschiedlichen Berichtszeitpunkten jeweils auch Informationen zum Therapiewechsel bereitzustellen („extend of treatment switching on a study level“). Der G-BA empfiehlt, dass diese Angaben ausreichend detailliert sind und beispielsweise auch Angaben zur Beobachtungsdauer (Mittelwert, Median, Minimum, Maximum, Quartile) enthalten.

[1] Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Konzept für eine anwendungsbegleitende Datenerhebung – Onasemnogen-Abeparvovec: Rapid Report; Auftrag A20-61; Version 1.0 [online]. 01.10.2020 [Zugriff: 12.01.2022]. URL: https://www.iqwig.de/download/a20-61_anwendungsbegleitende-datenerhebung-onasemnogen-abeparvovec_rapid-report_v1-0.pdf

[2] Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Konzepte zur Generierung versorgungsnaher Daten und deren Auswertung zum Zwecke der Nutzenbewertung von Arzneimitteln nach § 35a SGB V: Rapid Report; Auftrag A19-43; Version 1.1 [online]. 13.05.2020 [Zugriff: 12.01.2022]. URL: https://www.iqwig.de/download/a19-43_versorgungsnahe-daten-zum-zwecke-der-nutzenbewertung_rapid-report_v1-1.pdf.

6. Zur Beschreibung der geplanten Analysen hat der pharmazeutische Unternehmer das Studienprotokoll und den SAP weitreichend geändert und überarbeitet. Der Datenschnitt für die Analysen soll etwa 6 Monate vor dem jeweiligen Berichtszeitpunkt erfolgen. Dies ist für die finale Analyse nachvollziehbar, da hierfür ein vollständiges Dossier zur Nutzenbewertung zu erstellen ist. Für die weniger aufwändigen Berichte zu Zwischenanalysen erscheint dies jedoch nicht erforderlich. Der G-BA empfiehlt, dass die Datenschnitte für die Zwischenanalysen jeweils 4 Monate vor dem jeweiligen Berichtszeitpunkt erfolgen.
7. Der pharmazeutische Unternehmer beschreibt für die Berichte zu Zwischenanalysen und zur Prüfung auf Vergeblichkeit, dass er diese auf Basis des Moduls 4 der Dossiervorlagen für Nutzenbewertungen nach § 35a SGB V erstellen wird. Der G-BA empfiehlt, auf eine konkrete Benennung zu befüllender Abschnitte der Dossiervorlagen zu verzichten und für die finale Analyse klarzustellen, dass diese zwar mit dem vollständigen Dossier übermittelt wird, das Dossier aber darüber hinaus den Anforderungen an ein Dossier zur Nutzenbewertung nach § 35a SGB V genügen muss.

3. Verfahrensablauf

Zur Prüfung, ob die Anforderungen des G-BA an die anwendungsgleitende Datenerhebung und an Auswertungen für den Wirkstoff Onasemnogen-Abeparvovec gemäß den Angaben im Beschluss vom 4. Februar 2021 umgesetzt worden sind, hat der pharmazeutische Unternehmer dem G-BA Entwürfe für ein Studienprotokoll sowie einen SAP übermittelt. Die Unterlagen wurden vom G-BA unter Einbindung des Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) geprüft. Aufgrund umfangreichen Anpassungsbedarfes wurde dem pharmazeutischen Unternehmer seitens des G-BA eine entsprechende Überarbeitung des Studienprotokolls und des SAP aufgegeben. Die erneute Prüfung hat ergeben, dass einige Angaben in dem überarbeiteten Studienprotokoll (Version: 2.02, November 18, 2021) und SAP (Version: 2.02, November 18, 2021) als nicht sachgerecht und/oder unvollständig eingestuft und in einer weiteren Revision behoben werden müssen.

Der Sachverhalt wurde in der Arbeitsgruppe AG § 35a und im Unterausschuss Arzneimittel beraten.

Das Plenum hat in seiner Sitzung am 20. Januar 2022 einvernehmlich beschlossen, das Studienprotokoll (Version: 2.02, November 18, 2021) und den SAP (Version: 2.02, November 18, 2021) mit dem vorliegenden Feststellungsbeschluss unter der Auflage zu bestätigen, dass der pharmazeutische Unternehmer verpflichtet wird, verbleibende und weiterhin für erforderlich gehaltene Anpassungen an dem Studienprotokoll und dem SAP vorzunehmen.

Zeitlicher Beratungsverlauf

Sitzung	Datum	Beratungsgegenstand
AG § 35a	4. Januar 2022	Beratung über den Sachverhalt
Unterausschuss Arzneimittel	11. Januar 2022	Beratung über die Bestätigung des Studienprotokolls (Version: 2.02, November 18, 2021) und des SAP (Version: 2.02, November 18, 2021) unter Auflage
Plenum	20. Januar 2022	Beschlussfassung über die Bestätigung des Studienprotokolls (Version: 2.02, November 18, 2021) und des SAP (Version: 2.02, November 18, 2021) unter Auflage

Berlin, den 20. Januar 2022

Gemeinsamer Bundesausschuss
gemäß § 91 SGB V
Der Vorsitzende

Prof. Hecken

4. Beschluss

Beschluss des Gemeinsamen Bundesausschusses über eine Feststellung im Verfahren der anwendungsbegleitenden Datenerhebung und von Auswertungen nach § 35a Absatz 3b des Fünften Buches Sozialgesetzbuch (SGB V):
Onasemnogen-Abeparvovec (spinale Muskelatrophie) – Vorlage von Studienprotokoll und Statistischem Analyseplan

Vom 20. Januar 2022

Der Gemeinsame Bundesausschuss (G-BA) hat in seiner Sitzung am 20. Januar 2022 im Verfahren der anwendungsbegleitenden Datenerhebung und von Auswertungen nach § 35a Absatz 3b SGB V zum Wirkstoff Onasemnogen-Abeparvovec (spinale Muskelatrophie) folgendes beschlossen:

I. Es wird festgestellt, dass die Verpflichtung des pharmazeutischen Unternehmers, vorab der Durchführung der anwendungsbegleitenden Datenerhebung und von Auswertungen ein Studienprotokoll sowie einen statistischen Analyseplan zu erstellen und dem G-BA zur Überprüfung zu übermitteln unter der Auflage als erfüllt angesehen wird, dass der pharmazeutische Unternehmer verpflichtet wird, folgende weiter für erforderlich gehaltene Anpassungen an dem Studienprotokoll (Version 2.02, November 18, 2021) und dem Statistischen Analyseplan (Version: 2.02, November 18, 2021) vorzunehmen:

1. An dem Studienprotokoll (Version 2.02, November 18, 2021) sind folgende Anpassungen vorzunehmen:

   a) Fragestellung gemäß PICO: *Outcome (Nebenwirkungen)*

      Der Unternehmer plant den Endpunkt schwerwiegende unerwünschte Ereignisse (SUE) als unerwünschte Ereignisse (UE), die zu einer Hospitalisierung führen und Todesfällen jeglicher Ursache zu erheben, da im SMArtCARE-Register keine Daten zu UEs, die zum Tod führen, erhoben werden.

      Bezüglich der Todesfälle jeglicher Ursache muss dokumentiert werden, ob diese auf UEs zurückgehen. Nur diejenigen, die auf UEs zurückgehen, sollten in die Auswertung SUE eingehen. Ist dies nicht möglich, sind nur die UEs, die zur Hospitalisierung führen, zu erfassen.

   b) Studiendesign: *Prospektive / retrospektive Datenerhebung*

      Die Nutzung bereits erhobener Daten zu Nusinersen und Onasemnogen-Abeparvovec (aus dem Register SMArtCARE und ggf. weiteren Registern) müssen, sofern diese den genannten Anforderungen an die Datenqualität im Beschluss zur Forderung einer anwendungsbegleitenden Datenerhebung und von Auswertungen für den Wirkstoff Onasemnogen-Abeparvovec vom 4. Februar 2021 (nachfolgend: Beschluss zur Forderung der AbD für Onasemnogen-

Abeparvovec) entsprechen, für die Registerstudie eingeplant werden. Die Beschränkung der Berücksichtigung retrospektiver Daten auf Nusinersen entspricht nicht den Anforderungen des G-BA und ist nicht sachgerecht.

Die Berücksichtigung von retrospektiven Daten zu Onasemnogen-Abeparvovec, sofern diese den genannten Anforderungen an die Datenqualität im Beschluss zur Forderung der AbD für Onasemnogen-Abeparvovec entsprechen, muss entsprechend im Studienprotokoll ergänzt werden.

c) *Studiendesign*: *Auswahl von Confoundern*

Die Anpassung der Liste der relevanten Confounder an die Subpopulationen der Gesamtstudienpopulation ist sachgerecht. Die Einstufung des Confounders „Alter bei Symptombeginn“ in den Subpopulationen der symptomatischen Patientinnen und Patienten als „weniger wichtig“ ist jedoch nicht sachgerecht. Dieser Confounder muss als „sehr wichtig“ eingestuft werden.

2. An dem Statistischen Analyseplan (Version: 2.02, November 18, 2021) sind folgende Anpassungen vorzunehmen:

a) Auswertung der Datenerhebung: *Confounderadjustierung*

Die ergänzenden Angaben für die Propensity-Score-Analyse (Überprüfung der Güte, konkrete Kriterien für eine ausreichende Überlappung und Balanciertheit) sind unvollständig, nur zum Teil sachgerecht und insgesamt widersprüchlich:

aa) Kriterium für eine ausreichende Überlappung: Es wird angegeben, dass eine ausreichende Überlappung vorliegt, wenn in einer Behandlungsgruppe für 50% der Patientinnen und Patienten nicht gilt PS < 0,3 und in der anderen Behandlungsgruppe für 50% der Patientinnen und Patienten gilt PS > 0,7. Dadurch können Patientengruppen mit 0 % Überlappung als ausreichend und Patientengruppen mit 100% Überlappung als nicht ausreichend überlappend gelten.

bb) Beurteilung der Balanciertheit: Die Kriterien für die standardisierten Mittelwertdifferenzen (SMDs) aller Confounder zwischen den Behandlungsgruppen nach Gewichtung erscheinen sachgerecht, die Kriterien werden jedoch unter bestimmten Voraussetzungen abgeschwächt und dann nicht angewendet. Zudem wird nicht angegeben, dass keine PS-Analyse durchgeführt wird, wenn für einen der Confounder eine schwerwiegende Unbalanciertheit festgestellt wird.

cc) Es fehlt die Angabe, dass die Zielpopulation, für die der in der PS-Analyse (nach Trimming und Gewichtung) letztlich geschätzte Behandlungseffekt gilt, genau zu beschreiben ist und dass zu begründen ist, dass diese Zielpopulation für die Ausgangsfragestellung angemessen ist.

Die Mängel sind zu beheben.

b) Auswertung der Datenerhebung: *Confounderadjustierung*

In der überarbeiteten Version des SAP (Version 2.02, November 18, 2021) wird ein Entscheidungsalgorithmus zur Anpassung der Propensity-Score-Analyse bei fehlender Überlappung und Balanciertheit nach Anwendung des ersten Verfahrens ergänzt. Dieser Entscheidungsalgorithmus ist nicht sachgerecht:

aa) Die Kriterien zur Modellauswahl (Überlappung und Balanciertheit) sind, wie unter Punkt 2a) dargestellt, nicht sachgerecht.

bb) Es fehlt eine konkrete Angabe, wie das im Entscheidungsalgorithmus angegebene Trimming durchgeführt werden soll.

cc) Der Entscheidungsalgorithmus enthält auch einen Ansatz über Matching, bei dem es ausreichend ist, wenn nur mindestens 50 % der Confounder berücksichtigt werden. Dieser Ansatz ist per se nicht sachgerecht.

Die Mängel sind zu beheben.

c) Auswertung der Datenerhebung: *Analyse der Endpunkte*

In der überarbeiteten Version des SAP (Version 2.02, November 18, 2021) wird ergänzt, in welcher Form die Eignung von nicht-parallelen Daten zu Nusinersen überprüft wird. Der Entscheidungsalgorithmus ist nicht sachgerecht:

aa) Das Kriterium für eine ausreichende Überlappung ist, wie unter Punkt 2a) dargestellt, nicht sachgerecht.

bb) Der Wechsel von der kombinierten Stichprobe zu der Stichprobe mit ausschließlich parallelen Daten erfolgt im Entscheidungsalgorithmus zu früh. Es sind zunächst die anderen Verfahren, die zu einer verbesserten Überlappung und Balanciertheit führen können (Trimming, Gewichtungsmethode), anzuwenden.

cc) Es ist nicht sachgerecht, sofort nach Feststellung einer nicht ausreichenden Überlappung im 1. Schritt der PS-Analyse in allen weiteren Schritten nur noch die Stichprobe mit ausschließlich parallelen Daten zu verwenden.

dd) Die Stichproben der zeitlich parallel und nicht parallel erhobenen Daten sind auch deskriptiv zu vergleichen und bei zentralen Auswertungen der kombinierten bzw. der Teilstichprobe ist die jeweils andere Stichprobe für Sensitivitätsanalysen zu verwenden.

Die Mängel sind zu beheben.

d) Auswertung der Datenerhebung: *Geplante Analysen*

Im Zusammenhang mit der Prüfung auf Vergeblichkeit gibt der pharmazeutische Unternehmer an, dass eine nicht ausreichende Fallzahl ggf. bereits für einen einzelnen „key endpoint“ ausreichend ist, um die Beobachtung für die jeweilige Population zu beenden. In einem solchen Fall sollen die Ergebnisse nicht ausgewertet werden. Beides ist nicht sachgerecht. Die Prüfung auf Vergeblichkeit muss die Gesamtschau aller Daten umfassen. Die entsprechenden Berichte zu den

Zwischenanalysen müssen daher alle bis dahin erhobene Ergebnisse und die zugehörigen Analysen vollständig enthalten. Darüber hinaus muss die Entscheidung für oder gegen eine Fortsetzung der Beobachtung der Population in Abstimmung mit dem G-BA auf Basis des jeweiligen Zwischenberichts getroffen werden.

Die genannten Punkte sind im Studienprotokoll zu ergänzen.

II. Der Beschluss tritt, ungeachtet seiner Veröffentlichung, erst am 1. Februar 2022 in Kraft.

Die Tragenden Gründe zu diesem Beschluss werden auf den Internetseiten des G-BA unter www.g-ba.de veröffentlicht.

Berlin, den 20. Januar 2022

Gemeinsamer Bundesausschuss
gemäß § 91 SGB V
Der Vorsitzende

Prof. Hecken

B. Bewertungsverfahren

In seiner Sitzung am 4. Februar 2021 hat der G-BA die Forderung einer anwendungsbegleitenden Datenerhebung und von Auswertungen für den Wirkstoff Onasemnogen-Abeparvovec gemäß § 35a Absatz 3b Satz 1 SGB V beschlossen.

Der G-BA hat in seiner Sitzung am 4. Februar 2021 ebenfalls beschlossen, dass die Versorgungsbefugnis nach § 35a Absatz 3b Satz 2 SGB V für den Wirkstoff Onasemnogen-Abeparvovec auf solche Leistungserbringer beschränkt wird, die an der geforderten anwendungsbegleitenden Datenerhebung mitwirken. Mit Beschluss des G-BA vom 5. Mai 2021 wurde das Inkrafttreten des Beschlusses über die Beschränkung der Versorgungsbefugnis vom 4. Februar 2021 konkretisiert: Die im Beschluss geregelte Beschränkung der Versorgungsbefugnis auf solche Leistungserbringer, die an der geforderten anwendungsbegleitenden Datenerhebung mitwirken, entfaltet ihre Wirkung erst ab der Bestätigung des vom pharmazeutischen Unternehmer vorgelegten Studienprotokolls und des statistischen Analyseplans (SAP) und Veröffentlichung der Bestätigung auf den Internetseiten des G-BA.

Zur Prüfung, ob die Anforderungen des G-BA an die anwendungsgleitende Datenerhebung und an Auswertungen umgesetzt worden sind, hat der pharmazeutische Unternehmer dem G-BA mit Schreiben vom 11. August 2021 fristgerecht Entwürfe für ein Studienprotokoll sowie einen SAP übermittelt. Die Unterlagen wurden vom G-BA unter Einbindung des Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) geprüft.

C. Prüfung und Addenda des IQWiG

1. Erste Prüfung Studienunterlagen

1.1 Studienunterlagen

Der pharmazeutische Unternehmer hat dem G-BA mit Schreiben vom 11. August 2021 fristgerecht die finalen Entwürfe für ein Studienprotokoll (siehe D. Anhang der Zusammenfassenden Dokumentation) sowie einen statistischen Analyseplan (SAP) übermittelt. Der pharmazeutische Unternehmer hat der Veröffentlichung des SAP nicht zugestimmt.

1.2 A21-107_IQWiG Addendum

Das IQWiG hat auf Basis der finalen Entwürfe für ein Studienprotokoll sowie einen SAP ein Addendum zum Auftrag für ein Konzept für eine anwendungsbegleitende Datenerhebung und von Auswertungen erstellt (siehe D. Anhang der Zusammenfassenden Dokumentation). Dieses wurde dem G-BA am 14.September 2021 übermittelt.

1.3 Prüfung Studienunterlagen

Mit Schreiben vom 28. September 2021 hat der G-BA den pharmazeutischen Unternehmer über das Ergebnis der Prüfung der finalen Entwürfe für ein Studienprotokoll sowie einen SAP informiert.

Gemeinsamer Bundesausschuss

Gemeinsamer Bundesausschuss, Postfach 12 06 06, 10596 Berlin

Novartis Gene Therapies
Dr. Günter Harms
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c/o Regus
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gemäß § 91 SGB V
Unterausschuss
Arzneimittel

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Datum:
28. September 2021

Vorlage eines Studienprotokolls sowie eines statistischen Analyseplans für eine anwendungsbegleitende Datenerhebung und von Auswertungen nach § 35a Absatz 3b Satz 1 SGBV zur Abstimmung mit dem Gemeinsamen Bundesausschuss: Onasemnogen-Abeparvovec in der Behandlung der spinalen Muskelatrophie

Sehr geehrter Herr Harms,

in seiner Sitzung am 4. Februar 2021 hat der Gemeinsame Bundesausschuss (G-BA) beschlossen, eine anwendungsbegleitende Datenerhebung und Auswertungen zum Zwecke der Nutzenbewertung nach § 35a Absatz 3b Satz 1 SGBV für den Wirkstoff Onasemnogen-Abeparvovec in der Behandlung der spinalen Muskelatrophie zu fordern.

Mit Schreiben vom 11. August 2021, eingegangen am 13. August 2021, haben Sie dem G-BA fristgerecht die finalen Entwürfe für ein Studienprotokoll sowie einen statistischen Analyseplan (SAP) übermittelt. Unter Einbindung des Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) wurde vom G-BA eine Prüfung der Unterlagen vorgenommen.

Der diesem Schreiben beigefügten Anlage können Sie entnehmen, bei welchen Angaben im vorgelegten Studienprotokoll und statistischen Analyseplan Anpassungsbedarf besteht.

Für nähere Erläuterungen zu dem in der Anlage genannten Anpassungsbedarf verweisen wir auf die entsprechenden Abschnitte im Addendum A21-107 des IQWiG, welches diesem Schreiben ebenfalls beigefügt ist.

Gemeinsamer Bundesausschuss

Bitte übermitteln Sie uns die überarbeiteten Studienunterlagen bis spätestens zum 24. November 2021 und teilen Sie uns unter Angabe des jeweiligen Abschnittes mit, welche Anpassungen vorgenommen worden sind bzw. begründen Sie ggf. fehlende Anpassungen.

Im Anschluss prüft der G-BA unter Einbindung des IQWiG inwieweit die als notwendig erachteten Anpassungen in den überarbeiteten Studienunterlagen umgesetzt wurden und ob weiterhin Anpassungsbedarf besteht. Der G-BA teilt Ihnen innerhalb von 8 Wochen schriftlich das Ergebnis der Prüfung mit.

Sofern die Anpassungen an den Studienunterlagen als ausreichend eingeschätzt werden, wird der G-BA im Anschluss eine schriftliche Bestätigung der Prüfung des Studienprotokolls und des SAP auf den Internetseiten des G-BA veröffentlichen. Mit dieser Bestätigung und Veröffentlichung startet die anwendungsbegleitende Datenerhebung (AbD). Der G-BA behält sich andernfalls vor, die Studienunterlagen unter der Maßgabe zu bestätigen, dass seitens des pharmazeutischen Unternehmers verbleibende und weiterhin für erforderlich gehaltene Anpassungen an dem Studienprotokoll und SAP vorgenommen werden. Darüber hinaus behält sich der G-BA weiterhin die Option vor zu prüfen, ob die AbD unter den vorliegenden Umständen gemäß § 35a Absatz 3b Satz 9 SGB V in Verbindung mit 5. Kapitel § 59 Absatz 2 Satz 2 Nr. 1 Verfahrensordnung des G-BA (VerfO) nicht durchgeführt werden kann, mit der Rechtsfolge des § 130 b Absatz 3 Satz 9 SGB V.

Für Rückfragen stehen wir gerne zur Verfügung.

Mit freundlichen Grüßen

Anlage

- Information zur Prüfung der eingereichten Studienunterlagen
- IQWiG Addendum A21-107

Anlage: Position des G-BA zum Entwurf der Studienunterlagen
Anwendungsbegleitende Datenerhebung für Onasemnogen-Abeparvovec: Spinale Muskelatrophie
Datum: 28. September 2021

Studienprotokoll:

Thema	Position des G-BA
Fragestellung gemäß PICO: *Patientenpopulation*	Die Definition der Patientenpopulation und die Auswertung der Daten sollten entsprechend der Vorgaben des G-BA getrennt für präsymptomatische und symptomatische Patientinnen und Patienten erfolgen
Fragestellung gemäß PICO: *Outcome (Morbidität)*	Die durch die Vielzahl der Endpunkte zur Beschreibung der motorischen Funktion entstehende Multiplizität sollte verringert werden, indem die relevanten Endpunkte selektiert und die Endpunkte insgesamt hierarchisiert werden. Diese Entscheidungen müssen im Studienprotokoll präspezifiziert werden. Primär sollten Endpunkte, die den gesamten relevanten Beobachtungszeitraum abdecken, herangezogen werden.
Fragestellung gemäß PICO: *Outcome (Nebenwirkungen)*	Die Grenzwerte für die Erhebung der im Beschluss genannten spezifischen UE sollten vor Studienbeginn definiert und präspezifiziert sein. Als Annäherung an die Erhebung von SUE sollte ein kombinierter Endpunkt aus UE, die zum Tod führen und UE, die zu einer Hospitalisierung führen, ausgewertet werden.
Studiendesign: *Prospektive / retrospektive Datenerhebung*	Die Nutzung bereits erhobener Daten zu Nusinersen und Onasemnogen-Abeparvovec (aus dem Register SMArtCARE und ggf. weiteren Registern) sollte, sofern diese den genannten Anforderungen an die Datenqualität im Beschluss zur AbD zu Onasemnogen-Abeparvovec entsprechen, für die Registerstudie eingeplant werden.
Studiendesign: *Auswahl von Confoundern*	Die Liste der Confounder sollte an die im Beschluss genannten Patientenpopulationen und an die für die Registerstudie genutzten Datenquellen (*siehe nachfolgende Punkte*) angepasst werden.
Datenquelle	Der pharmazeutische Unternehmer sollte an dem selbst geführten RESTORE-Register die notwendigen Anpassungen gemäß finalem Studienprotokoll und SAP für die AbD vornehmen, um Auswertungen auf Basis des RESTORE-Registers gemeinsam mit der vorliegenden Registerstudie z.B. in Form einer Metaanalyse für die AbD nutzen zu können.
Datenquelle	SMArtCARE-Zentren außerhalb Deutschlands sollten nicht grundsätzlich als Datenquelle ausgeschlossen werden, da diese u.a. auch prospektiv Daten für symptomatische Patienten liefern können.

Datenquelle	Es sollte keine ausschließliche Beschränkung auf Zentren, die die Qualitätssicherungs-Richtlinie des G-BA für die Anwendung von Onasemnogen-Abeparvovec erfüllen, vorgenommen werden. Vielmehr sollte die Entscheidung, ob ein Zentrum eingeschlossen wird oder nicht, von der tatsächlich in diesem Zentrum umgesetzten Qualität bzw. Versorgung abhängen.

Statistischer Analyseplan:

Thema	Position des G-BA
Auswertung der Datenerhebung: *Fallzahlplanung*	Die Beschreibung der Rekalkulation der Fallzahlplanung (36-Monats-Analyse) im SAP sollte deutlich detaillierter erfolgen, darüber hinaus sollte die genaue Verwendung des Maß R^2 und dessen genaue Definition ergänzt werden. Die Beschreibung der Rekalkulation sollte auf Basis einer verschobene Hypothesengrenze für die Beurteilung der Effekte erfolgen.
Auswertung der Datenerhebung: *Confounderadjustierung*	Die Aufteilung der Patienten in die vorgeschlagenen „Behandlungsgruppen“ für die Confounderadjustierung sollte geändert werden. Eine Aufteilung der Patienten muss durch Informationen erfolgen, die zu Studienbeginn vorliegen.
Auswertung der Datenerhebung: *Confounderadjustierung*	Fehlende Details für die Propensity-Score-Analyse sollten ergänzt werden (Überprüfung der Güte, konkrete Kriterien für eine ausreichende Überlappung und Balanciertheit).
Auswertung der Datenerhebung: *Confounderadjustierung*	Eine Beschreibung eines Entscheidungsalgorithmus zur Anpassung der Propensity-Score-Analyse bei fehlender Überlappung und Balanciertheit nach Anwendung des ersten Verfahrens sollte ergänzt werden. Gleichfalls sollte die korrekte Konsequenz benannt werden, wenn kein Propensity-Score-Verfahren gefunden werden kann, mit dem eine ausreichende Überlappung und eine ausreichende Balanciertheit der zu vergleichenden Gruppen erreicht werden kann. In einem solchen Fall ist der Versuch einer Effektschätzung weder mithilfe von Propensity Scores noch mithilfe von Regressionsmodellen sinnvoll.
Auswertung der Datenerhebung: *Analyse der Endpunkte*	Die Modelle für die Effektschätzung sollten im Detail dargestellt werden. In die Analyse sollte das Zentrum weder als zufälliger noch als fester Effekt eingehen. Ein möglicher Zentrumseffekt sollte in einer Sensitivitätsanalyse untersucht werden.
Auswertung der Datenerhebung: *Analyse der Endpunkte*	Im SAP sollte im Detail beschrieben werden, in welcher Form die Confounder als feste Effekte in das jeweilige Endpunkt-Modell eingehen sollen.
Auswertung der Datenerhebung:	Angaben, wie überprüft werden soll, ob zeitlich parallel und nicht parallele Daten bzw. Daten aus unterschiedlichen Datenquellen für gepoolte Analysen herangezogen werden können, fehlen und sollten ergänzt werden.

Analyse der Endpunkte	
Auswertung der Datenerhebung: *Berücksichtigung verschobener Hypothesengrenzen*	Die Berücksichtigung einer verschobenen Hypothesengrenze bei der Auswertung der Daten fehlt und sollte ergänzt werden. Diese Ergänzungen könnten beispielsweise bei der (bisher fehlenden) Formulierung einer Hypothese erfolgen.
Auswertung der Datenerhebung: *Subgruppenanalysen*	Aufgrund der zu erwartenden geringen Fallzahlen wird vorgeschlagen, alle relevanten Subgruppenanalysen ohne die Anforderung einer statistisch signifikanten Interaktion zu rechnen und darzustellen.
Auswertung der Datenerhebung: *Umgang mit fehlenden Daten*	Für die Berücksichtigung von Daten sollten die entsprechenden Register / Datensätze grundsätzlich Informationen zu allen relevanten Baseline-Confoundern enthalten. Ein Ausschluss von einzelnen Personen mit verbleibenden fehlenden Daten aus allen Analysen, die diese Confounder berücksichtigen, erscheint in Anbetracht geringer Fallzahlen jedoch nicht sachgerecht. Es wird vorgeschlagen, verbleibende fehlende Werte bei einzelnen Personen durch den Ansatz der Multiplen Imputation zu ersetzen. Darüber hinaus sollten Angaben, in welchem Umfang bzw. aus welchen Gründen fehlende Daten zu erwarten sind, und Angaben zum Umgang mit unplausiblen Daten bzw. Ausreißern ergänzt werden. Des Weiteren sollte eine Beschreibung der Anteile fehlender Daten vorgesehen werden.
Auswertung der Datenerhebung: *Umgang mit Behandlungswechseln*	Die Aufteilung der Patienten in die vorgeschlagenen „Behandlungsgruppen“ sollte geändert werden, da eine adäquate Aufteilung der Patienten durch Informationen erfolgen muss, die zu Studienbeginn vorliegen.
Auswertung der Datenerhebung: *Umgang mit Behandlungswechseln*	Ein Cox-Modell mit zeitabhängigen Kovariablen wird im vorliegenden Fall nicht als adäquate Methode für den Umgang mit Behandlungswechseln erachtet. Es wird eine Zuordnung therapienaiver Patientinnen und Patienten zur jeweiligen Erstbehandlung (New-User-Design) empfohlen. Als Sensitivitätsanalyse sollten ergänzende Auswertungen mit Zensierungen bei Behandlungswechseln erfolgen, wobei der Zeitpunkt der Zensierung variiert werden sollte, um „Carry-over“-Effekte für die vorherige Behandlung zu berücksichtigen.

	Sofern die Ausgangsfragestellung aufgrund eines zu hohen Anteils an Behandlungswechseln nicht mehr beantwortet werden kann, kann ggf. alternativ ein Prevalent-New-User-Design für die Auswertung genutzt werden. Ob diese Option herangezogen werden sollte, kann jeweils nach Übermittlung von Daten zum Verlauf der AbD (*siehe nachfolgenden Punkt*) an den G-BA entschieden und in einem Amendment zum Protokoll und SAP implementiert werden.
Auswertung der Datenerhebung: *Umgang mit Behandlungswechseln*	Angaben zur Anzahl von Patienten, die die Behandlung wechseln einschließlich der jeweils vorliegenden Zeiten unter den verschiedenen Behandlungen, sollten Bestandteil der regelmäßig dem G-BA vorzulegenden Angaben zum Verlauf der AbD sein.
Auswertung der Datenerhebung: *Geplante Analysen*	Die geplanten Zeitpunkte für die Interimsanalysen und die finale Analyse weichen von den im Beschluss genannten Zeitpunkten ab. Die vorzulegenden Analysen sollten in Relation zum Beschlussdatum, nicht in Relation zum Studienstart geplant und entsprechend der Angaben im Beschluss durchgeführt werden. Zu jeder Zwischenanalyse sollte entsprechend auch eine Prüfung auf Abbruch wegen Vergeblichkeit vorgenommen werden.

2. Prüfung2.1 Studienunterlagen

Der pharmazeutische Unternehmer hat dem G-BA mit Schreiben vom 21. November 2021 innerhalb der angesetzten Frist die überarbeiteten Entwürfe für ein Studienprotokoll (siehe D. Anhang der Zusammenfassenden Dokumentation) sowie einen statistischen Analyseplan (SAP) übermittelt. Der pharmazeutische Unternehmer hat der Veröffentlichung des SAP nicht zugestimmt.

2.2 A21-149_IQWiG Addendum

Das IQWiG hat auf Basis der überarbeiteten Entwürfe für ein Studienprotokoll sowie einen SAP ein 2. Addendum zum Auftrag für ein Konzept für eine anwendungsbegleitende Datenerhebung und von Auswertungen erstellt (siehe D. Anhang der Zusammenfassenden Dokumentation). Dieses wurde dem G-BA am 21. Dezember 2021 übermittelt.

2.3 Prüfung Studienunterlagen

Die erneute Prüfung der überarbeiteten Entwürfe für ein Studienprotokoll sowie einen SAP hat ergeben, dass die Unterlagen auf Basis der Anforderungen des G-BA, die dem pharmazeutischen Unternehmer mit Schreiben vom 28. September 2021 übermittelt wurden, angepasst wurden. Einige Angaben in dem überarbeiteten Studienprotokoll (Version: 2.02, November 18, 2021) und SAP (Version: 2.02, November 18, 2021) werden jedoch als nicht sachgerecht und/oder unvollständig eingestuft und müssen nach Einschätzung des G-BA in einer weiteren Revision behoben werden.

Mit dem vorliegenden Feststellungsbeschluss werden das Studienprotokoll (Version: 2.02, November 18, 2021) und der SAP (Version: 2.02, November 18, 2021) daher unter der Auflage bestätigt, dass der pharmazeutische Unternehmer verpflichtet wird, die im Beschluss aufgelisteten, verbleibenden und weiterhin für erforderlich gehaltenen Anpassungen am Studienprotokoll und SAP vorzunehmen.

D. Anhang der Zusammenfassenden Dokumentation

1. Studienprotokoll
2. Addendum 1 IQWiG zum Auftrag A20-61
3. Studienprotokoll
4. Addendum 2 IQWiG zum Auftrag A20-61

Routine data collection and evaluations of onasemnogene abeparvovec in Germany

Study Protocol

Protocol Number: COAV101A1DE01

Version: 1.01

August 05, 2021

This document is subject to changes after review by G-BA and IQWiG.

Signature Page

The signatories agree to the content of the final study protocol as presented.

Marketing authorization holder (MAH): *MAH sponsored non-interventional study carried out based on resolution (February 4, 2021) of the G-BA.:* Novartis Gene Therapies EU Ltd. Street: Theresienhöhe 28 City/Zip: 80399 München Country: Germany	DocuSigned by: Hardo Fischer E02204A4C2CA4A9... DocuSigned by: Gunter Harms 9F0278DE432442B... DocuSigned by: Omar Dabbous FEF6D3467FB0426... DocuSigned by: Sandra P. Reyna 50D75DC408144EC... 08-Aug-21 | 11:27:06 PM PDT Place, Date, Signature DocuSigned by: Deepa Chand 26CA34D4CA094E7...
Principal Investigator (PI): Prof. Dr. med. Janbernd Kirschner Universitätsklinikum Bonn Zentrum für Kinderheilkunde Abteilung für Neuropädiatrie Street: Venusberg-Campus 1 City/Zip: 53127 Bonn Country: Germany	DocuSigned by: J Kirschner 105FC14191364E7... 06-Aug-21 | 6:41:03 AM PDT Place, Date, Signature
Statistical Analysis: IGES Institut GmbH Berlin Street: Friedrichstraße 180 Zip/State: 10117 Berlin County: Germany	DocuSigned by: Fabian Berkemeier 20E020DB32394BA... 06-Aug-21 | 6:07:09 AM PDT Place, Date, Signature

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Content

Figures

Tables

Index of abbreviations and definition of terms

Abbreviation	Term/Definition
AAV	Adeno-associated virus serotype
AbD	Routine Data Collection and Evaluations (Anwendungsbegleitende Datenerhebung)
ACT	Appropriate Comparative Therapy
ASO	Antisense oligonucleotide
ATT	Average Treatment Effect on Treated
AWMF	Working Group of the Scientific Medical Societies e.V. (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.)
BO-Ä	Professional Code for Physicians in Germany (Berufsordnung Ärzte)
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CMA Infobase: (CPGs)	Canadian Medical Association Infobase: Clinical Practice Guidelines
CMAP	Compound muscle action potential
COV	Close-Out Visit
CRF	Case report form
DMD	Disease modifying drug
DNA	Deoxyribonucleic acid
EFS	Event free survival
EMA	European Medicines Agency
G-BA	Federal Joint Committee (Gemeinsamer Bundesausschuss)
GLMM	Generalized linear mixed model
HFMSE	Hammersmith Functional Motor Scale Expanded
HINE	Hammersmith Infant Neurological Examination
HR	Hazard ratio

Abbreviation	Term/Definition
HRQoL	Health-related quality of life
HSP	Healthcare service provider
ICD	International Statistical Classification of Diseases and Related Health Problems
IPCW	Inverse-probability-of-censoring weighting
IQWiG	Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
ISS	Intronic splice silencing site
ITC	Indirect treatment comparison
ITT	Intention to treat
LTFU	Loss-to-follow-up
MAH	Marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Affairs
mRNA	Messenger ribonucleic acid
n.a.	Not applicable
NGT	Novartis Gene Therapies
OS	Overall survival
PICO	Patient-Intervention-Comparator-Outcome
PS	Propensity Score
PT	Preferred term (MedDRA)
RMV	Routine Monitoring Visit
RPSFT	Rank Preserving Structural Failure Time Model
RULM	Revised Upper Limb Module
RWE	Real World Evidence
SAP	Statistical analysis plan
SGB V	Social Code Book V (Sozialgesetzbuch V)

Abbreviation	Term/Definition
SLR	Systematic literature review
SMA	Spinal muscular atrophy
SMN	Survival motor neuron
SMN1	Survival motor neuron 1 gene
SMN2	Survival motor neuron 2 gene
SmPC	Summary of Product Characteristics
SOC	System Organ Class (MedDRA)
Treat-NMD Neuromuscular Network	Translational Research in Europe for the Assessment and Treatment of Neuromuscular Disease Neuromuscular Network
TRIP Database	Turning Research Into Practice Database
TTE	Time to event
WHO	World Health Organization

Revision History

Version	Date	Revised by	Change made – Reason for the change
0.1	Jul 02, 2021	Fabian Berkemeier (IGES)	Set up protocol
0.2	Jul 16, 2021	Fabian Berkemeier (IGES)	Implementation of feedback from NGT project team
0.3	Jul 21, 2021	Fabian Berkemeier (IGES)	Implementation of feedback from NGT project team
1.0	Aug 04, 2021	Fabian Berkemeier (IGES)	Implementation of feedback from ISRC review
1.01	Aug 05, 2021	Fabian Berkemeier (IGES)	Changed role of Omar Dabbous from Project Management to Project Lead

Synopsis and Milestones

Table 1: Synopsis

Title	Routine data collection and evaluations of onasemnogene abeparvovec in Germany
Study responsibilities	Marketing authorization holder (MAH) sponsored non-interventional study carried out based on resolution (February 4, 2021) of the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA). SMArtCARE is responsible for patient data collection. Statistical analysis will be performed by IGES Institut GmbH. Source data verification will be performed by CSG (Clinische Studiengesellschaft mbH).
Principal Investigator	Prof. Dr. Janberndt Kirschner Universitätsklinikum Bonn Venusberg-Campus 1 53127 Bonn
Rationale and background	Federal Joint Committee (G-BA) demanded Routine Data Collection and Evaluations for Zolgensma® (onasemnogene abeparvovec) compared to Spinraza® (nusinersen) with its resolution from February 4, 2021. The present study is conducted to fulfill the requirements specified therein.
Study objective and related endpoints	The objective of this study is to evaluate the overall effectiveness and safety in patients with spinal muscular atrophy (SMA) treated with gene therapy Zolgensma® (onasemnogene abeparvovec) compared to Spinraza® (nusinersen). The following endpoints are subject to investigation in this study: ▪ **Effectiveness** ○ <u>Survival</u> ▪ Overall survival ▪ Event-free survival ○ <u>Motor function</u> ▪ Sitting without support at the age of 18 months ▪ Sitting without support at the age of 24 months ▪ Standing without support at the age of 24 months ▪ Walking without support at the age of 24 months ▪ Head control at the age of 8 months ▪ Sustained head control at the age of 24 months ▪ Achievement of motor milestones according to age ▪ Sustainability of motor milestones • Loss of ability to sit without support

- Loss of ability to stand without support
- Loss of ability to walk without support

- CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) (exploratory)
  - Change from baseline at 6M
  - Change from baseline at 12M
- HINE (Hammersmith Infant Neurological Examination) (exploratory)
  - Change from baseline at 12M
  - Change from baseline at 24M
- HFMSE (Hammersmith Functional Motor Scale-Expanded) at 36 months of age (exploratory)
- RULM (Revised Upper Limb Module) at 36 months of age (exploratory)
- Time to sitting without support (exploratory)
- Time to standing without support (exploratory)
- Time to walking without support (exploratory)

- <u>Nutrition</u>
  - Difficulties in swallowing
    - at 12 months of age
    - at 24 months of age
    - at 36 months of age
  - Difficulties in chewing
    - at 12 months of age
    - at 24 months of age
    - at 36 months of age
  - Gastric or nasal feeding tube
    - Any type of tube feeding (supplementary or exclusively)
    - Supplementary (e.g. for fluids)
    - Exclusively
- <u>Orthopedic complications</u>
  - Scoliosis or orthopedic surgery
  - Scoliosis
  - Orthopedic surgery
- <u>Respiratory function</u>
  - Time of ventilator use
    - Any ventilator support
    - Ventilator support at night (during sleep)
    - Intermittent ventilator support at day time and continuous at night
    - Permanent ventilator support

	(>16 hours per day) • Intermittent ventilator support with acute illnesses ▪ Type of ventilator use • Non-invasive ventilation • Invasive ventilation ▪ Improvement in time of ventilator support from baseline ○ Planned hospitalizations ▪ Safety ○ (Related) adverse events ▪ Any adverse event with or without hospitalization ▪ Any adverse event related to treatment (yes/possibly) with or without hospitalization ○ (Related) adverse events with hospitalization ▪ Any adverse event with hospitalization ▪ Any adverse event related to treatment (yes/possibly) with hospitalization
Population	Treatment-naïve patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the survival motor neuron 2 (SMN2) gene as well as symptomatic patients with 5q-associated SMA type I treated with onasemnogene abeparvovec or nusinersen
Inclusion criteria	▪ Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene or ▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and clinically diagnosed type 1 SMA or ▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene ▪ Treatment initiation with nusinersen (12 mg / 5 ml per administration) or onasemnogene abeparvovec (dosage according to body weight as per summary of product characteristics (SmPC)) ▪ Body weight at treatment initiation ≤ 21 kg ▪ Treatment at a site that administrates both interventions of this study (onasemnogene abeparvovec and nusinersen) and is located in Germany ▪ Appropriate consent/assent has been obtained for participation in the study
Exclusion criteria	▪ Pretreatment with an approved disease-modifying therapy

	(nusinersen, onasemnogene abeparvovec, risdiplam) ▪ Pretreatment with any of the following investigational drugs for the treatment of SMA: albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea ▪ Currently or previously enrolled in an interventional clinical trial involving an investigational product to treat SMA
Study design	Non-interventional, non-randomized data collection using secondary data from the SMArtCARE registry
Sample Size	All patients fulfilling inclusion/exclusion criteria during study duration will be included in the study. As the study is conducted in a standard of care setting, there the actual numbers of subjects per study population cannot be controlled. Also, as SMA is a rare disease, there is a finite number of patients that can be enrolled. An additional restriction is that included patients need to be stratified for 2 vs. 3 copy SMN2 due to the relevant differences expected to be caused by these characteristics. Based on the results of pilot newborn screening in Germany, the study is anticipated to enroll approximately 354 patients within 60 months. Approximately 160 patients with 2 copy SMN and 112 patients with 3 copy SMN are expected to be evaluated at interim analysis about 60 months after study start. The number of the retrospective nusinersen patients fulfilling quality criteria that may be included in this study is unknown. Sample size calculations for this non-randomized study consider patient shares and association between baseline confounders and treatment effects. Based on assumptions derived from indirect treatment comparison of START, STR1VE-US, SHINE results, alpha of 0.05 (two-sided), power of 0.9 and 20% drop-out rate, about 50-80 patients are required for 2 copy SMN for event free survival (EFS) depending on association between baseline confounders and treatment effects. About 155-261 patients would be required for independent sitting at 18 months of age for 2 copy SMN. Due to a lack of estimates on effect size and event rates in 3 copy SMN, effect size and event rates were reduced by a factor of 2 for 3 copy SMN. About 256-410 patients are required for EFS in 3 copy SMN. Based on current estimates of patient enrollment the study will only be powered for EFS in study population A (2 copy SMN2). For all other endpoints that were included in sample size calculations, expected patient numbers are expected to be insufficient to ensure adequate power. Assumptions for sample size calculation will be re-evaluated at the time of descriptive analyses (18 and 36 months after study start) using actual observed patient shares, event rates, effect

	sizes, and association between baseline confounders and treatment.
Statistical methods	All endpoints will be evaluated using a treatment episode design to address the possibility of treatment changes between study interventions in this non-interventional study. For time to event (TTE) end-points, treatment episodes and their durations are considered in the context of a Cox regression with time-dependent covariates. To address unobserved heterogeneity due to the study centers, a frailty model is estimated. For binary endpoints, scores and count data, weighting with the length of treatment episodes is appropriate within the generalized linear mixed model framework with study centers taken into account as random effect. Potential confounders and patient characteristics are evaluated descriptively: ▪ Continuous characteristics: Measures of position and dispersion (arithmetic. mean with 95% confidence interval, standard deviation, minimum, maximum and quartiles) ▪ Categorical characteristics: absolute and relative frequencies. The comparison of both interventions is carried out descriptively with appropriate statistical methods. If the treatment episodes turn out to be inhomogeneous with regard to the following confounders, an improvement of the structural comparability is achieved by appropriate methods (propensity score methods and/or conditional regression models): ▪ Age at symptom onset ▪ Symptom status at treatment initiation ▪ Age at treatment initiation ▪ Nutrition support ▪ Ventilation support ▪ Contractures ▪ Motoric function: Highest motor milestone ▪ Motoric function: CHOP-INTEND Survival curves and median survival time as well as hazard ratios are used for the representation of the time-to-event endpoints. Binary endpoints are analyzed using Odds Ratio as effect measure. Scores will be evaluated using mean differences and Hedges' g. For all effect measures 95% confidence interval limits are presented. Adverse events are summarized by SOC/PT in terms of absolute and relative frequencies as well as time to first event by treatement episode.
Duration of study	The duration of the study is dependent on final sample size number calculations as well as the actual inclusion rate. Interim analysis is planned once the final sample size (calculated 36 months after study start) has been reached for a patient population. It is

	expected that this will be the case approx. 60 months after start of study. Patients will be enrolled until final sample size has been reached and will be observed until 60 months after reaching final sample size.

Table 2: Milestones

Study milestones	**Planned Date**
Submission of study protocol and SAP to G-BA	August 15, 2021
Written results of assessment of study protocol and SAP by G-BA and IQWiG	September 30, 2021
Finalization of study protocol and SAP, approval from responsible ethics committee	December 31, 2021
First status report (descriptive analysis) First re-calculation of sample sizes	July 1, 2023 18 months after study start
Second status report (descriptive analysis) Final re-calculation of sample sizes Feasibility assessment: decision on historic data	January 1, 2025 36 months after study start
Third status report	July 1, 2026 54 months after study start
Fourth status report	January 1, 2027 60 months after study start
Interim analysis	After final sample size has been included per population Approx. 60 months after study start
Final analysis	60 months after interim analysis

1. Background

Spinal muscular atrophy (SMA) is a rare, genetic, neuromuscular disease associated with progressive, irreversible motor neuron loss that results in muscle atrophy leading to progressive muscle weakness and paralysis, impairment of swallowing and breathing, and premature death in its more severe forms (1, 2). SMA is caused by a homozygous absence of the survival motor neuron gene 1 (SMN1), resulting in a lack of survival motor neuron (SMN) protein (1, 2). The SMN protein is also encoded by the survival motor neuron 2 (SMN2) back-up gene that is closely homologous to SMN1; however, only 10–15% of the protein produced by SMN2 is a full-length, functional SMN protein (3–6). SMA is historically classified into five clinical types (0 through 4) based on the age at onset and highest motor milestone achievement. SMN2 copy number is inversely associated with disease severity and is correlated with SMA type; 97% of infants with two SMN2 copies will develop type 1, and infants with three copies of SMN2 have a 7% chance of developing SMA type 1 and 83% chance of developing SMA type 2 (7–9).

Although infants with SMA type 1 are alert and aware, they lose the ability to swallow and safely feed by mouth, never gain developmental milestones after initial presentation and develop progressive skeletal muscle weakness and atrophy, and suffer from chronic ventilatory failure (10–15). SMA type 2 is defined by the maximum motor ability to be able to sit unsupported, which is achieved at the average age of 1 year (16–20). SMA type 3 is distinguished from SMA type 2 by the ability to walk independently (20). While infants with a later age of onset have better functional ability initially, their condition deteriorates over time and often results in severe disability, regardless of SMA type.

The main cause of mortality is respiratory failure (21, 22). Infants experience rapid, significant, and progressive muscle weakness, leading to the inability to breathe or swallow and ultimate death, typically following a severe respiratory illness (11). Without intensive respiratory and nutritional intervention and disease-modifying treatment, the life expectancy of infants with SMA type 1 is typically <2 years (23). The findings from various neurophysiological and animal studies have shown an early loss of motor neurons in the embryonic and early postnatal periods (24–26).

Until recently, the mainstay of treatment for these patients was supportive medical care. However, advances in medical treatment focusing on gene replacement, modulation of splicing, motor neuron protection and muscle enhancement are continually changing the management and prognosis of these patients.

Onasemnogene abeparvovec (Zolgensma®) is a gene therapy medicinal product that expresses the human SMN protein. It is delivered by a one-time intravenous infusion.

Onasemnogene abeparvovec was approved by the European Commission on 18 May 2020 for the following indication:

- Patients with 5q SMA with a biallelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or

- Patients with 5q SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.

According to section 35a of the German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) evaluates the additional benefit of reimbursable medicinal products with new active ingredients, and pharmaceutical companies are obliged to submit a dossier on product benefit when a new product is launched on the German market or authorized for new indications. The purpose of early benefit assessment in Germany is to compare newly authorized drugs to an appropriate comparative therapy (ACT) in order to establish a ruling on their additional benefit, which serves as the basis for price negotiations between the manufacturer and the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband).

Novartis Gene Therapies EU Ltd. initially submitted a dossier for the benefit assessment on 1 July 2020 and submitted for a renewed benefit assessment on 15 May 2021 as per the requirement of G-BA. G-BA determined nusinersen as ACT. On 4 February 2021 G-BA requested the first-ever Routine Data Collection and Evaluations according to section 35a paragraph 3b SGB V for onasemnogene abeparvovec (27). The resolution was preceded by a G-BA resolution of 16 July 2020 (28), which initiated the procedure as well as a concept development by the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) of 1 October 2020 (29). Prior to the initiation of the specific procedures mandating the Routine Data Collection and Evaluations for onasemnogene abeparvovec, IQWiG was commissioned to develop methodological guidance for this new form of evidence generation, which was published as a Rapid Report in January 2020 (30).

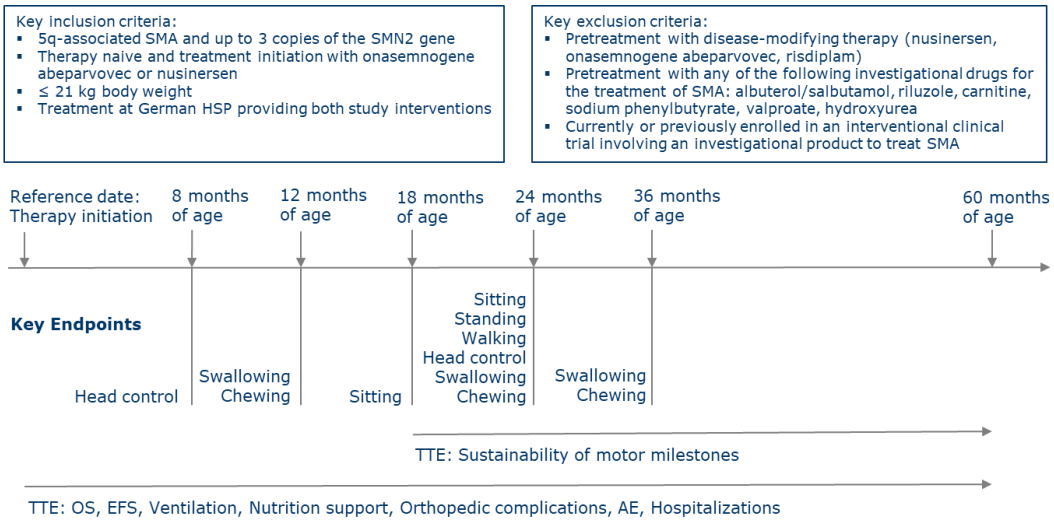
The Routine Data Collection and Evaluations have to be conducted as a non-randomized comparison of onasemnogene abeparvovec and nusinersen as a parallel control within one data source, whereby the SMArtCARE register is to be used as the data source (27). Reimbursement of onasemnogene abeparvovec is limited to healthcare service providers (HSP) participating in this study (31). Study results will serve as a basis for the early benefit assessment of onasemnogene abeparvovec.

2. Overview of Study design and study schematic

The study is a non-interventional, non-randomized, registry-based data collection in therapy-naïve subjects with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene as well as symptomatic patients with 5q-associated SMA type I treated with onasemnogene abeparvovec or nusinersen. The study is based on secondary use of data from the SMArtCARE registry (47).

Participants are enrolled when they first meet the inclusion and exclusion criteria of the study and are observed for 60 months after therapy initiation with onasemnogene abeparvovec or nusinersen. Figure 1 shows an overview of the study design.

Figure 1: Overview study design

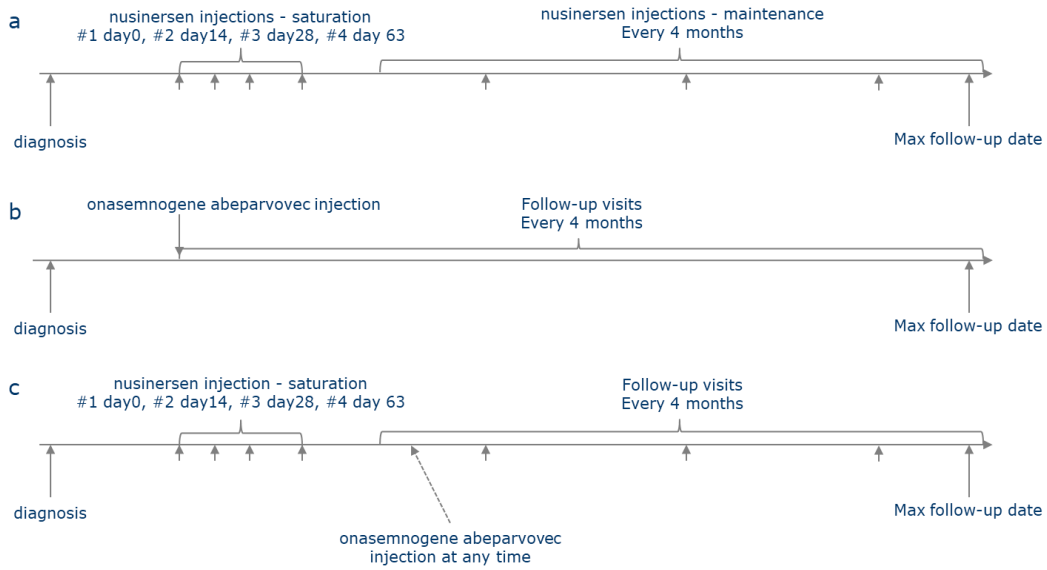


Three types of treatment schemes regarding onasemnogene abeparvovec and nusinersen are expected in the registry data (Figure 2). In addition to subjects who are (a) treated exclusively with nusinersen or (b) with onasemnogene abeparvovec according to the SmPC, there will also be (c) patients who switch from nusinersen to onasemnogene abeparvovec at a given time point.

Due to the non-interventional nature of Routine Data Collection and Evaluations, it is not possible to regulate therapy changes within the study protocol. No methodological approach exists, which can completely exclude possible bias of treatment effects due to therapy changes. For main analysis, group c) is analyzed in terms of treatment episodes under each treatment rather than treatment arms. A treatment episode starts with the day of first administration and ends with the first administration of the respective follow-up intervention or the date of analysis. For sensitivity analysis, group c) will be analyzed as a separate treatment arm (section 8.5 of SAP). Interpretation of results, especially on the effects of treatment switching, will be based on both the main analysis (treatment episodes) as well as the

sensitivity analysis (separate treatment arms for onasemnogene abeparvovec, nusinersen, and treatment switchers from nusinersen to onasemnogene abeparvovec).

Figure 2: Expected treatment schemes



Furthermore, switches from nusinersen to risdiplam, risdiplam to onasemnogene abeparvovec, and onasemnogene abeparvovec to risdiplam are expected. These will not be investigated in this study, as only nusinersen was defined as the comparator for this study (27).

Subjects switching from risdiplam to onasemnogene abeparvovec violate the inclusion criteria of this study. Subjects switching from nusinersen or onasemnogene abeparvovec to risdiplam will be censored at the time of the switch. In case of substantial number of patients switching from nusinersen to other therapies suggesting a potential deterioration under treatment that might not have been reflected yet into the key study outcomes, missing data handling approaches that consider patients as missing not at random (MNAR) would be considered via an amendment and discussed with G-BA to ensure that appropriate methodology to handle such patients is defined. Due to the non-interventional nature of Routine Data Collection and Evaluations, it is not possible to regulate therapy changes within the study protocol. See SAP section 2 for details on therapy switches.

3. Compared therapies

3.1 Onasemnogene abeparvovec

3.1.1 Mechanism of action

Onasemnogene abeparvovec is a gene therapy medicinal product that expresses the human SMN protein. It is designed to introduce a functional copy of the SMN1 gene in the transduced cells to address the monogenic root cause of SMA. By providing an alternative source of SMN protein expression in motor neurons, it is expected to promote the survival and function of transduced motor neurons (32).

Onasemnogene abeparvovec is a non-replicating recombinant adeno-associated virus serotype (AAV) vector that utilizes AAV9 capsid to deliver a stable, fully functional human SMN transgene. The SMN1 gene present in onasemnogene abeparvovec is designed to reside as episomal deoxyribonucleic acid (DNA) in the nucleus of transduced cells and is expected to be stably expressed for an extended period of time in post-mitotic cells. The transgene is introduced to target cells as a self-complementary double-stranded molecule. Expression of the transgene is driven by a constitutive promoter (cytomegalovirus enhanced chicken-β-actin-hybrid), which results in continuous and sustained SMN protein expression (32).

3.1.2 Method of administration and dosage

Onasemnogene abeparvovec is administered as a single-dose intravenous infusion. It should be administered with a syringe pump as a single intravenous infusion with a slow infusion of approximately 60 minutes. It must not be administered as an intravenous push or bolus (32).

It is recommended to initiate an immunomodulatory regimen with oral prednisolone starting 24 hours prior to infusion of onasemnogene abeparvovec and continue for 30 days post infusion (including the day of infusion). The further immunomodulatory therapy with gradually lower doses lasts 28 days and can be conducted with oral prednisolone or systemic corticosteroids, depending on the patient´s liver function (32).

The SmPC recommends a dose of nominal 1.1 x 10^{14} vg/kg onasemnogene abeparvovec and determines the total volume by patient body weight (32).

3.2 Nusinersen

3.2.1 Mechanism of action

Nusinersen acts to enhance the amount of functional SMN protein in infants/children and adults with SMA. It replaces the SMN protein deficit which causes SMA, by increasing the splicing efficiency of the SMN2 pre-messenger ribonucleic acid.

More specifically, nusinersen is an antisense oligonucleotide (ASO) which increases the proportion of exon 7 inclusion in SMN2 messenger ribonuclei acid (mRNA) transcripts by binding to an intronic splice silencing site (ISS-N1) found in intron 7 of the SMN2 pre-mRNA. By binding, the ASO displaces splicing factors, which normally suppress splicing. Displacement of these factors leads to retention of exon 7 in the SMN2 mRNA and hence when SMN2 mRNA is produced, it can be translated into the functional full length SMN protein (33).

3.2.2 Method of administration and dosage

Nusinersen is for intrathecal use by lumbar puncture. It is administered as an intrathecal bolus injection over 1 to 3 minutes, using a spinal anesthesia needle. Sedation may be required for administration, as indicated by the clinical condition of the patient. Ultrasound (or other imaging techniques) may be considered to guide intrathecal administration of nusinersen, particularly in younger patients and in patients with scoliosis (33).

The recommended dosage is 12 mg (5 ml) per administration. Nusinersen treatment should be initiated as early as possible after diagnosis with 4 loading doses on Days 0, 14, 28 and 63. A maintenance dose should be administered once every 4 months thereafter (33).

A recent study on nusinersen (DEVOTE) is currently investigating the clinical efficacy and safety of higher doses of nusinersen in a different regimen (34). For example, in deviation from the approved dose, treatment-naïve patients with SMA receive 50 mg nusinersen on days 0 and 14 as a loading dose followed by a maintenance dose of 28 mg after 4-5 months. Patients who have already received the maintenance dose of 12 mg nusinersen for one year will receive 50 mg once 4 months after their last dose and 28 mg every 4 months thereafter.

In case of a positive benefit-risk ratio of the results of the DEVOTE study, a corresponding adjustment of the approval is conceivable. In this case, an amendment of the protocol and SAP of this study will be initiated to depict the exact changes of nusinersen's marketing authorization that may arise.

4. Objectives

The objective of this study is to evaluate the overall effectiveness and safety in therapy-naïve patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene as well as symptomatic patients with 5q-associated SMA type I treated with gene therapy Zolgensma® (onasemnogene abeparvovec) compared to Spinraza® (nusinersen).

The effectiveness and safety will be assessed based on patient-relevant endpoints, which are derived from the G-BA resolution mandating this study (27).

Effectiveness covers the following:

- Survival
- Motor function
- Nutrition
- Orthopedic complications
- Respiratory function
- Planned hospitalizations

Safety covers the following:

- Adverse events related/unrelated to treatment
- Adverse events leading to hospitalization

The outcomes of this study are to be used in a future benefit assessment according to section 35a SGB V in Germany.

5. Endpoints

Due to the non-interventional nature of this real world data collection, the definition of endpoints as primary or secondary is omitted formally. This is in line with the general methods of the German benefit assessment according to section 35a SGB V, which requires the assessment of patient relevant endpoints irrespective of their character as primary vs. secondary in a specific study (35, 36). An endpoint is considered patient relevant if it depicts how a patient feels, can perform his or her functions and activities, or whether he or she survives (36).

The endpoints depicted in this study are based on the Patient-Intervention-Comparator-Outcome (PICO)-Scheme included in the G-BA resolution mandating this study (27). As per the justification to the resolution, mortality and at least one endpoint per morbidity category depicted in the PICO-Scheme is covered in this study:

"In particular, deaths (mortality category) and at least one endpoint from each of the following patient-relevant morbidity categories should be surveyed: Motor functioning (surveyed with age-appropriate instruments), achievement of motor development milestones of the WHO, respiratory function (need for [continuous] ventilation), bulbar function (e.g. ability to swallow and speak), need for oral nutritional support), and further complications of the disease (e.g. pain, orthopedic complications)." (37).

All endpoints and in particular their definitions were coordinated with clinical experts as well as representatives from the SMArtCARE registry. The endpoints event free survival (EFS) / ventilatory support and motor milestones are considered key endpoints and provide reliable results independent of the age of the treated children. They were thus used for initial sample size calculations (section 8.2).

In addition to the endpoints mandated by G-BA, planned hospitalizations are included upon recommendation by clinical experts. Reasons for planned hospitalizations may include – but are not limited to – the administration of disease modifying therapies, the placement of a gastric tube, or orthopedic complications. This combined endpoint thus depicts a patient relevant burden of the disease and its therapy. This is in line with IQWiG's general methods, which clarify that "the intervention- and disease-related effort of the treatment can be taken into account" in assessing the additional benefit of an intervention (36).

The following sections list endpoints and definitions used for the comparison. Health-related quality of life (HRQoL) is not surveyed in German routine care and not included in the SMArtCARE registry. HRQoL thus cannot be depicted in this registry-based, non-interventional study.

5.1 Effectiveness

5.1.1 Survival

Table 3: Effectiveness endpoints: Survival

Endpoint	Definition	Fields of SMArtCARE CRF (38)
Overall Survival (OS)	Time from the date of first treatment to the date of death due to any cause	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ End of data collection: Date of death ▪ Medical assessment: Visit date
Event Free Survival (EFS)	Time from the date of first treatment to the date of death due to any cause or first of two consecutive documentations of permanent ventilation of at least 16 hours per day	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ End of data collection: Date of death ▪ Medical assessment: Visit date ▪ Medical assessment: Time of ventilator use = Continuous (>16h/day)

5.1.2 Motor function

Table 4: Effectiveness endpoints: Motor function

Endpoint	Definition	Fields of SMArtCARE CRF (38)
Sitting without support at the age of 18 months	Proportion of patients achieving the motor milestone of sitting without support at or before the age of 18 months	▪ Medical assessment: Best current motor function = Sitting without support or higher motor milestone (Crawl on hands and knees, Standing without support, Walking without support, or Climb stairs) ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled) *Note: SMArtCARE refers to the WHO performance criteria (39) as guidance: "Child sits up straight with the head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position."*
Sitting without support at the age of 24 months	Proportion of patients achieving the motor mile-	▪ Medical assessment: Best current motor function = Sitting without support or higher motor milestone

Endpoint	Definition	Fields of SMArtCARE CRF (38)
	stone of sitting without support at or before the age of 24 months	(Crawl on hands and knees, Standing without support, Walking without support, or Climb stairs) ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled) *Note: SMArtCARE refers to the WHO performance criteria (39) as guidance: "Child sits up straight with the head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position."*
Standing without support at the age of 24 months	Proportion of patients achieving the motor milestone of standing without support at or before the age of 24 months	▪ Medical assessment: Best current motor function = Standing without support or higher motor milestone (Walking without support or Climb stairs) ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled) *Note: SMArtCARE refers to the WHO performance criteria (39) as guidance: "Child stands in upright position on both feet (not on the toes) with the back straight. The legs support 100% of the child's weight. There is no contact with a person or object. Child stands alone for at least 10 seconds."*
Walking without support at the age of 24 months	Proportion of patients achieving the motor milestone of walking without support at or before the age of 24 months	▪ Medical assessment: Best current motor function = Walking without support or higher motor milestone (Climb stairs) ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled) *Note: SMArtCARE refers to the WHO performance criteria (39) as guidance: "Child takes at least five steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a*

Endpoint	Definition	Fields of SMArtCARE CRF (38)
		person or object."
Head control at the age of 8 months	Proportion of patients achieving a score of 2 for head control according to HINE until reaching 8 months of age	▪ Medical assessment: Age at visit ▪ Medical Assessment: HINE: Head control
Sustained head control at the age of 24 months	Proportion of patients achieving a score of 2 for head control according to HINE at the first examination after reaching 24 months of age	▪ Medical assessment: Age at visit ▪ Medical Assessment: HINE: Head control
Achievement of motor milestones according to age	Proportion of patients achieving motor milestone as appropriate to their age at the time of outcome analysis Age limits per milestone (based on WHO (40)) ▪ Sitting without support: 9.2 months ▪ Crawl on hands and knees: 13.5 months ▪ Standing without support: 16.9 months ▪ Walking without support: 17.6 months	▪ Medical assessment: Best current motor function ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled) *Note: SMArtCARE refers to the WHO performance criteria (39) as guidance.*
Sustainability of motor milestones	Time from gaining motor milestone to permanent loss of milestone ability ▪ Loss of the ability to sit without support ▪ Loss of the ability to stand without support ▪ Loss of the ability to walk without support Documentation of the new (worsened) highest motor milestone at 2 consecutive visits is required.	▪ Medical assessment: Visit date ▪ Medical assessment: Best current motor function ▪ Medical assessment: Changes in motor milestones ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age lost of previous motor milestone ▪ Baseline: Sitting without support (if gained: Age gained) ▪ Baseline: Standing without support (if gained: Age gained) ▪ Baseline: Walking without support (if gained: Age gained)
HFMSE (Hammersmith Functional Motor Scale-Expanded) at 36 months of age *(exploratory)*	Mean difference of HFSME score at the first examination after reaching 36 months of age	▪ Medical assessment: Age at visit ▪ HFMSE: total hfms

Endpoint	Definition	Fields of SMArtCARE CRF (38)
	Note: Endpoint of exploratory nature due to uncertainties regarding experience, training, and certification of physical therapists in using the scoring instrument	
RULM (Revised Upper Limb Mod-ule) at 36 months of age *(exploratory)*	Mean difference of RULM score at the first examination after reaching 36 months of age *Note: Endpoint of exploratory nature due to uncertainties regarding experience, training, and certification of physical therapists in using the scoring instrument*	▪ Medical assessment: Age at visit ▪ RULM: Total Rulm score
CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders): Change from baseline *(exploratory)*	Change in CHOP-INTEND score from baseline at ▪ 6 months after initial treatment ▪ 12 months after initial treatment *Note: Endpoint of exploratory nature due to uncertainties regarding experience, training, and certification of physical therapists in using the scoring instrument*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ CHOP-INTEND: Date of evaluation ▪ CHOP-INTEND: Score
HINE (Hammersmith Infant Neurological Examination): Change from baseline *(exploratory)*	Change in HINE score from baseline at ▪ 12 months after initial treatment ▪ 24 months after initial treatment *Note: Endpoint of exploratory nature due to uncertainties regarding experience, training, and certification of physical therapists in using the scoring instrument*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical Assessment: HINE: Visit date ▪ Medical Assessment: HINE: Score
Time to sitting without support *(exploratory)*	Time from the age at first treatment to the age at reaching motor milestone of sitting without support	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Best current motor function = Sitting without support or higher motor milestone

Endpoint	Definition	Fields of SMArtCARE CRF (38)
	Note: Endpoint of exploratory nature due to uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed)	(Crawl on hands and knees, Standing without support, Walking without support, or Climb stairs) ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled) *Note: SMArtCARE refers to the WHO performance criteria (39) as guidance: "Child sits up straight with the head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position."*
Time to standing without support *(exploratory)*	Time from the age at first treatment to the age at reaching motor milestone of standing without support *Note: Endpoint of exploratory nature due to uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed)*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Best current motor function = Standing without support or higher motor milestone (Walking without support or Climb stairs) ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled) *Note: SMArtCARE refers to the WHO performance criteria (39) as guidance: "Child stands in upright position on both feet (not on the toes) with the back straight. The legs support 100% of the child's weight. There is no contact with a person or object. Child stands alone for at least 10 seconds."*
Time to walking without support *(exploratory)*	Time from the age at first treatment to the age at reaching motor milestone of walking without support *Note: Endpoint of exploratory nature due to uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed)*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Best current motor function = Walking without support or higher motor milestone (Climb stairs) ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled) *Note: SMArtCARE refers to the WHO performance criteria (39) as guidance:*

Endpoint	Definition	Fields of SMArtCARE CRF (38)
		"Child takes at least five steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object."

Selected motor function endpoints are included in this study as exploratory endpoints.

For age appropriate motor function scores (CHOP-INTEND, HINE, HFMSE, and RULM) it is essential to ensure sufficient and comparable level of experience, training, and certification among all physical therapists to generate reliable results. During the first 18 months of the study, levels of experience, training, and certification will be surveyed among all participating sites. Results of this evaluation may trigger an amendment of study protocol and SAP 18 months after study start.

For TTE analyses of motor milestones, there are uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed) as well as potential bias from different frequencies of visits between the study interventions.

5.1.3 Nutrition

Table 5: Effectiveness endpoints: Nutrition

Endpoint	Definition	Fields of SMArtCARE CRF (38)
Difficulties in swallowing	Proportion of patients with difficulties in swallowing at the first examination after ▪ reaching 12 months of age ▪ reaching 24 months of age ▪ reaching 36 months of age	▪ Medical assessment: Age at visit ▪ Medical assessment: Swallowing? = With difficulties
Difficulties in chewing	Proportion of patients with difficulties in chewing at the first examination after ▪ reaching 12 months of age ▪ reaching 24 months of age ▪ reaching 36 months of age	▪ Medical assessment: Age at visit ▪ Medical assessment: Chewing? = With difficulties

Endpoint	Definition	Fields of SMArtCARE CRF (38)
Gastric or nasal feeding tube	Time from the date of first treatment to the start date of first tube feeding of two consecutive documentations ▪ Any type of tube feeding (supplementary or exclusively) ▪ Supplementary (e.g. for fluids) ▪ Exclusively	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes - exclusively fed by tube ▪ Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes – supplementary e.g. for fluids ▪ Medical assessment: Start of tube feeding (date) ▪ Medical assessment: Visit date (if start date of feeding tube not filled)

5.1.4 Orthopedic complications

Table 6: Effectiveness endpoints: Orthopedic complications

Endpoint	Definition	Fields of SMArtCARE CRF (38)
Scoliosis or orthopedic surgery	Time from the date of first treatment to first documentation of scoliosis or orthopedic surgery	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Visit date ▪ Medical assessment: Does the patient have scoliosis? ▪ Medical assessment: Orthopedic surgery since last visit?
Scoliosis	Time from the date of first treatment to first documentation of scoliosis	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Visit date ▪ Medical assessment: Does the patient have scoliosis?
Orthopedic surgery	Time from the date of first treatment to first documentation of orthopedic surgery	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Visit date ▪ Medical assessment: Orthopedic surgery since last visit?

5.1.5 Respiratory function

Table 7: Effectiveness endpoints: Respiratory function

Endpoint	Definition	Fields of SMArtCARE CRF (38)
Time of ventilator use	Time from the date of first treatment to the first of two	▪ Nusinersen/Zolgensma: MIN(Date of treatment)

Endpoint	Definition	Fields of SMArtCARE CRF (38)
	consecutive documentations of ▪ Any ventilator support ▪ Ventilator support at night (during sleep) ▪ Intermittent ventilator support at day time and continuous at night ▪ Permanent ventilator support (>16 hours per day) ▪ Intermittent ventilator support with acute illnesses Documentation of same or higher ventilator support time required at 2 consecutive visits.	▪ Medical assessment: Visit date ▪ Medical assessment: Does the patient receive ventilator support? ▪ Medical assessment: Time of ventilator use o Night (during sleep) o Intermittent day time and continuous at night o Continuous (>16h/day) o Intermittent with acute illnesses
Type of ventilator use	Time from the date of first treatment to the first of two consecutive documentations of (each separately) ▪ Non-invasive ventilation ▪ Invasive ventilation Documentation of same or higher ventilator support type required at 2 consecutive visits.	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Visit date ▪ Medical assessment: Does the patient receive ventilator support? ▪ Medical assessment: Type of ventilation o Non-invasive o Invasive
Improvement in time of ventilator support from baseline	Time from the date of first treatment to the first of two consecutive documentations of an improvement in time of ventilator use. An improvement is defined as any of the following ▪ Change from permanent ventilator support (>16 hours per day) to ventilator support at night (during sleep) or intermittent ventilator support at day time and continuous at night or no ventilator support OR ▪ Change from intermittent ventilator support at day time and continu-	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Visit date ▪ Medical assessment: Does the patient receive ventilator support? ▪ Medical assessment: Time of ventilator use o Night (during sleep) o Intermittent day time and continuous at night o Continuous (>16h/day)

Endpoint	Definition	Fields of SMArtCARE CRF (38)
	ous at night to ventilator support at night (during sleep) or no ventilator support OR ▪ Change from ventilator support at night (during sleep) to no ventilator support	

5.1.6 Planned hospitalizations

Table 8: Effectiveness endpoints: Planned hospitalizations

Endpoint	Definition	Fields of SMArtCARE CRF (38)
Planned hospitalizations	Cumulative number of planned hospitalizations across all patients per patient-year of being at risk	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Visit date ▪ Medical assessment: Planned hospitalisation since last visit (except for treatment administration)? ▪ Medical assessment: Reason for hospitalisation ▪ Nusinersen/Zolgensma: Care Setting = Inpatient (overnight) *Note: Onasemnogene abeparvovec is exclusively administered in an inpatient setting in Germany. SMArtCARE SAP accordingly refers to the hospitalization for treatment. One planned hospitalization is counted for each patient receiving onasemnogene abeparvovec at the date of treatment.*

5.2 Safety

Table 9: Safety Endpoints

Endpoint	Definition	Fields of SMArtCARE CRF (38)
(Related) adverse events	Cumulative number of patients with and number of adverse events across all patients per patient-year of being at risk ▪ Any adverse event with or without hospitalization	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Any unexpected events without hospitalisation? ▪ Adverse events: MedDRA code of

Endpoint	Definition	Fields of SMArtCARE CRF (38)
	▪ Any adverse event related to treatment (yes/possibly) with or without hospitalization Reporting by MedDRA (SOC/PT) if documented	acute event ▪ Adverse events: Type of unexpected event ▪ Adverse events: Start date ▪ Adverse events: Date recorded (in case start date is not filled) ▪ Adverse events: Is the adverse event related to drug treatment? ▪ Adverse events: name of drug
(Related) adverse events with hospitalization	Cumulative number of patients with and number of adverse events with hospitalizations across all patients per patient-year of being at risk ▪ Any adverse event with hospitalization ▪ Any adverse event related to treatment (yes/possibly) with hospitalization Reporting by MedDRA (SOC/PT) if documented	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: MedDRA code of acute event ▪ Adverse events: Start date ▪ Adverse events: Is the adverse event related to drug treatment? ▪ Adverse events: name of drug

According to the G-BA justification of resolution mandating this study, serious specific unwanted side effects identified on the basis of the information provided in the Risk Management Plan and the European Public Assessment Report (EPAR) of the intervention onasemnogene abeparvovec and the comparator nusinersen should be surveyed. This should include hepatotoxicity, thrombocytopenia, cardiac events, dorsal root ganglia cell inflammation, renal toxicity, and hydrocephalus (37). This requirement was discussed with clinical experts as well as representatives from the SMArtCARE registry and deemed clinically unfeasible at current. Criteria for clinically relevant thresholds for hepatotoxicity, thrombocytopenia, and cardiac events on the context of treatment with gene therapy in SMA are currently discussed but not yet established. They may be established in the future and will be included in the study via an amendment once added by SMArtCARE.

6. Data sources

6.1 SMArtCARE registry

G-BA mandated the non-randomized comparison of onasemnogene abeparvovec and the comparator therapy nusinersen as parallel control within one data source (37). The SMArtCARE registry is to be used as the data source, as this registry meets the minimum data quality requirements described in the IQWiG concept (29). This applies especially to the quality criteria for standardization and validity of data collection as well as for sample collection. The mentioned criteria were considered particularly relevant for the present requirement (37).

IQWiG identified the RESTORE registry (43), the German Patient SMA registry (as part of the Global TREAT-NMD SMA Global Registry (44–46) and the SMArtCARE registry (47) as potentially suitable registries via literature research. Their suitability for the present Routine Data Collection and Evaluations was evaluated in detail.

According to IQWiG, the RESTORE-Registry bears risk of selection bias as there are differences in the completeness of patients treated with onasemnogene abeparvovec and nusinersen. Moreover, the recruiting centers are almost exclusively based in the United States of America, whereas there are no recruiting centers in Germany so far. It is not intended to standardize data collection of the participating centers, and it remains unclear if adequate measures are in place or planned to ensure correctness and completeness of the data (29).

The German Patient SMA registry (as part of the Global TREAT-NMD SMA Registry) does not collect longitudinal data and is therefore not eligible as data source (29).

Data for the SMArtCARE registry is collected mainly in German centers and includes information on potential confounders. Data quality is ensured by standardized collection of data, staff training at the participating centers, plausibility checks and queries. Physiotherapeutic evaluation is performed by appropriately trained physiotherapists and according to WHO criteria (48). Source data verification will be implemented as described in section 10.2 of this protocol. IQWiG concludes that the SMArtCARE registry sufficiently meets the quality criteria and qualifies as data source for the mandated Routine Data Collection and Evaluations (29).

The SMArtCARE registry is a joined initiative of academic institutions and patient organizations and supported by pharmaceutical industry. The contractual framework in set up in a way that the academic network has full data ownership and publication rights. SMArtCARE does not transfer patient level data to pharmaceutical companies. If data analysis is needed for regulatory purposes, this is done via an independent third party. All studies and data analysis require prior approval of the SMArtCARE steering committee.

When data from international registries is taken into consideration, it has to be assured that the minimum data quality requirements mandated by G-BA for the

Routine Data Collection and Evaluations are equally met (27). Moreover, transferability to the German health care context is indispensable. An international analysis revealed relevant differences in the standard of care between different countries, e.g. with regard to standards for and availability of non-medical measures, and different standards for ventilation (invasive vs. non-invasive), (44). In addition, the Drug Commission of the German Medical Association expressed concern that inclusion of non-national registries might induce bias due to different national regulations of reimbursement (49). Finally, countries may differ significantly with regard to newborn screening. While the study will take place after introduction of newborn screening in Germany (50) and patients will thus mostly be treated presymptomatically, patients are expected to be treated after initial onset of symptoms more frequently in countries without newborn screening.

For international registries, full compliance with the data quality criteria mandated by G-BA cannot undoubtedly be assured. Differences between the data sources might be a source of additional bias, e.g. in relation to time points of data collection, definition of endpoints or availability of potential confounders. Because of these reasons, which G-BA explicitly mentions as sources of potential bias (37), data from international registries is not included in this study. Data for the non-randomized comparison of onasemnogene abeparvovec and nusinersen will be collected exclusively via the SMArtCARE registry. Details of IQWiG's assessment of SMArtCARE are listed in Table 10.

Table 10: Fulfillment of quality criteria by SMArtCARE Registry (29)

No.	Quality criterion	Fulfillment by SMArtCARE
	Consistent systematics	
1	Detailed description of registry (registry protocol)	yes
	Standardization	
2	Exact definition/ operationalization of expositions, clinical events, endpoints and confounders	yes
3	Current data plan/ coding list	yes
4	Use of standard classifications (e.g. ICD-10) and terminologies (e.g. MedDRA)	yes
5	Use of validated standard assessment instruments (questionnaires, scales, tests)	yes, but no assessment of health-related quality of life
6	Training on data collection and - acquisition	yes
7	Implementation of a disease-specific core data set	yes
8	Use of exact patient-specific dates (e.g. birth, death, pregnancy)	yes
9	Use of exact dates in medical history (e.g. diagnosis, clinical relevant events)	yes

No.	Quality criterion	Fulfillment by SMArtCARE
10	Use of exact dates of important medical assessments	yes
11	Use of exact dates for treatments and interventions (e.g. start/stop, dosage, dosage adjustment)	yes, with limitations (no documentation of nusinersen dosage)
	Achievement of recruitment target/sample collection	
12	Clearly defined inclusion/exclusion criteria for registry population	yes
13	Completeness of registry patients (complete registration or representative sample)	unclear
14	Strategies to avoid unintentional recruitment bias to attain representative status	yes (consecutive inclusion)
	Validity of data collection	
15	Completeness of data per assessment	shall be assured through standards
16	Completeness of assessments (loss to follow-up, drop outs)	shall be assured through standards
17	Accuracy of data	limited as there is actually no source data verification[a]
18	Consistency of data over time	yes
19	Source data verification (e.g. for 10% randomly selected patients per participating center)	No[a]
20	Internal audits	no
21	External audits	no
22	Quality management system (with regular evaluation of quality indicators, where appropriate)	yes
23	Standard Operating Procedures regarding data collection	yes
	Superordinate quality criteria	
24	Transparency of the registry (including funding, decision-making, conflict of interest, amongst others)	yes
25	Scientific independence	yes
26	Secured funding (for planned study period)	yes
27	Steering committee	yes
28	Up-to-date registry documents (e.g. protocol, data plan, statistical analysis plan, informed consent etc.)	yes

No.	Quality criterion	Fulfillment by SMArtCARE
29	Protection of patients´ rights and data protection, consideration of ethical aspects	yes
30	Timeliness (current status/quick availability/timeliness of requested results)	yes
31	Flexibility and adaptability (e.g. implementation of trials, further assessments, changing medical care situation)	yes
32	Documentation trail - documentation of all changes to processes and definitions	yes
33	Audit trail - documentation and attribution of all data transactions	yes
34	Interconnect ability with other data sources	planned
	Further possible criteria from a regulatory point of view	
46	Assessment and handling of adverse events (AE) in accordance with regulatory requirements	yes

[a)] Source Data Verification will be implemented in the course of this study as described in section 10.2 of this protocol.

6.2 Study sites

Due to the design of a registry-based, non-interventional study, available data in the SMArtCARE registry is provided by all HSPs participating in the registry. According to public information, 53 entities of 46 hospitals are currently participating in the SMArtCARE registry, of which 41 entities of 34 hospitals are located within Germany (51).

Only patients treated in centers that meet the quality criteria of the G-BA resolution of November 20, 2020 for the use of onasemnogene abeparvovec (52) and offer both interventions of this study (onasemnogene abeparvovec and nusinersen) will be included in the study (see section 7.1). This approach ensures a minimization of potential bias from different infrastructure, treatment, and documentation standards between HSPs. It also avoids using data from HSPs that use only one of the two study interventions and whose specific standards of care are therefore not reflected in the effects for both study interventions. Limiting the study to these HSPs also allows for the most efficient implementation of measures to avoid missing data (see section 10.3) and to implement full source data verification (see section 10.2)

There are currently 18 HSPs in Germany that offer both onasemnogene abeparvovec and nusinersen, which are depicted in Table 11. Because administration of onasemnogene abeparvovec is limited to HSPs fulfilling the quality criteria, it is

ensured that all HSPs offering both interventions fulfill the highest quality standards. Participation in the SMArtCARE registry as well as the documentation of patients is required by the G-BA quality criteria (52). In addition, reimbursement of onasemnogene abeparvovec is limited to HSPs participating in this study, while reimbursement of nusinersen is not restricted to HSPs participating in this study (31). By limiting study sites to those offering both interventions of this study, it is ensured that the data utilized for this study is as complete and consistent as is possible in a real-world setting.

HSPs outside of Germany do not fall under the jurisdiction of the G-BA quality criteria or reimbursement restrictions and are thus not included in this study. Due to differences in standards of care, especially with regard to newborn screening, the patient populations in different countries are also expected to differ with regard to their baseline characteristics and outcomes. While the study will take place after introduction of newborn screening in Germany (50), patients are expected to be symptomatic at diagnosis more frequently in other countries (e.g. Austria, where newborn screening has yet to be introduced).

Table 11 lists all HSPs offering both onasemnogene abeparvovec and nusinersen as of June 2021. Should additional HSPs fulfill G-BA quality criteria and offer both study interventions in the future, they will be included in the study. Study inclusion will start at the day of treatment of the first patient with onasemnogene abeparvovec at the respective HSP. Changes in HSPs providing both interventions will not be captured in protocol amendments but will be depicted in detail in all in study reports (section 12).

Table 11: Participating German HSPs in SMARTCARE and inclusion in study

City	HSP	Study Inclusion
Augsburg	Universitätsklinikum Augsburg ▪ Klinik für Kinder und Jugendliche / Mutter-Kind-Zentrum Schwaben	No
Berlin	Charité Universitätsmedizin Berlin: Campus Virchow Klinikum ▪ Sozialpädiatrisches Zentrum Neuropädiatrie	Yes
Berlin	DRK Kliniken Berlin Westend ▪ Klinik für Kinder- und Jugendmedizin Epilepsiezentrum / Neuropädiatrie	Yes
Bochum	Ruhruniversität Bochum im St. Josef Hospital ▪ Klinik für Kinder- und Jugendmedizin: Neuropädiatrie	No
Bonn	Universitätsklinikum Bonn ▪ Zentrum für Kinderheilkunde Abteilung Neuropädiatrie	Yes

City	HSP	Study Inclusion
Dresden	Universitätsklinikum Carl Gustav Carus Dresden an der Technischen Universität Dresden ▪ Klinik und Poliklinik für Neurologie ▪ Neuropädiatrie Klinik und Poliklinik für Kinder- und Jugendmedizin	Yes
Erlangen	Universitätsklinikum Erlangen ▪ Neurologische Klinik ▪ Kinder und Jugendklinik Neuropädiatrie	Yes
Essen	Universitätsklinikum Essen ▪ Neurologische Klinik und Poliklinik ▪ Klinik für Kinderheilkunde Neuropädiatrie	Yes
Freiburg	Universitätsklinikum Freiburg ▪ Klinik für Neuropädiatrie und Muskelerkrankungen	Yes
Gießen	Universitätsklinikum Gießen und Marburg GmbH - Klinikum der Justus-Liebig-Universität ▪ Zentrum für Kinderheilkunde und Jugendmedizin. Abteilung für Kinderneurologie, Sozialpädiatrie und Epileptologie	Yes
Göttingen	Universitätsmedizin Göttingen ▪ Klinik für Neurologie ▪ Klinik für Kinder- und Jugendmedizin Sozialpädiatrisches Zentrum	No
Halle	Universitätsklinikum Halle ▪ Klinik und Poliklinik für Neurologie	No
Hamburg	Asklepios Klinik Nord Hamburg ▪ Neuropädiatrie	No
Hamburg	Universitätsklinikum Hamburg-Eppendorf Zentrum für Geburtshilfe, Kinder- und Jugendmedizin ▪ Klinik und Poliklinik für Kinder- und Jugendmedizin	Yes
Hannover	Medizinische Hochschule Hannover ▪ Klinik für Neurologie ▪ Zentrum für Kinderheilkunde u. Jugendmedizin	Yes
Heidelberg	Universitätsklinikum Heidelberg ▪ Neurologische Klinik ▪ Zentrum für Kinder- und Jugendmedizin	Yes
Homburg	Universitätsklinikum des Saarlandes	Yes

City	HSP	Study Inclusion
	▪ Klinik für Allgemeine Pädiatrie und Neonatologie	
Jena	Universitätsklinikum Jena ▪ Neurologische Klinik und Poliklinik ▪ Klinik für Neuropädiatrie Sozialpädiatrisches Zentrum	Yes
Kassel	Klinikum Kassel ▪ Neuropädiatrie	Yes
Kiel	Universitätsklinikum Schleswig-Holstein ▪ Klinik für Neurologie	No
Cologne	Kliniken der Stadt Köln GmbH Kinderkrankenhaus ▪ Sozialpädiatrisches Zentrum	No
Leipzig	Universitätsmedizin Leipzig ▪ Klinik und Poliklinik für Neurologie	Yes
Mannheim	Universitätsmedizin Mannheim ▪ Neurologische Klinik	No
Munich	Klinikum der Universität München ▪ Friedrich-Baur-Institut	No
Munich	Dr. von Haunersches Kinderspital ▪ Kinderklinik und Kinderpoliklinik der Ludwig Maximilian Universität München	Yes
Munich	Technische Universität München Klinikum rechts der Isar ▪ Klinik und Poliklinik für Neurologie	No
Münster	Universitätsklinikum Münster ▪ Klinik und Poliklinik für Kinder- und Jugendmedizin Allgemeine Pädiatrie - Neuropädiatrie	Yes
Oldenburg	Klinik und Poliklinik für Kinder- und Jugendmedizin Allgemeine Pädiatrie – Neuropädiatrie ▪ Klinik für neurologische Intensivmedizin und Frührehabilitation	No
Rostock	Universitätsklinikum Rostock ▪ Klinik und Poliklinik für Neurologie Zentrum für Nervenheilkunde	No
Stuttgart	Klinikum Stuttgart Olgaspital ▪ Päd. Neurologie, Psychosomatik und Schmerztherapie	No
Tübingen	Universitätsklinikum Tübingen ▪ Kinderklink Abteilung III	Yes

City	HSP	Study Inclusion
Ulm	Universitätsklinikum Ulm ▪ Sektion Sozialpädiatrisches Zentrum und Pädiatrische Neurologie / Stoffwechsel	No
Wiesbaden	DKD Helios Klinik Wiesbaden ▪ FB Neurologie und Klin. Neurophysiologie	No
Würzburg	Universitätsklinikum Würzburg ▪ Kinderklinik und Poliklinik Sozialpädiatrisches Zentrum Neuropädiatrie ▪ Neurologische Klinik und Poliklinik	No

Source: SMArtCARE, Novartis Gene Therapies

In case historic data for nusinersen is utilized in this study (see sections 7.3, 8.4), only patients treated at the HSPs depicted in Table 11 will be included. In contrast to the prospective data collection, it is not possible to retrospectively verify compliance with the G-BA quality criteria (52). To minimize the risk of bias, only historical data from the same centers that prospectively participate in the study from the study start will be included. This approach will ascertain best possible homogeneity regarding documentation standards between individual centers. In addition, limiting historical data to centers participating in the prospective part of the study allows for the most efficient implementation of measures to avoid missing data (see section 10.3) and to implement full source data verification for historic data (see section 10.2).

7. Population Selection

This analysis will use individual patient data from patients included in SMArtCARE registry which are treated with onasemnogene abeparvovec or nusinersen and fulfill the inclusion and exclusion criteria.

7.1 Inclusion Criteria

Patients included in the study need to fulfill the criteria listed in Table 12.

Table 12: Inclusion criteria and operationalization in SMArtCARE registry

#	Inclusion criteria	Definition in SMArtCARE (38)
1	Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene OR	▪ Enrolment: Genetically proven 5q SMA AND ▪ Baseline: Was diagnosis made pre-symptomatically? = yes AND ▪ Baseline: SMN2 copy number ≤ 3
	Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA OR	▪ Enrolment: Genetically proven 5q SMA AND ▪ Baseline: Was diagnosis made pre-symptomatically? = no AND ▪ Baseline: Age at symptom onset < 6 months
	Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene	▪ Enrolment: Genetically proven 5q SMA AND ▪ Baseline: Was diagnosis made pre-symptomatically? = no AND ▪ Baseline: SMN2 copy number ≤ 3 AND ▪ Baseline: Age at symptom onset ≥ 6 months AND ▪ Baseline: Age at symptom onset < 18 months
2	Treatment initiation with nusinersen (12 mg / 5 ml per administration) or onasemnogene abeparvovec (dosage according to body weight as per SmPC)	▪ Medical Assessment: Is the patient on any approved medication for SMA? = no for all visits

#	Inclusion criteria	Definition in SMArtCARE (38)
		before Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Name of drug = onasemnogene abeparvovec/Zolgensma OR nusinersen/Spinraza ▪ Nusinersen/Zolgensma: MIN(Date of treatment) ≥ study start date (not applied to nusinersen if historic data is used, see section 8.4)
3	Body weight at treatment initiation ≤ 21 kg	▪ Medical assessment: Body weight (kg) ≤ 21 AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treatment)
4	Treatment at a site that administrates both interventions of this study (onasemnogene abeparvovec and nusinersen) and is located in Germany *The current status of the list of centers offering both study interventions is shown in Table 11*	▪ No field in CRF, identification via SMArtCARE database on documenting HSP per submitted CRF
5	Appropriate consent/assent has been obtained for participation in the study	▪ Enrolment: Date of consent <> “”

The first inclusion criterion depicted in Table 12 depicts the population mandated for this study by G-BA (27).

The second criterion depicted in Table 12 ensures compliance with the concept of “emulation of target trial” set forth by IQWiG. The IQWiG methodological framework for RWE application in the benefit assessment (30) and the IQWiG concept for Routine Data Collection and Evaluations for onasemnogene abeparvovec (29) recommend the explicit emulation of the planning of randomized trials for planning of non-randomized Real World Evidence (RWE) studies for the benefit assessment ("emulation of target trial"). Within the components of the emulation of the target trial from a non-randomized data set, a "new user design" is required:

"Patients who meet the inclusion/exclusion criteria are assigned to the intervention they received at the beginning of their treatment for the disease or indication under investigation". (30).

To implement these requirements, only therapy-naïve patients will be included in the study.

The third criterion depicted in Table 12 is introduced to ensure that only patients eligible for treatment with both interventions of this study are included. While the EU marketing authorization for onasemnogene abeparvovec does not recommend an age limit, the use of onasemnogene abeparvovec is expected to be almost exclusive to newborns and infants. This is also reflected in the G-BA's quality criteria for the use of onasemnogene abeparvovec (52). Onasemnogene abeparvovec is administered by intravenous infusion. Patients receive a dosage based on body weight. The SmPC specifies a recommended dosage for patients with a body weight up to 21.0 kg body weight (32). For this reason, only patients ≤21 kg body weight are included in the in-use data collection to ensure the best possible comparability of the patient populations for both interventions.

The fourth criterion depicted in Table 12 serves to minimize potential bias from different treatment and documentation standards between individual HSPs (see section 6.2).

The fifth criterion depicted in Table 12 serves to ensure compliance with all legal requirements of this study (see section 11).

7.2 Exclusion Criteria

Patients characterized by any of the criteria listed in Table 13 will not be included in the study.

Table 13: Exclusion criteria and operationalization in SMArtCARE registry

#	Exclusion criteria	Fields in SMArtCARE CRF (38)
1	Pretreatment with disease-modifying therapy (nusinersen, onasemnogene abeparvovec, risdiplam)	▪ Medical Assessment: Is the patient on any approved medication for SMA? = yes for any visit before Nusinersen/Zolgensma: MIN(Date of treatment)
2	Pretreatment with any of the following investigational drugs for the treatment of SMA: albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea	▪ Medical Assessment: Other medication taken on a regular basis? = yes AND ▪ Medical Assessment: Name of medication (other medication) includes albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, or hydroxyurea AND ▪ Medical Assessment: Start Date (other medication) ≤ Nusinersen/Zolgensma: MIN(Date of treatment)

#	Exclusion criteria	Fields in SMArtCARE CRF (38)
3	Currently or previously enrolled in an interventional clinical trial involving an investigational product to treat SMA	▪ Baseline: Is the patient currently or was previously included in a clinical trial? = Yes OR ▪ Medical assessment: Is the patient currently in a clinical trial? = Yes for any visit before Nusinersen/Zolgensma: MIN(Date of treatment)

The first criterion depicted in Table 13 serves to ensure patients are not pre-treated with any authorized disease modifying drug (DMD) prior to their inclusion in the study.

The second and third criteria depicted in Table 13 ensures that patients are not treated with any DMD not authorized but investigated for use in SMA prior to their inclusion in the study.

7.3 Criteria for historic data

The SMArtCARE registry has been enrolling patients since July 2018 (29) and prospectively collected data for patients treated with nusinersen since then. Historical data on nusinersen patients, i.e. data prospectively captured in SMArtCARE prior to the start of this study, may be utilized in this study if final sample size cannot be enrolled exclusively from prospective patients (section 8.4). As per the G-BA resolution, historical data for patients treated with onasemnogene abeparvovec will not be used (27). At the same time, the use of data that was collected at different times per intervention generally results in a relevant potential for bias. Even if significant confounders are mapped and data was collected at the time of treatment, it cannot be ruled out that non-measurable confounders, e.g. in the form of changes in the standard of care over time, may have an impact on the results.

If the use of historical data on nusinersen is necessary to ensure the feasibility of the study, best possible minimization of bias is of decisive importance for the reliability of study results. In this case, all historical nusinersen patients must meet the following criteria in addition to fulfilling the inclusion and exclusion criteria depicted in sections 7.1 and 7.2:

- The treatment of the patient as well as the documentation of confounders and endpoints used must have consistently taken place in a treatment center that, at the time of study start, offers both interventions of this study (onasemnogene abeparvovec and nusinersen). Table 11 depicts the treatment centers eligible for inclusion of historic data on nusinersen patients.

- Information must be available on all baseline confounders that were categorized as clinically "very important" during validation by clinical experts. The corresponding confounders are depicted in Table 20.
- Information on key endpoints of the study must be available, which are used for sample size calculation. This includes event-free survival and motor milestones. Should other endpoints be used for final sample size calculations, which is possible and explicitly allowed by the G-BA resolution (27), information on these endpoints needs to be available.
- The data on baseline confounders and endpoints used to calculate treatment effects must be quality assured retrospectively by 100% source data verification (section 10.2). As such, informed consent from living patients must have been obtained (section 11.2).

Fulfillment of all criteria required for inclusion of historic nusinersen patients will be assessed to determine the number of eligible historic patients treated with nusinersen. The results of this assessment will be included in the first status report submitted to G-BA (section 12).

8. Study Design & Methods: Statistical Considerations

8.1 Analysis Populations

In the resolution of February 4, 2021, the G-BA defined the following patient groups within the PICO-scheme for the Routine Data Collection and Evaluations for inclusion (27):

- Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene
- Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and clinically diagnosed type 1 SMA
- Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene

The stratification of patients within the study has been subject to intense exchange with clinical experts. It was explicitly recommended that only a stratification based on the copy number of the SMN2 gene should be depicted in the study.

The exclusive stratification by SMN2 copy number is predominantly based on significant advances in early detection and treatment of SMA that have occurred in recent years and are expected to continue in the coming years. Nationwide newborn screening will be introduced in Germany starting in October 2021 (50) and three approved DMDs are now available. As a consequence of early detection and immediate treatment, the importance of the copy number of the SMN2 gene versus the clinical phenotype of the disease is increasing from a clinical perspective (9, 8).

It is expected that with the introduction of newborn screening before the start of the study, almost all therapy-naïve patients will be identified immediately after birth by genetic testing and treated with a disease-modifying therapy. Accordingly, it can be assumed that clinically symptomatic patients will play a minor role in the context of the Routine Data Collection and Evaluations. The symptom status at diagnosis will nevertheless be considered as a baseline confounder in the context of the study.

In the setting of care for this study, it is thus appropriate to only stratify study populations based on the copy number of the SMN2 gene. Control of the influence of the symptom status at diagnosis is achieved via adequate adjustment methods for confounders (section 8.6). In addition, possible effect modification in symptomatic patients will be investigated in the planned subgroup analyses for all confounders (section 8.7).

Patients with 5q-associated SMA with biallelic mutation in the SMN1 gene will thus be stratified by number of copies of the SMN2 gene: up to 2 copies vs. 3 copies. Therefore, the following study populations are defined for analyses:

- Population A: Patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 2 copies of the SMN2 gene.
- Population B: Patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and 3 copies of the SMN2 gene.

All patients in each population are targeted for effectiveness and safety analyses. The analysis will not be performed on the combined overall population of A and B.

8.2 Sample Size

Due to the non-interventional design of this study, Novartis Gene Therapies has no control over enrollment in the study. All patients fulfilling the inclusion and exclusion criteria (section 7) will be included in the study.

As SMA is a rare disease, there is a finite number of patients that can be enrolled with the additional restriction that the study needs to be stratified into two analysis subsets defined by patients' number of SMN2 gene copies (section 8.1). This patient characteristic is expected to relevantly affect the prognosis. Despite these limitations, sample size calculation and fulfillment of minimum patient numbers is essential to ensure that there will be sufficient numbers of patients to generate interpretable results. If patient numbers are too low compared to required sample size, statistically insignificant results are to be expected irrespective of the true treatment effect.

8.2.1 Assumptions of effect measures and event rates

Sample size calculations for this non-randomized study need to consider patient shares and association between baseline confounders and treatment effects. Estimates of relative treatment effects are only available from indirect treatment comparisons (ITC) and only for patients with SMA type 1 (29). Sample size calculations for the study population of 2 copy SMN2 patients are thus based on unpublished results of an ITC of study results from START, STR1VE-US, and SHINE trials, which was performed by Novartis Gene Therapies and used for the purpose of planning this study. Adjustments were made for the confounders CHOP-INTEND and ventilatory support at baseline; additional confounders could not be considered due to lack of convergence of the statistical models. The results are shown in Table 14.

Table 14: Effect measures and event rates: SMA type I

Endpoint	Type	Effect measure [95% CI]	Overall event rate for patient ratio 1:1
EFS until month 18	TTE	HR: 0.19 [0.07-0.54]	35.2%
OS until month 18	TTE	HR: 0.35 [0.09-1.32]	10.4%

Endpoint	Type	Effect measure [95% CI]	Overall event rate for patient ratio 1:1
Standing without support to month 18	binary	OR: 3.62 [1.31-10.8]	43.9%

Source: (53).

For patients with 3 copies of the SMN2 gene, no results from indirect comparisons are available, which could be used as a basis for a sample size calculation. Against this background, sampe size estimates were performed based on very rough assumptions.

Because of the generally slower disease progression in patients with 3 copies of the SMN2 gene, reductions in event rates for TTE endpoints (EFS/OS) were assumed to be 20% for EFS (vs. 35.2% in SMA type I) and 5% for OS (vs. 10.4% in SMA type I).

Based on the mechanism of action of nusinersen, which modulates alternative splicing of the SMN2 gene, it is hypothesized that nusinersen will show relatively better effectiveness in patients with 3 copies of SNM2 than in patients with 2 copies of SNM2. For this reason, the assumed effect measure in TTE endpoints of onasemnogene abparvovec versus nusinersen in patients with 3 copies of the SMN2 gene was reduced by a factor of approximately 2 compared with the results of the indirect comparison for patients with type I SMA.

Because of the high proportion of patients with 3 copies of the SMN2 gene who achieve unassisted sitting and the low proportion of patients who require permanent ventilation at a young age, other end points (e.g. standing, walking, or motor function as measured via age appropriate instruments) are more likely to show relevant differences. Because no evidence or assumptions are currently available for these endpoints, it was assumed that event rates and effect size for independent standing may be comparable to those observed for independent sitting in SMA type I. The resulting assumptions on effect measures and event rates are shown in Table 15.

Table 15: Assumend effect measures and event rates: patients with 3 copies of the SMN2 gene

Endpoint	Type	Assumend effect measure [95% CI]	Assumend average event rate for patient ratio 1:1
EFS until month 18	TTE	HR: 0.38	20%
OS until month 18	TTE	HR: 0.70	5%
Standing without support to month 18	binary	OR: 3.62 [1.31-10.8]	45%

8.2.2 Further assumptions and methods of case number calculation

Sample size calculations were performed for both TTE and binary endpoints. Due to unknown patient proportions in the non-interventional setting, calculations were performed for both a 1:1 ratio and a 1:2 ratio. Also, the assumed association between treatment and baseline confounders after adjustment in terms of R^2 was kept variable between 0 (perfect balance, "RCT-like") and 30% (strong association). The following assumptions were used for both types of endpoints:

- Alpha: 0.05 two-sided
- Power: 0.9
- Drop-out/loss-to-follow-up (LTFU): 20% (e.g., due to censoring when changing treatment to risdiplam).

For TTE endpoints, it was additionally assumed:

- Effect measure: HR
- Method for estimating sample size: Cox regression (54)

For binary endpoints, it was additionally assumed:

- Effect measure: OR
- Method for estimating sample size: logistic regression - binomial distribution, enumeration procedure (55) if N < 100.000

8.2.3 Results of the sample size calculations

Based on the assumptions presented, for patients with up to 2 copies of the SMN2 gene, the sample sizes presented in Table 16 result.

Table 16: Required total sample size for patients with up to 2 copies of the SMN2 gene

Endpoint	Input	R^2 between confounders and treatment	Patient ratio 1:1	Patient ratio 1:2
EFS until month 18	HR=0.2, event rate = 35%	0% 5% 10% 30%	48 50 53 68	54 56 60 76
OS until month 18	HR=0.4, event rate = 10%	0% 5% 10% 30%	511 538 568 729	575 605 639 820
Sitting without support to month 18	OR=3.5, event rate = 45%	0% 5% 10% 30%	155 163 175 221	183 192 203 261

The calculations show that a statistical power of 0.9 for sitting at month 18 might require about 3 times more patients than for EFS. Sufficient power for OS requires about 10 times more patients than for EFS. Changing the assumed patient ratio from 1:1 to 1:2 only moderately increases the sample size required for that power. Also, changing the association between confounders and treatment from 0 to 30% results in a change of about 50% in the number of patients required.

For the study population of patients with 3 copies of the SMN2 gene, the sample sizes shown in

Table 17 result. For patients with 3 copies of the SMN2 gene, it is more likely to achieve power = 0.9 for motor milestones than for EFS or OS.

Table 17: Required total sample size for patients with 3 copies of the SNM2 gene

Endpoint	Input	Association between confounders and treatment R^2	Ratio 1:1	Ratio 1:2
EFS until month 18	HR=0.4, event rate = 20%	0% 5% 10% 30%	256 269 284 365	288 303 320 410
OS until month 18	HR=0.7, event rate = 5%	0% 5% 10% 30%	6,733 7,086 7,480 9,618	7,574 7,973 8,415 10,820
Standing without support to month 24	OR=3.5, event rate = 45%	0% 5%	155 163	183 192

Endpoint	Input	Association between confounders and treatment R^2	Ratio 1:1	Ratio 1:2
		10%	175	203
		30%	221	261

Based on current estimates of patient enrollment (section 8.3) the study will only be powered for EFS in study population A (up to 2 copy SMN2). For all other endpoints that were included in sample size calculations, patient numbers are expected to be insufficient to ensure adequate power.

8.2.4 Update of sample size calculations after 18 and 36 months

Due to substantial uncertainties regarding patient proportions, drop-out rates, event rates, effect sizes, and the association of confounders and treatment outcomes, sample size will be re-calculated 18 and 36 months after study start (section 8.5). Sample size re-calculation at 36 months will include endpoints that could not be included prior to the study due to a lack of evidence of comparative treatment effects and event rates. The study may thus be powered for endpoints not considered in the a-priori sample size considerations, which will be evaluated 36 months after study start.

After 18 months, due to the observation period required between inclusion in the study and reaching first motor milestones, very few patients will be available for an outcome analysis to inform sample size calculations regarding effect sizes and event rates. A first recalculation of sample size after 18 months will thus be based on updated assumptions on patient shares per intervention and drop-out rates.

A second and final update of sample size calculations will be performed 36 months after study initiation. While patient numbers at 36 months are not expected to be sufficient to perform outcome analysis that is sufficiently powered for reaching statistical significance, it is possible to estimate the key parameters for sample size calculations from the study results available at that time:

- Updated patient proportions with treatment episodes per intervention
- Drop out rates (e.g. for censoring of treatment switches and LTFU)
- Effect measure based on approximately 50% of patients targeted for outcome analysis
- Event rates for key endpoints, especially EFS and motor milestones
- Association between baseline confounders and treatment

Final sample size calculation will be performed either including or excluding eligible historic data for patients treated with nusinersen, depending on the results of feasibility assessment (section 8.4). As per the G-BA resolution mandating this study, other endpoints than those used for the initial sample size calculations may be used for final sample size calculation (27) .

8.3 Expected patient numbers

Due to the non-interventional design of this study, Novartis Gene Therapies has no control over enrollment in the study. All patients fulfilling in inclusion and exclusion criteria (section 7) will be included in the study.

Nationwide newborn screening for SMA will be performed in Germany starting in October 2021 (50). The estimates of expected patient numbers are therefore based on the results of the pilot project for newborn screening for SMA in Germany (56). Based on 297,163 screened newborns, the SMA incidence was determined to be 1 per 6,910 births. Based on aprox. 780,000 live births in Germany per year (57), this results in 113 patients with SMA being born in Germany each year.

All estimates of the required case numbers as well as the included patient numbers are subject to considerable uncertainty, as Novartis Gene Therapies has no influence on the course of this non-interventional study. It is currently unknown how many historical patients treated with nusinersen per study population are recorded in the SMArtCARE registry, who meet both the inclusion and exclusion criteria of the study and the eligibility criteria depicted in section 7. The number of these patients, in turn, influences the proportions of patients available for pooled comparison between interventions and, therefore, the final case number calculation in the event that historical data are used.

8.3.1 Population A: Up to 2 SMN2 copies

Pilot newborn screening reports 40% of SMA incidence to show up to 2 copies of the SMN2 gene. It is assumed that 100% of diagnosed patients will be treated with onasemnogene abeparvovec or nusinersen, since risdiplam is not authorized for use under the age of 2 months (58). Patients switched to risdiplam are covered in the drop-out rate used for sample size calculations and thus do not need to be taken into account when estimating patient numbers.

It is expected that treatment will be initiated within the first month of being born, resulting in a period of 17 months between enrollment and availability of data for first motor milestone assessment (sitting at 18 months of age). For other motor milestones (assessed at 24 months of age), an observation period of 23 months results. As such, 60 months after study start, patients recruited during the first 43 months of the study will be available for first outcome of motor milestone sitting while patients recruited during the first 37 months will be available for assessment of other motor milestones.

Due to early symptom onset and treatment initiation for patients with 2 SMN2 copies, no patients are expected to be included that were born prior to the introduction of newborn screening. Table 18 summarizes the calculation of expected patient numbers for population A.

Table 18: Expected patient numbers: Population A (up to 2 SMN2 copies)

Step	Description	No.
1	Patients diagnosed from newborn screening per year	45
2	Treatment initiation with nusinersen or Zolgensma for patients identified from newborn screening Calculation: 100% of (1)	45
3	Total number of patients enrolled within 60 months Calculation: 5*(1)	223
4	Patients available for outcome analysis of motor milestone sitting 60 months after study start Calculation: (2)/12*43	160
5	Patients available for outcome analysis of other motor milestones 60 months after study start Calculation: (2)/12*37	138

Note: Illustration of rounded numbers. Calculation based on exact numbers.

8.3.2 Population B: 3 SMN2 copies

Pilot newborn screening reports 23% of SMA incidence to show 3 copies of the SMN2 gene. It is assumed that 100% of diagnosed patients will be treated with onasemnogene abeparvovec or nusinersen, since risdiplam is not authorized for use under the age of 2 months (58). Patients switched to risdiplam are covered in the drop-out rate used for sample size calculations and thus do not need to be taken into account when estimating patient numbers.

It is expected that treatment will be initiated within the first month of being born, resulting in a period of 17 months between enrollment and availability of data for first motor milestone assessment (sitting at 18 months of age). For other motor milestones (assessed at 24 months of age), an observation period of 23 months results. As such, 60 months after study start, patients recruited during the first 43 months of the study will be available for first outcome of motor milestone sitting while patients recruited during the first 37 months will be available for assessment of other motor milestones.

Due to a later symptom onset in patients with 3 SMN2 copies, it is expected that patients born before the introduction of newborn screening will be enrolled in the study. Based on symptom onset of SMA type II between 6 and 18 months of age, it is expected that patients born within one year prior to introduction of newborn screening may be diagnosed after study start. Two thirds of these patients are assumed to be treated with onasemnogene abeparvovec or nusinersen, while one third will be treated with risdiplam as an initial therapy after diagnosis. The latter will not be included in the study. All patients born before the introduction of newborn screening will be enrolled within the first year of the study and motor milestones can thus be analyzed 60 months after study start.

Table 19 summarizes the calculation of expected patient numbers for population B.

Table 19: Expected patient numbers: Population B (3 SMN2 copies)

Step	Description	No.
1	Patients diagnosed from newborn screening per year	26
2	Treatment initiation with nusinersen or Zolgensma for patients identified from newborn screening Calculation: 100% of (1)	26
3	Patients born before introduction of newborn screening and treatment initiation with onasemnogene abeparvovec or nusinersen after study start Calculation: 66.6% of (1)	18
4	Total number of patients enrolled within 60 months Calculation: 5*(2)+(3)	131
5	Patients available for outcome analysis of motor milestone sitting 60 months after study start Calculation: (2)/12*43+(3)	112
6	Patients available for outcome analysis of other motor milestones 60 months after study start Calculation: (2)/12*37+(3)	98
Note: Illustration of rounded numbers. Calculation based on exact numbers.		

8.4 Feasibility assessment & utilization of historic data

Due to considerable uncertainties regarding the required number of cases (section 8.2), the actual number of patients included, as well as the suitability of historical data (section 7.3), an a priori assessment of the study feasibility as well as the necessity and possibility of using historical data on nusinersen for each study population is impossible. Therefore, an assessment of study feasibility as well as the possibility and necessity of using historical data on nusinersen will be conducted after the final sample size calculations have been performed 36 months after study start.

The assessment will be made per study population based on the following information:

- Final sample size calculations (section 8.2)
- Number of eligible patients from historical data on nusinersen (section 7.3)
- Extrapolation of patient numbers for nusinersen and onasemnogene abeparvovec based on study enrollment until month 36
- Patient proportions per intervention with and without use of historical data on nusinersen

The study feasibility assessment results in one of three possible outcomes per study population:

- If results indicate that the sample size will be reached until 60 months after study start solely on prospective patients, historical data for Nusinersen will not be utilized for this study. This to avoid the fundamental potential for bias in using data collected at different times. Outcome analysis will be conducted once the sample size for the study population in question has been reached.
- If results indicate that the sample size will not be reached until 60 months after study start exclusively with prospective patients, historical data for nusinersen will be utilized for this study. The feasibility assessment is then performed including historic data on nusinersen based on the number of patients fulfilling inclusion and exclusion criteria as well as quality criteria (section 7). Final sample size calculations will be performed based on patient shares and association of confounders and effects including historical nusinersen patients (section 8.2). If enrollment of the required number of patients to reach the final sample size is feasible until 60 months after study start, the respective study population will be continued. Outcome analysis will be performed once the sample size for the relevant study population is reached.
- If the results indicate that final sample size requirements will not be reached, even with including all eligible historic nusinersen patients, the study population will be terminated for infeasibility. No outcome analysis will be performed. If infeasibility is only determined for one study population, other study populations will continue. If all study populations are deemed unfeasible, the study will be terminated for infeasibility.

If historical data for nusinersen will be utilized in the study, the inclusion criterion of treatment initiation after start of this study is formally omitted. All other inclusion and exclusion criteria are re-applied and may result in patients to be included in the study that previously did not fulfill inclusion and exclusion criteria (sections 7.1, 7.2). Two examples of such patient groups are:

- Patients initiated with nusinersen prior to the start date of this study with treatment ongoing during the prospective part of this study
- Patients initiated with nusinersen prior to the start date of this study and switched from nusinersen to onasemnogene abeparvovec during the prospective part of this study.

If historic data for nusinersen patients is used and if such patients were treatment-naïve at the time of treatment initiation with nusinersen, the respective inclusion and exclusion criteria are fulfilled at the time of treatment initiation with nusinersen. Such patients will then be included with their reference date (see SAP section 7.1) set to the treatment initiation with nusinersen.

8.5 Planned Analyses

Due to substantial uncertainties regarding effect measures, patient proportions, drop-out rates, event rates, and the association of confounders and treatment, it is necessary to review and, if necessary, adjust the previous sample size estimates during the course of the study.

8.5.1 1st descriptive analysis (18 months after study initiation)

In its resolution of February 4, 2021, the G-BA determined that the sample size calculations should be updated as part of the first interim analysis after 18 months. However, due to the observational period required between start of the study and reaching 18 months of age for a first outcome assessment of the motor milestone sitting, hardly any patients will be available for an outcome analysis 18 months after study initiation. TTE endpoints will have very short observation times for most patients and all other binary endpoints except for head control are only assessed at 24 or 36 months of age.

A first recalculation of sample sizes based on up-dated assumptions on patient proportions and drop-out rates can be performed for the patients included in the first 18 months of the study. In addition to sample size re-calculation, the extent of (dis)balance of confounders in the respective treatment groups will be described as frequencies, percentages, and means as appropriate. Propensity score (PS) densities overlap between the two treatment groups is analyzed (before and after weighting) and reported.

8.5.2 2nd descriptive analysis (36 months after study initiation)

If the feasibility assessment results in no utilization of historical data for nusinersen, sample size calculations are updated with study results available at that time:

- Updated patient proportions with treatment episodes per intervention
- Drop out rates (e.g. for censoring of treatment switches and LTFU)
- Effect measure based on approximately 50% of patients targeted for outcome analysis
- Event rates for key endpoints, especially EFS as well as motor milestones
- Association between baseline confounders and treatment

If the feasibility assessment (section 8.4) indicates that historical data for nusinersen will be used, sample size calculations are updated with event rates, effect sizes, and a correlation estimate between confounders and treatment derived of the pooled prospective and historic data.

Therefore, it is necessary to perform a final sample size calculation based on the above parameters 36 months after the start of the study. As per the G-BA resolution mandating this study, other endpoints than those used for the initial sample size calculations may be used for final sample size calculation (27).

In addition to sample size re-calculation, the extent of (dis)balance of confounders in the respective treatment groups will be analyzed descriptively. PS densities overlap between the two treatment groups is analyzed (before and after weighting) and reported.

8.5.3 3rd descriptive analysis (54 months after study initiation)

Analysis for the status report will include the number and the respective medicinal treatment of the patients included so far, patient-related observation times, and possible deviations regarding the expected number of included patients. In addition, the extent of (dis)balance of confounders in the respective treatment groups will be analyzed descriptively. PS densities overlap between the two treatment groups is analyzed (before and after weighting) and reported.

8.5.4 4th descriptive analysis (60 months after study initiation)

Analysis for the status report will include the number and the respective medicinal treatment of the patients included so far, patient-related observation times, and possible deviations regarding the expected number of included patients. In addition, the extent of (dis)balance of confounders in the respective treatment groups will be analyzed descriptively. PS densities overlap between the two treatment groups is analyzed (before and after weighting) and reported.

8.5.5 Interim analysis

In the context of the final sample size calculation and the number of eligible patients, an evaluation date may arise that lies before or after the date of an interim analysis after 60 months as proposed by the G-BA resolution of February 4, 2021. Outcome analysis is performed per study population once the final sample size for that study population is enrolled and observable for the duration required by the endpoints chosen for sample size calculation in the final sample size calculation.

8.5.6 Final Analysis

Final analysis will be performed after the end of study, which is 60 months after 3rd interim analysis.

8.6 Prognostic factors and potential confounders

8.6.1 Confounder identification and validation

Based on a systematic identification of potential confounders in national and international guidelines and publications as well as their validation by clinical experts, the convergence to structural comparability in the study arms is achieved by appropriate adjustment methods for pre-specified confounders. Validation of the identified confounders was performed by six German clinical SMA experts. Validation was performed by categorizing each confounder identified via systematic literature review (SLR) into one of the following three categories:

- **Very important:** These parameters have a significant effect on patient's outcomes and are essential for adjustment of statistical analyses in a non-randomized trial.
- **Less important:** These parameters have a moderate effect on patient's outcomes and should be controlled in statistical analysis. However, if selected confounders of this category cannot be controlled, results would still be considered valid.
- **Not important:** These parameters are not considered relevant for the specific study, e.g. due to coverage as endpoints or because of the specific study setting (quality controlled centers in Germany).

The confounders listed in Table 20 have been identified as clinically (very or less) important and are thus potentially relevant for the population included in this study. All confounders identified in the literature and categorized as clinically very important and less important for the population of this study are depictable in SMArtCARE and included in the study. All confounders identified via SLR and considered not important in the context of this study are depicted in annex A1.

Table 20: Overview of identified confounders, their clinically relevance and corresponding availability in SMArtCARE

Confounder	Clinical relevance[1]	Included in Study	Definition	Definition in SMArtCARE CRF (38)
Age at symptom onset	Less important	Yes	Age of symptom onset in months for symptomatic patients	▪ Baseline: Age at symptom onset
Symptom status at	Very important	Yes	Symptomatic: Diagnosis not	Symptomatic: ▪ Baseline: Was diagnosis

[1] According to the assessment of the six clinical experts consulted during the confounder validation process

Confounder	Clinical relevance[1]	Included in Study	Definition	Definition in SMArtCARE CRF (38)
treatment initiation			made pre-symptomatically OR documentation of symptoms related to SMA at any medical assessment prior to treatment initiation <u>Pre-symptomatic:</u> Diagnosis made pre-symptomatically AND no symptoms related to SMA at any medical assessment prior to treatment initiation	made pre-symptomatically? = No OR ▪ Medical Assessment: Neurology: Symptoms related to SMA = Yes AT ▪ Medical Assessment: Visit date ≤ Nusinersen/Zolgensma: MIN(Date of treatment) Pre-symptomatic: ▪ Baseline: Was diagnosis made pre-symptomatically? = Yes AND ▪ Medical Assessment: Neurology: Symptoms related to SMA = No AT ▪ Medical Assessment: Visit date ≤ Nusinersen/Zolgensma: MIN(Date of treatment)
Age at treatment initiation	Very important	Yes	Age in weeks at treatment initiation	▪ Medical Assessment: Age at visit AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treatment)
Nutrition support	Very important	Yes	Gastric tube or nasal feeding tube (exclusive/supplemental/none) at treatment initiation	▪ Medical assessment: Does the patient use a gastric or nasal feeding tube? AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treatment)
Ventilation support	Very important	Yes	Duration of ventilator use (nighttime/intermittent/permanent (≥16h/day) at	▪ Medical assessment: Does the patient receive ventilator support? = Yes AND ▪ Medical assessment:

Confounder	Clinical relevance[1]	Included in Study	Definition	Definition in SMArtCARE CRF (38)
			treatment initiation	Time of ventilator use ○ Night (during sleep) ○ Intermittent day time and continuous at night ○ Continuous (>16h/day) AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treatment)
Contractures	Less important	Yes	Contractures limiting function (yes/no) at treatment initiation	▪ Medical Assessment: Are any contractures present? = Yes AND ▪ Medical assessment: Type of limitation = Severe (imposing limits to function) AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treatment)
Motoric function: Highest motor milestone	Very important	Yes	Highest motor milestone at treatment initiation: ▪ None/n.a. ▪ Sitting without support ▪ Crawl on hands and knees ▪ Standing without support ▪ Walking without support ▪ Climb stairs	▪ Medical assessment: Best current motor function AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treatment)
Motoric function: CHOP-INTEND	Very important	Yes	CHOP-INTEND score at treatment initiation	▪ CHOP-INTEND: Score AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treatment)

Confounder	Clinical relevance[1]	Included in Study	Definition	Definition in SMArtCARE CRF (38)
Ulnar CMAP (compound muscle action potential) (only for sensitivity analysis)	n.a.	Sensitivity analysis only	Ulnar CMAP at treatment initiation ▪ Response, amplitude > 1mV ▪ No response or response ≤ 1mV ▪ Unknown	▪ Medical Assessment: CMAP amplitude (mV): Ulnar AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treatment)

A detailed description of the process of confounder identification and validation is given in Annex A1 to this protocol. The clinically very important confounder of SMN2 copy number is depicted in this study via stratification of study populations (section 8.1).

Potential effects from different standards of care between HSPs will be addressed in statistical analysis (see sections 8.1 and 11 of SAP).

For sensitivity analysis, ulnar compound muscle action potential (CMAP) amplitude will be included in baseline confounders (see section 8.5 of SAP).

8.6.2 Adjustment for confounders

Registry data are tainted with several disadvantages: missing randomization and thus unbalanced covariates and potentially different treatment time periods between study interventions. Bias due to time-shifts needs to be discussed in the study report, missing randomization will be countered with adjustment methods.

To get an impression of the extent of treatment switchers and the extent of (dis)balance of confounders in the respective treatment groups, the distributions of confounders in the three treatment groups are described descriptively.

Using a generalized linear mixed model (GLMM) for binary data assuming a binomial distribution with a logit link function, the propensity score (PS) to receive onasemnogene abeparvovec is determined taking into account the confounders as fixed effects and the study centers as a random effect.

According to the analyses and decision scheme provided in Desai & Franklin (2019) (59), the PS for patients receiving onasemnogene abeparvovec is clustered into 10 approximately equal sized strata and Average Treatment Effect on Treated (ATT) fine stratification weights are subsequently calculated to account for stratum membership of nusinersen patients. Patients receiving onasemnogene abeparvovec are not weighted. For details regarding the examination of the PS density overlap and the balance achieved, see section 8.1 of the SAP.

If it is not possible to balance the two populations sufficiently using fine stratification weights, the comparison will be made using regression models (GLMM, Cox/Frailty-Regression) to adjust for confounders and centers.

If structural comparability of the patient groups after adjustment for baseline confounding variables is insufficient or if improvement of structural comparibility is not possible using conditional regression models, the feasibility of a formal comparison and potential analyses approaches will be depicted in an amendment that will be aligned with G-BA.

8.7 Subgroup analyses

8.7.1 Subgroups

As far as possible subgroup analyses for all endpoints are planned based on the following patients' baseline characteristics. Table 21 contains all planned subgroup analyses in this study.

Table 21: Overview of planned subgroup analyses in this comparative analysis

Planned subgroups	Patients' baseline status	Fields of SMArtCARE CRF
Age at treatment initiation	▪ ≤ 4 weeks ▪ > 4 weeks	▪ Enrolment: Date of birth ▪ Nusinersen/Zolgensma: Date of treatment MIN(Date of treatment)
Gender	▪ Male ▪ Female ▪ Undifferentiated ▪ Unknown	▪ Enrolment: Gender
Symptom status at treatment initiation	▪ Symptomatic ▪ Pre-symptomatic	▪ Baseline: Was diagnosis made pre-symptomatically? ▪ Medical Assessment: Neurology: Symptoms related to SMA AT ▪ Medical Assessment: Visit date ≤ Nusinersen/Zolgensma: MIN(Date of treatment)
Nutrition support (Does the patient use a gastric or nasal feeding tube?)	▪ No ▪ Yes - exclusively fed by tube ▪ Yes – supplementary e.g. for fluids	▪ Medical assessment: Does the patient use a gastric or nasal feeding tube? AT

Planned subgroups	Patients' baseline status	Fields of SMArtCARE CRF
		▪ Medical Assessment: Visit Date = Nusinersen/Zolgensma: MIN(Date of treatment)
Ventilation support (Does the patient receive ventilator support?)	▪ No ▪ Yes	▪ Medical assessment: Does the patient receive ventilator support? AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treatment)
Contractures (Contractures limiting function)	▪ No ▪ Yes	▪ Medical Assessment: Are any contractures present? = Yes AND ▪ Medical assessment: Type of limitation = Severe (imposing limits to function) AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treatment)
Motor function: Highest motor milestone	▪ None/n.a. ▪ Sitting without support ▪ Crawl on hands and knees ▪ Standing with-out support ▪ Walking with-out support ▪ Climb stairs	▪ Medical assessment: Best current motor function AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treatment)
Motor function: CHOP-INTEND score	▪ ≤ Median CHOP-INTEND ▪ > Median CHOP-INTEND	▪ CHOP-INTEND: Score AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treatment)
Ulnar CMAP	▪ Response, amplitude > 1mV ▪ No response or response ≤ 1mV ▪ Unknown	▪ Medical Assessment: CMAP amplitude (mV): Ulnar AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treatment)

8.7.2 Analysis methods

Subgroups analyses are planned for all endpoints in all study populations.

Effect measures are calculated for each subgroup category as well as overall. A p-value for the interaction treatment * subgroup is derived within the GLMM- and Cox-/Frailty-Framework as described in section 11 of the SAP.

Subgroup analyses are conducted only for variables resulting in subgroups of at least 10 patients.

Subgroup analyses for binary events per variable are conducted only if at least 10 events occurred in one of the subgroups.

For TTE endpoints, survival curves for individual subgroups are presented only for subgroup analyses with a statistically significant interaction term ($p < 0.05$).

If fine stratification weights are used for adjustment of covariates, the same weights will be used to report the endpoints by subgroups.

Additional analyses may be added based on results of descriptive analyses (section 8.5), availability, completeness, and quality of the data, as well as input from clinical experts. Additional analyses will be covered in an amendment to the study protocol and SAP.

9. Safety

As this is a study based on secondary use of data, safety monitoring and safety reporting, where there is a safety relevant result, will be provided on an aggregate level only; no reporting on an individual case level to NGT is required.

In studies based on secondary use of data with a safety relevant result, reports of adverse events/adverse reactions will be summarized in the study report, i.e. the overall association between an exposure and an outcome will be presented. Relevant findings from the study report will be included in the periodic aggregated regulatory reports submitted to Health Authorities.

10. Data Handling and Monitoring

10.1 Data Management

All clinical data for this project are collected and stored exclusively in the SMArtCARE registry. Study site personnel is responsible for patient data collection and data entry into SMArtCARE. Data will be entered into electronic case report forms (eCRFs) of the SMArtCARE registry.

SMArtCARE uses a clinical database provided by OpenApp. According to SMArtCARE, the clinical database offers a query workflow for a documented and efficient data review process. Validation of patient data in the clinical database is carried out via automated edit checks as well as manual checks raised by clinical research associates during on-site routine monitoring visits (RMVs).

10.2 Source Data verification

To minimize the potential for bias in the use of registry data as part of the Routine Data Collection and Evaluations, 100% on-site source data verification will be performed for all data fields in the SMArtCARE registry that are applied to determine inclusion and exclusion criteria, confounders, and endpoints for the study (Annex A2).

Source data verification will be performed by CSG Clinische Studiengesellschaft mbH. A site initiation visit (SIV) will be performed at each study site. Approx. 18 routine monitoring visits (RMVs) at each study site will be conducted. It is expected that two visits per site will be carried out with a focus on the historical data for nusinersen and 16 RMVs (4 p.a. per site) for the prospective data. The first RMV at each study site will be performed within 2 weeks after inclusion of the first patient. The frequency of further RMVs will be dependent on the enrollment rate and the site's data documentation. A close-out visit (COV) at each study site will be performed at the end of the study.

Source data verification will be performed by clinical monitors on the basis of all available patient records. Novartis Gene Therapies will bear the financial expenses for the implementation of the source data verification.

At current, there are uncertainties regarding the possibilities and limitations of performing source data verification as part of the study. The extent of archived documentation, especially for historical nusinersen patients, cannot be estimated at present and could differ between the participating centers. Based on the assessments of clinical experts as well as those responsible for the SMArtCARE registry, the use of the paper-based CRF of the SMArtCARE registry has also become established in the care setting as part of the documentation for patient records. The extent to which independent documentation is carried out in paper-based or electronic patient records is also currently unclear and probably varies between individual centers. If necessary, changes to the possible extend of SDV will be depicted in an amendment to the study protocol.

10.3 Minimization of missing data

Due to the non-interventional nature of a Routine Data Collection and Evaluation, complete avoidance of missing or implausible data is impossible. Source data verification as described in section 10.2 will significantly reduce the frequency of missing or implausible data. Remaining missing data will be addressed in statistical analysis (see section 8.2 of the SAP).

In addition, all participating centers will be supported with "flying study nurses" at their request to further reduce the incidence of missing data. This support is aimed at processing any backlog of paper-based CRFs completed but not entered into the SMArtCARE registry's clinical database. This support is to be applied to patients who meet the inclusion and exclusion criteria of the study. It is planned to be implemented during the first months of the study for historical nusinersen patients and in preparation of each planned analysis (section 8.5).

10.4 Data analysis

Data for analysis is transferred to IGES Institute GmbH via a secure data transfer for statistical analysis. Data transfer is strictly limited to the purpose of the study and as far as required for intended statistical analysis.

11. Ethical and regulatory aspects

11.1 Regulatory and ethical compliance

This non-interventional, non-randomized, registry-based data collection will be performed in accordance with the ethical principles laid down in the Declaration of Helsinki and in consistence with applicable regulatory requirements.

According to the Professional Code for Physicians in Germany (Berufsordnung Ärzte, BO-Ä) Art 15, the final study protocol will be reviewed and approved by an Independent Ethics Committee before study start depending on the local requirements.

11.2 Informed Consent

The legal guardian of prospective patients will be asked for informed consent at the time of the patients' initial enrollment in SMArtCARE. The legal guardian of historical patients for nusinersen will be contacted to give informed consent for this study, unless the patients are documented as deceased. Eligible patients may only be included in the study after written consent of their legal guardian.

It is currently explored by SMArtCARE if the existing informed consent for participation in SMArtCARE will be amended to also include all aspects of this study or if a separate informed consent for data collection for this study will be used. In any case, informed consent will be obtained by SMArtCARE and cover the secondary use of the data for the purposes of this study.

12. Outcome

Only aggregated data will be presented to Novartis Gene Therapies, no patient-level data will be disclosed.

Results of the first descriptive analysis (section 8.5.1) will be depicted in a status report that is submitted to G-BA. It will include the number and the respective medicinal treatment of the patients included so far, study sites, patient-related observation times, and possible deviations regarding the expected number of recruits. In addition, it will include the number of eligible historic patients treated with nusinersen that fulfill all criteria for study inclusion (section 7.3). It will also cover updated sample size calculations and the results of eligibility assessment of historic data for nusinersen (section 7.3). In addition, it will include information on the balance of confounders before and after adjustment to inform about potential limitations in adjusting for observed inhomogeneity. Based on the results and an alignment with G-BA, an amendment to the study protocol may be required.

Results of the second descriptive analysis (section 8.5.2) will be depicted in a status report that is submitted to G-BA. It will include the number and the respective medicinal treatment of the patients included so far, study sites, patient-related observation times, and possible deviations regarding the expected number of recruits. It will also cover updated sample size calculations and the results of the feasibility assessment (section 8.4). In addition, it will include information on the balance of confounders before and after adjustment to inform about potential limitations in adjusting for observed inhomogeneity. Based on the results and an alignment with G-BA, an amendment to the study protocol may be performed.

Results of the third descriptive analysis (section 8.5.3) will be depicted in a status report that is submitted to G-BA. It will include the number and the respective medicinal treatment of the patients included so far, study sites, patient-related observation times, and possible deviations regarding the expected number of recruits. In addition, it will include information on the balance of confounders before and after adjustment to inform about potential limitations in adjusting for observed inhomogeneity.

Results of the fourth descriptive analysis (section 8.5.4) will be depicted in a status report that is submitted to G-BA. It will include the number and the respective medicinal treatment of the patients included so far, study sites, patient-related observation times, and possible deviations regarding the expected number of recruits. In addition, it will include information on the balance of confounders before and after adjustment to inform about potential limitations in adjusting for observed inhomogeneity.

Upon completion of the interim analysis (section 8.5.5) and final analysis (section 8.5.6), a study report with all results of the comparison is prepared and serves as the basis for the description of the results that will be submitted to G-BA.

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14. Annex

A1 Methodology for Confounder Identification

A2 Relevant variables in SMArtCare Registry

A1 Methodology for Confounder Identification

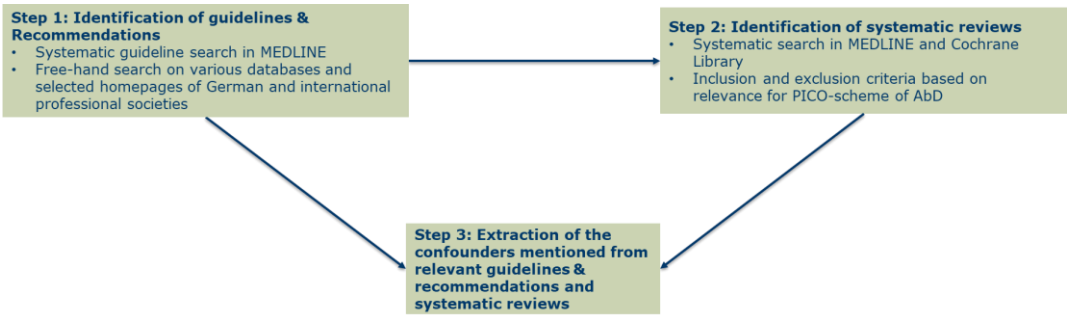
1. Methodical approaches for identifying confounders in SMA

The Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) rapid report „Konzepte zur Generierung versorgungsnaher Daten und deren Auswertung zum Zwecke der Nutzenbewertung von Arzneimitteln nach § 35a SGB V“ (Concepts for the generation of data in health care settings and their evaluation for the purpose of assessing the benefit of drugs according to § 35a SGB V), version 1.1 as of May 13, 2020, provides some guidance for the analysis of patient-specific data within the framework of the benefit assessment according to § 35a SGB V. Therein, IQWiG not only discusses various aspects of study and statistical analysis planning, but also the relevance of confounders in studies without randomization (1). It is stated, that confounders putatively relevant for the research question must be defined *a priori* on the basis of scientific literature and, if necessary, by clinical expert validation.

In order to meet these requirements for confounder identification in non-randomized studies, a methodological 2-step-approach was applied (steps 1 and 2) as shown in Figure A3. First, evidence-based guidelines and recommendations were identified via a systematic search of the MEDLINE bibliographic database. Further, a supplementary structured free-hand search on various databases and on selected websites of German and international professional societies was conducted, as this type of publication provides a broad and expert-validated data basis. Secondly, a systematic search was conducted in the bibliographic databases MEDLINE and the Cochrane Database of Systematic Reviews to identify systematic reviews and meta-analyses, since these documents would fundamentally supplement the data basis provided by the evidence-based guidelines.

The applied search strings have been designed analogously to the evidence search performed by the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) to identify the appropriate comparator therapy (2). Literature search was followed by a literature selection process performed by two independent reviewers. This process comprised an initial title-abstract screening step as per pre-specified inclusion and exclusion criteria followed by an according full-text screening procedure.

Figure A3: Overview of the methodical procedure



1.1 Indication/question

Confounders were identified specifically for the present indication according to the PICO scheme given in G-BA resolution of February 4, 2021 (3):

- Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.
- Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and clinically diagnosed type 1 SMA.
- Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene

1.2 Systematic research and data sources

A systematic evidence collection was carried out to identify relevant confounders in the above mentioned question. For this purpose, based on the systematic literature search carried out by G-BA to determine the appropriate comparator therapy according to § 35a SGB V for onasemnogene abeparvovec (2), systematic literature searches were carried out for evidence-based guidelines and recommendations (step 1) and systematic reviews and meta-analyses (step 2) in the indication of spinal muscular atrophy (SMA). The results were selected according to the previously defined inclusion and exclusion criteria (see section 2.3 and section 3.2). Two independent reviewers performed the screening of the retrieved results.

The bibliographic databases MEDLINE (PubMed) and the Cochrane Library (Cochrane Database of Systematic Reviews) were used for systematic information retrieval. Structured free-hand search was carried out in the databases and websites of the following organizations: AWMF, CMA Infobase, TRIP Database, google scholar. In addition, a free internet search was conducted for current German (Gesellschaft für Neuropädiatrie, Deutsche Gesellschaft für Muskelkranke e.V.) and international guidelines (Treat-NMD Neuromuscular Network, SMA Europe, Cure

SMA) as well as in PubMed. A detailed description of the search strategies is given in section 5.1 and section 5.2.

The research was completed on March 23th 2021.

Table A22: Overview

Population	▪ Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene ▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA ▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene
Intervention	-
Comparators	-
Endpoints	Confounders, risk factors, prognostic factors
Language	German and English
Publication types	(I) Guidelines, recommendations (II) Systematic reviews, meta-analyses

Sections 2 (Identification of relevant guidelines and recommendations (step 1)) and 3 (Identification of systematic reviews and meta-analyses (step 2)) describe the procedure for identifying the confounders, the inclusion and exclusion criteria and the results of the two search areas in detail.

2. Identification of relevant guidelines and recommendations (step 1)

2.1 Bibliographic literature research – Guidelines and recommendations

In accordance with the above-mentioned specifications, the search was carried out on March 23th, 2021 in the MEDLINE bibliographic database. The search strategy was individually adapted and structured to the database. The detailed search strategy is described in section 5.1 Search strategy – Bibliographic literature search (Guidelines and recommendations in the indication SMA). The PRISMA flow-chart representing the selection process as per pre-specified inclusion- and exclusion criteria (section 2.3) is shown in Figure A4 and the final results of the search and selection process are listed in section 2.4.

2.2 Free-hand search – Guidelines and recommendations

In accordance with the above-mentioned specifications, the structured free-hand search was carried out on March 23th 2021 in the various databases and websites shown in Table A23. The search strategies were individually adapted and structured to the respective databases and websites. The search results are presented in section 5.3.

Table A23: Various Guidelines databases and selected websites

Guidelines databases
AWMF Guidelines
CMA Infobase: (CPGs) – Clinical Practice Guidelines Database
TRIP Database
Selected websites of German and international professional societies
Gesellschaft für Neuropädiatrie
Deutsche Gesellschaft für Muskelkranke e.V.
Treat NMD Neuromuscular Network
SMA Europe
Cure SMA
Additional Free-hand search & PubMed
PubMed
Google
Google-Scholar

2.3 Inclusion / exclusion criteria – Guidelines and recommendations

The identification of relevant guidelines and recommendations comprised the entire indication area of SMA. The applied inclusion- and exclusion criteria are listed in Table A24.

Table A24: Inclusion / exclusion criteria – Guidelines and recommendations

	Inclusion criteria		Exclusion criteria	
Patient population	I1	Guideline for SMA Recommendation for SMA	E1	I1 not fulfilled.
Intervention	I2/E2	No limitation		
Appropriate comparator therapy	I3/E3	No limitation		
Endpoints	I4	Information on prognostic factors contained in guideline	E4	I4 not fulfilled.
(Study) guideline type	I5	Current valid version	E5	I5 not fulfilled.
Language	I6	English or German	E6	I6 not fulfilled.

I: inclusion criteria; SMA: spinal muscular atrophy; E: exclusion criteria

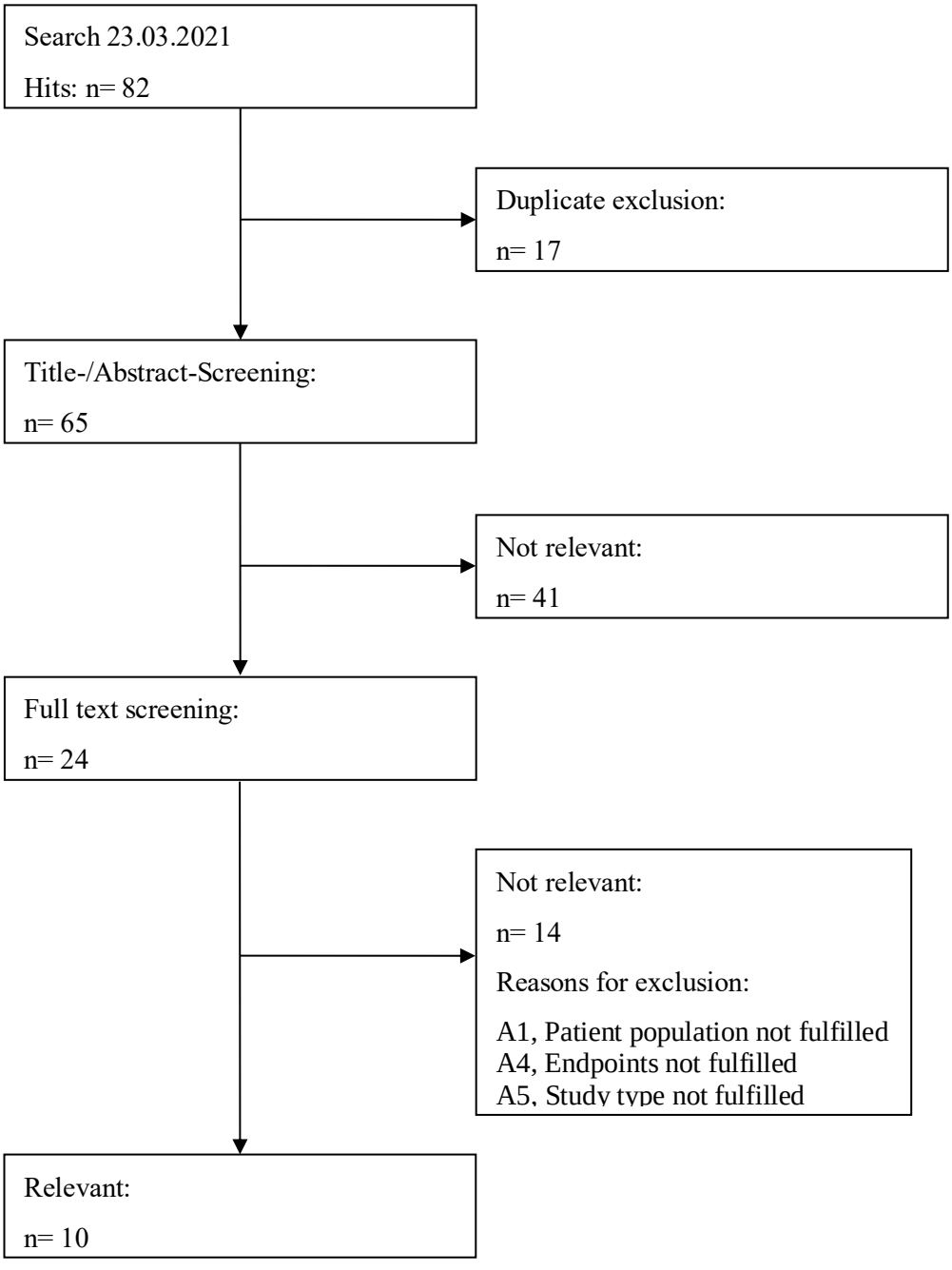
2.4 Results – Guidelines and recommendations

The PRISMA diagram shown in Figure A4 illustrates the screening and selection process for relevant guidelines and recommendations, which form the basis for the identification of confounders.

The search yielded 34 hits in the MEDLINE bibliographic database. In the structured free-hand search, 48 potentially relevant publications were identified. After excluding duplicates, 65 hits remained to be evaluated via the 2-step selection/screening procedure.

During the first screening, non-relevant publications were excluded based on title and abstract by checking for population, study type and language. In total, 41 publications were excluded. In the second screening, full texts of publications remaining from the first screening (24 hits) were reviewed and checked for relevance. In addition to the criteria from the first screening, the full texts were also be checked for information on prognostic endpoints. As a result, a total of 10 guidelines and recommendations for the indication spinal muscle atrophy were included.

Figure A4: PRISMA diagram – Guidelines and recommendations



3. Identification of relevant systematic reviews and Meta-analyses (step 2)

3.1 Bibliographic literature research – Systematic reviews and Meta-analyses

The bibliographic search was conducted in accordance with the above-mentioned specifications, the search was carried out on March 23th 2021 in the MEDLINE bibliographic database and in the Cochrane Database of Systematic Reviews. The search strategies were individually adapted and structured to each database. The detailed search strategy is described in section 5.2 Search strategy – Bibliographic literature search (systematic reviews and Meta-analyses in the indication SMA).

3.2 Inclusion / exclusion criteria – Systematic reviews and Meta-analyses

Inclusion / exclusion criteria for the literature selection have been designed analogously to the evidence search performed by the G-BA to identify the appropriate comparator therapy (2). The criteria listed in Table A25 were taken into account for the inclusion of systematic reviews and meta-analyses as a basis for the identification of confounders.

Table A25: Inclusion / exclusion criteria – Systematic reviews and Meta-analyses

	Inclusion criteria		Exclusion criteria	
Patient population	I1	▪ Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene ▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA ▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene	E1	I1 not fulfilled.
Intervention	I2/E2	No limitation		
Appropriate comparator therapy	I3/E3	No limitation		
Endpoints	I4	Collection of at least one patient-relevant outcome in the dimensions	E4	I4 not fulfilled, or no separate evaluation for the

Inclusion criteria			Exclusion criteria	
		of: ▪ Mortality ▪ Deaths ▪ Morbidity ▪ motor function (assessed with age-appropriate instruments, depending on disease severity, especially achievement of WHO milestones of motor development) ▪ respiratory function (need for [permanent] ventilation) ▪ bulbar function (ability to swallow and speak, need for non-oral nutritional support) ▪ other complications of the disease (e.g., pain, orthopedic complications) ▪ Side effects ▪ Adverse events ▪ Health-related quality of life ▪ health-related quality of life (assessed with an age-appropriate instrument)		relevant population.
Study type	I5	▪ Systematic reviews ▪ Meta-Analyses	E5	I5 not fulfilled ▪ HTA report ▪ Dose-finding ▪ studies ▪ Non-interventional studies ▪ narrative reviews ▪ Case reports ▪ Retrospective studies and cohort study ▪ Opinions ▪ Animal studies / in vitro studies
Duration of study	I6	No limitation		
Type of documentation	I7	Full text publication	E7	Document types other than full text publication

Inclusion criteria			Exclusion criteria	
				(e.g. conference abstracts, editorials, notes, letters to the editor)
Language	I8	English or German	E8	I8 not fulfilled

I: inclusion criteria; SMA: spinal muscular atrophy; E: exclusion criteria

3.3 Results – Systematic reviews and Meta-analyses

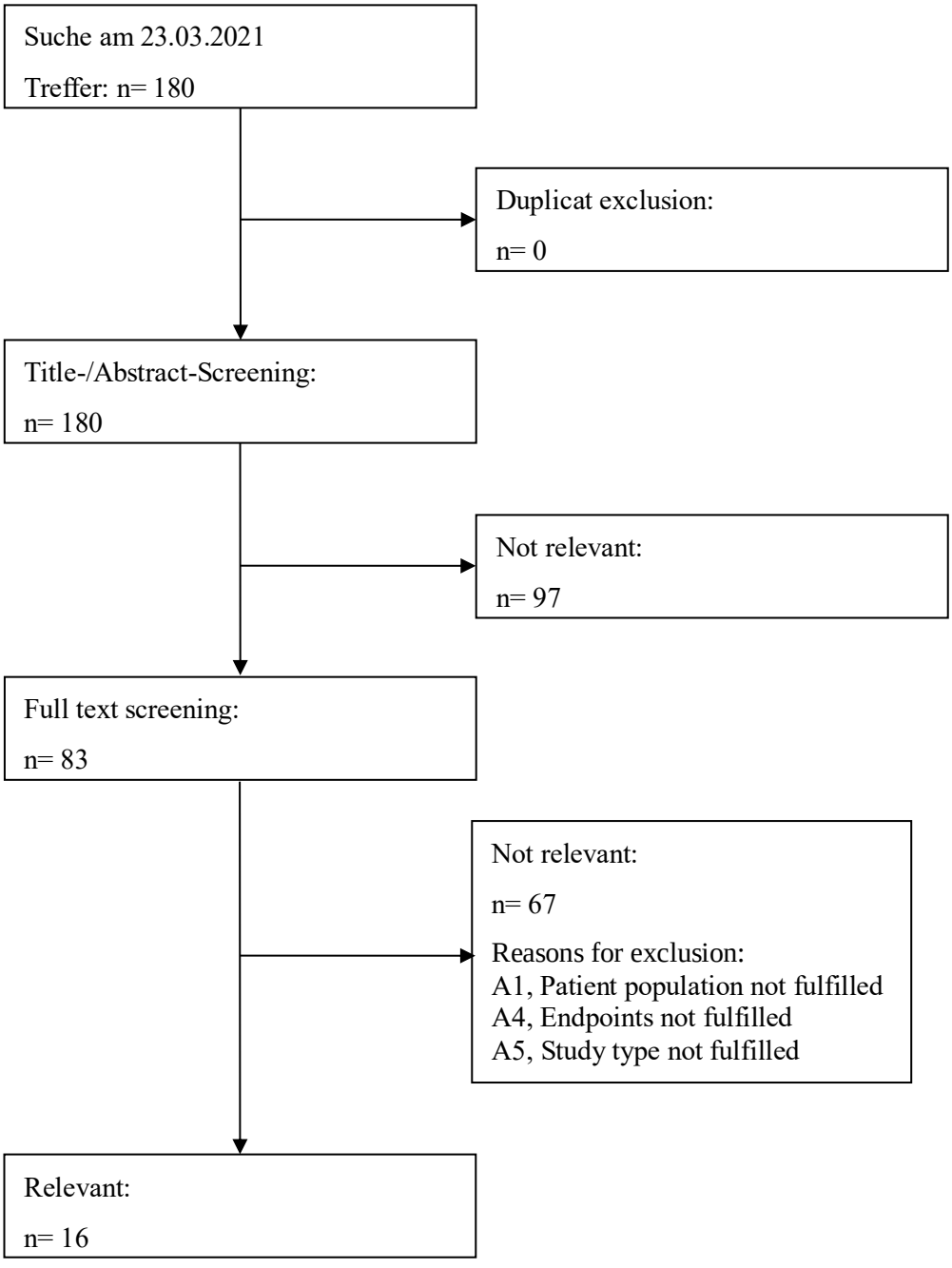
The PRISMA diagram shown in Figure A5 illustrates the screening and selection process for relevant systematic reviews and meta-analyses, which form the second basis for the identification of confounders.

The search yielded 165 hits in the MEDLINE bibliographic database and 15 hits were identified in the Cochrane Library. After excluding duplicates, 180 hits remained to be evaluated via the 2-step selection / screening procedure.

During the first screening, non-relevant publications were excluded based on title and abstract by checking for population, endpoints, study type, documentation type and language. In total, of 97 publications were excluded.

In the second screening, full texts of publications remaining from the first screening (83 hits) were reviewed and checked for relevance. The same criteria were used as in the first screening. As a result, 16 systematic review was included for the indication.

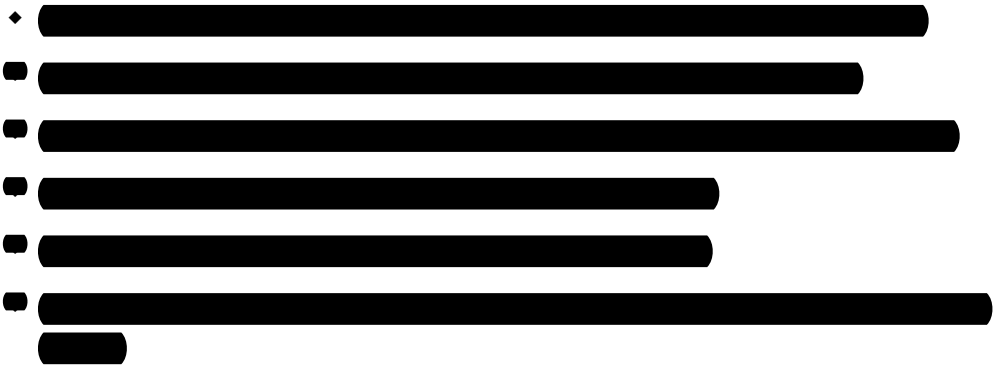
Figure A5: PRISMA diagram – Systematic reviews and Meta-analyses



4. Result presentation of the confounder identification and clinical perspective

After identification of the relevant national and international guidelines and recommendations as well as systematic reviews and meta-analyses, all confounders that were considered potentially relevant for SMA were identified and extracted.

The results were then validated by clinical experts in a joint workshop on May 12, 2021. For this purpose, all identified and potentially relevant confounders were discussed regarding their importance for the target population with the following six clinical experts:



The systematic literature searches revealed two potential categories of confounders. The majority of potential confounders manifest at baseline (Table A26 – A31). The clinical experts agreed that baseline should be equated with the time of treatment initiation. Some confounders, called progression confounders, that occur after baseline during treatment were also identified in the systematic literature research (Table A32 – A35). According to the clinical experts, the relevance of these confounders is not proven. For this reason, only baseline confounders are considered relevant and included in the study.

The assessment from a clinical perspective resulted in a categorization of the identified confounders into one of three groups:

- Very important: these confounders have a significant impact on the results and are essential for adjusting the statistical analyses in a non-randomized study
- Less important: These confounders have a minor influence on the results and should be controlled in the statistical analysis if possible. However, if selected confounders in this category cannot be controlled, the results are still considered valid
- Not important: These confounders are not considered relevant to this study, e.g., due to being captured as endpoints or due to the specific study setting

Operationalization of confounders for the study was directly proposed and whether they could currently be mapped in the SMArtCARE registry was queried.

Table A26: Confounders at baseline - Category Patient characteristics

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies 3	SMA Type I	SMA Type II				
Age onset	▪ Age at symptom onset	n.a.	n.a.	X	X	▪ Age at symptom onset	Less important	Yes	(4, 5)
Age Treatment initiation	▪ Age at treatment ▪ Age at study start (first dose)	X	X	X X	X X	▪ Age at study start (first dose)	Very important	Yes	(6–8)
Comorbidities	▪ Comorbidities	X	X	X	X	▪ Include as general flag (yes/no) specific ones?	Not relevant in routine care due to rarity	Yes	(9, 8)
Lean body mass	▪ Lean body mass	n.a.	n.a.	X	X	▪ BMI?	Not important	Yes ▪ Weight ▪ Height	(10)
Race	▪ Race				X	Do not include	Not important	No	(11)

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies 3	SMA Type I	SMA Type II				
Region	▪ Regional and cultural standards	X	X	X	X	Do not include ▪ Study limited to Germany If Austria were included: Potentially include Austria vs. Germany	Not important	Yes ▪ Place of birth ▪ Location of treatment center?	(10)

Table A27: Confounders at baseline - Category Origin of SMA disease

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic SMN2 copies 3	SMA Type I	SMA Type II				
SMA Type	▪ SMA Type	n.a.	n.a.	X	X	Individual study populations: ▪ Pre-symptomatic 1-2 copy SMN2 ▪ Pre-symptomatic 3 copy SMN2 ▪ Symptomatic Type I ▪ Symptomatic Type II	Not important: Age at onset & highest motor milestone at baseline captured individually	SMA type not explicitly available? Derivation from age at symptom onset: ▪ <6M: Type I ▪ 6M-18M: Type II	(10, 6, 12–14),
SMN2 copy number	▪ SMN2 copy number	X	X	X	X	SNM2 copy number	Very Important[2]	Yes	(15, 10, 16–19, 4, 20–22, 12, 23, 6, 14)
SMN2 genotype/ variants	▪ Genotype of SMN2	X	X	X	X		Not important	No ▪ SNM1 mutation type only	(15, 10, 16, 22, 11)

[2] Due to the stratification according to SMN2 copy number, this confounder is not taken into account

Table A28: Confounders at baseline - Category Impact on the Treatment response

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic SMN2 copies 3	SMA Type I	SMA Type II				
Pre-symptomatic/ symptomatic at treatment initiation	▪ Pre-symptomatic vs. symptomatic at the time of disease-modifying therapy (DMT)	X	X	(X)	(X)	Individual study populations: ▪ Pre-symptomatic 1-2 copy SMN2 ▪ Pre-symptomatic 3 copy SMN2 ▪ Symptomatic Type I ▪ Symptomatic Type II at treatment initiation	Very important	Yes	(11, 15, 5)

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic SMN2 copies 3	SMA Type I	SMA Type II				
Treatment delay	▪ Time between diagnosis and start of treatment	X	X	X	X	Do not include ▪ Age at symptom onset and age at treatment initiation included	Not important: ▪ Age at symptom onset and age at treatment initiation relevant	No ▪ Time of diagnosis not specified?	(10, 17, 9)
	▪ Time between symptom onset and 1st DMT	X	X	X	X				(9)

Table A29: Confounders at Baseline - Category Nutrition manifestations

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies 3	SMA Type I	SMA Type II				
Gastroesopha-geal reflux	▪ Gastroesophageal reflux	X	X	X	X	?	Not important	No	(10)
Gastrostomy	▪ Gastrostomy tube feeding ▪ Gastrostomy placement	(X)	(X)	X X	X X	Nutritional support: ▪ Proportion with nutritional support part-time ▪ Proportion with Nutritional support full time Use gastric/ nasal feeding tube information?	Nutritional Support general: Very important Gastrostomy vs. nasal feeding: not important	Does the patient use a gastric or nasal feeding tube? ▪ Exclusively ▪ Supplemen-tary	(22) (24, 10, 25)

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies 3	SMA Type I	SMA Type II				
Nutrition	▪ Growth and Undernutrition ▪ Overnutrition problems	X	X	X	X	Weight at or above the 3rd percentile of age group → If included likely other percentile relevant for SMA, (above 1st?) Nutrition support via gastric/nasal feeding tube (see above)	Not important because captured via nutritional support Suggestion: Eliminate weight at or above the 3rd percentile of age group because not influenced by DMD but by standard of care	Yes ▪ Weight ▪ Height ▪ Age	(10) (10, 26) (27)
	▪ Nutrition	X	X	X	X				
	▪ Nutrition support			X	X				
Bone mineral density	▪ Bone mineral density	X	X	X	X	Do not include	Not important	No	(10)

Table A30: Confounders at Baseline - Category Orthopedic and motoric manifestations

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies	SMA Type I 3	SMA Type II				
Contractures	▪ Contractures	(X)	(X)	X	X	Yes/No ▪ Limit to selected lo-calizations / types?	Less important	Yes ▪ Are any contractures present? (including limitations by contrature and localisation/ type)	(8, 22) (10)
	▪ Flexion Contractures	X	X	X	X				
Motoric function	▪ CHOP-INTEND score at baseline	X	X	X	X	▪ Mean CHOP-INTEND score at baseline (as applicable) → Include for all (also pre-symptomatic) ▪ Mean Hammersmith score at baseline	Very important	Yes? ▪ Physiotherapy assessment on day 1, 30, 60, 180, followed by 4-monthly	(4) (28)
	▪ HFMSE score from baseline			X	X				

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies	SMA Type I 3	SMA Type II				
	▪ Highest motor milestone at base-line					(as applicable) → Do not include (only measured at age 2+) ▪ Highest motor milestone at baseline → include		examinations → **CHOP-IN-TEND, HMFSE?** ▪ Motor Func-tion: Best current mo-tor function: Sitting without support; Crawl on hands an knees; Standing without support; Walking without support; Climb stairs; Other	(6)

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies	SMA Type I 3	SMA Type II				
Physical activity	▪ Physical activity	X	X	X	X	▪ Do not include	Not important	No	(5)
Orthotics	▪ Scoliosis	(X)	(X)	X	X	▪ Yes/no	Not important	Yes. Does the Patient have scoliosis?	(10, 25)

Table A31: Confounders at Baseline - Category Access to and quality of treatment

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symptom -matic 3 SMN2 copies	SMA Type I	SMA Type II				
Access/ Quality	▪ COVID-19 Pandemic	X	X	X	X	Not relevant for study? ▪ Inclusion in case of treatment requires access ▪ Application of G-BA quality criteria for participating centers	Not important if study only includes HSPs qualifying for Zolgensma If other HSPs are included for Nusinersen: potentially important and should be included	No	(29)
	▪ Medical practitioners' knowledge	X	X	X	X				(10)
	▪ Multidisciplinary or interdisciplinary team	X	X	X	X				(10, 16)
	▪ Treatment Center			X	X				(10)

Table A32: Confounders after Baseline – Category Access to and quality of treatment

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic 3 SMN2 copies	SMA Type I	SMA Type II				
Access/ Quality	▪ Engagement with health care	X	X	X	X	No./Proportion of missed routine visits And	Not important	Yes ▪ Date of each visit	(10)
	▪ Providing families with information	X	X	X	X	No. of missed doses for nusinersen			(10)
	▪ Access to therapeutic interventions	X	X	X	X	Discussion: ▪ All routine visits performed at participating treatment center?			(18)
Adaptation	▪ Mechanical ventilation			X		Do not include ▪ Changes in ventilator and ▪ nutritional support represent endpoints	Not important (endpoint, not confounder)	Yes	(18)
	▪ Tracheostomy			X					(18)
	▪ Gastrostomy			X					(18)
	▪ Motor and respiratory physiotherapy			X					(18)
	▪ Nursing care			X					(18)
				X					(18)

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic 3 SMN2 copies	SMA Type I	SMA Type II				
	▪ Occupational therapy ▪ Speech therapy for alternative communication and dysphagia			X					(18)

Table A33: Confounders after Baseline – Category Assistive equipment

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies	SMA Type I 3	SMA Type II				
Assistive equip-ment	▪ Assistive equip-ment			X	X	Do not include	Not important	Yes	(4)
	▪ Wheelchair	X	X	X	X			▪ Assistance in airway clearance and secretion mobilization (type, frequency) ▪ Wheelchair use (including type and frequency of use)	(10)

Table A34: Confounders after Baseline – Category Orthopedic and motoric manifestations

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies	SMA Type I 3	SMA Type II				
Orthotics	▪ Kneeankle- foot orthoses				X	Do not include ▪ Contractures at baseline included ▪ Baseline motor function included Discussion: ▪ Confounder on pain?	Not important	Yes ▪ Orthoses/ Devices (incl. Type, type of use, and frequency)	(26)
	▪ Limb orthotics								(26)
	▪ Orthosis			X	X				(10)
	▪ Positioning and seating alterations and orthotic devices	X	X	X	X				(10)
	▪ Posture management	X	X	X	X				(10)
	▪ Surgical correction of scoliosis			X	X				(10)
Physiotherapy	▪ Occupational therapy			X	X	Yes/no (per time between visits) Reliable operationalization not possible,	Less important: No evidence on effect of physio-therapy	Yes ▪ Therapy interventions (physio, feeding/	(5)
	▪ Physical therapy			X	X				(10)
	▪ Physiotherapy	X	X	X	X				(10)

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies	SMA Type I 3	SMA Type II				
	▪ Regular exercise	X	X	X	X	because it would require quantity and quality → Do not include in study		speech, occupational, other)	(10)
Motoric function	▪ Position (supine/ seated)	X	X	X	X	Do not include ▪ Baseline confounder and end-point	Not important (endpoint, not confounder)		(25)

Table A35: Confounders after Baseline – Category Others

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies 3	SMA Type I	SMA Type II				
Nutrition	▪ Education about nutrition	X	X	X	X	Do not include?	Not important	Unclear ▪ Therapy interventions: feed/speech includes Education?	(10)
Pain management	▪ Pain management			X	X	Do not include?	Not important	Unclear ▪ May be partly covered by "Other medication taken on a regular basis?"	(20, 5)
Support	▪ Support ▪ support from family	X X	X X	X X	X X	Do not include	Not important	No	(19) (4, 5)

5. Detailed presentation of the search strategy

5.1 Search strategy – Bibliographic literature search (Guidelines and recommendations in the indication SMA)

Table A36: Search string for guidelines and recommendations

Database	MEDLINE	
Search interface	PubMed	
Search date	24.03.2021	
#	Search terms	Results
1	"Muscular Atrophy, Spinal"[mh] OR "Motor Neuron Disease"[mh:noexp]	9.563
2	motor[Title/Abstract] AND neuron*[Title/Abstract] AND disease*[Title/Abstract]	22.950
3	spinal[tiab] OR bulbo-spinal[tiab] OR bulbospinal[tiab] OR myelopath*[tiab] OR progressiv*[tiab] OR spinobulbar[tiab] AND (muscular[tiab] OR muscle[tiab]) AND atroph*[tiab]	10.585
4	(spinal[tiab] OR (neurogenic scapuloperonea*[tiab])) AND amyotroph*[tiab]	5.453
5	(Spinal[tiab] OR bulbo-spinal[tiab] OR bulbospinal[tiab] OR spinobulbar[tiab] OR spinopontin*[tiab] OR (hereditary motor[tiab])) AND neuronopath*[tiab]	289
6	#1 OR #2 OR #3 OR #4 OR #5	36.514
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title])	95
8	(#7) AND ("2015/06/01"[PDAT] : "3000"[PDAT])	34
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])	34

5.2 Search strategy – Bibliographic literature search (systematic reviews and Meta-analyses in the indication SMA)

Table A37: Search string for systematic reviews in MEDLINE

Database	MEDLINE	
Search interface	PubMed	
Search date	24.03.2021	
#	Search terms	Results
1	"muscular atrophy, spinal"[MeSH Terms]	5.299
2	("spinal"[Title/Abstract] OR "bulbo-spinal"[Title/Abstract] OR "bulbospinal"[Title/Abstract] OR "myelopath*"[Title/Abstract] OR "progressiv*"[Title/Abstract] OR "spinobulbar"[Title/Abstract]) AND ("muscular"[Title/Abstract] OR "muscle"[Title/Abstract]) AND "atroph*"[Title/Abstract]	10.585
3	("spinal"[Title/Abstract] OR "neurogenic scapuloperonea*"[Title/Abstract]) AND "amyotroph*"[Title/Abstract]	5.453

4	("spinal"[Title/Abstract] OR "bulbo-spinal"[Title/Abstract] OR "bulbospinal"[Title/Abstract] OR "spinobulbar"[Title/Abstract] OR "spinopontin*"[Title/Abstract] OR "hereditary motor"[Title/Abstract]) AND "neuronopath*"[Title/Abstract]	289
5	#1 OR #2 OR #3 OR #4	16.385
6	(#5) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review[ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri*[tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication[tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab])) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))	278
7	(#6) AND ("2015/06/01"[PDAT] : "3000"[PDAT])	169
8	(#7) NOT "The Cochrane database of systematic reviews"[Journal]	165
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])	165

Table A38: Search string for systematic reviews in Cochrane.

Database	Cochrane Database of Systematic Reviews	
Search interface	Cochrane Library	
Search date	24.03.2021	
#	Search terms	Results
1	[mh "spinal muscular atrophy"]	91
2	[mh "motor neuron disease"]	718
3	(motor NEXT neuron* NEXT disease*):ti,ab,kw	459
4	(spinal OR "bulbo spinal" OR bulbospinal OR myelopath* OR progressiv* OR spinobulbar):ti,ab,kw AND (Muscular OR muscle):ti,ab,kw AND (Atroph*):ti,ab,kw	520
5	(Spinal OR (neurogenic NEXT scapuloperonea*)):ti,ab,kw AND (Amyo-troph*):ti,ab,kw	127
6	(Spinal OR "bulbo spinal" OR bulbospinal OR spinobulbar OR spinopontin* OR "hereditary motor"):ti,ab,kw AND (Neuronopath*):ti,ab,kw	2
7	{OR #1-#6}	1310
8	#7 with Cochrane Library publication date from Jun 2015 to Jun 2020, in Cochrane Reviews and Cochrane Protocols	15

5.3 Search Results – Free-hand search (Guidelines and recommendations for the indication SMA)

Table A39: List of guidelines found by the freehand search and their reasons for inclusion and exclusion

Plattform	Hits	Inclusion/exclusion
Systematic search - various databases		
AWMF Leitlinien Suche	Guideline application: **S1: Spinale Muskelatrophie (SMA), Diagnostik und Therapie** Registration number: 022-030 Planned completion: 15.01.2021	Exclusion No current version available
CMA Infobase: Clinical Practice Guidelines Database (CPGs)	**1. Pediatric home mechanical ventilation: a Canadian Thoracic Society clinical practiceguideline executive summary** Amin et al. Canadian Thoracic Society Published on: 2017	Inclusion
Trip Database	**Evidence in focus: Nusinersen use in spinal muscular atrophy** Michelson et al. Neurology Published on: 2018	Exclusion Duplicate

	Pediatric home mechanical ventilation: A Canadian Thoracic Society clinical practiceguideline executive summary Amin et al. Respiratory, critical care and Sleep Medicine Published on: 2017	Exclusion Duplicate
	Genetic Testing for Reproductive Carrier Screening and Prenatal Diagnosis Anonym Published on: 2020	Exclusion A4, Endpoints not fulfilled
	Carrier Screening for Genetic Conditions Committee on Genetics Published on: 2011	Exclusion A4, Endpoints not fulfilled
Google-Suche	**Handlungsempfehlungen zur Gentherapie der spinalen Muskelatrophie mit Onasemnogene Abeparvovec – AVXS-101 : Konsensuspapier der deutschen Vertretung der Gesellschaft für Neuropädiatrie (GNP) und der deutschen Behandlungszentren unter Mitwirkung des Medizinisch-Wissenschaftlichen Beirates der Deutschen Gesellschaft für Muskelkranke (DGM) e. V.** Hagenacker et al. Published on: 2017 Fortschritte Neurologie Psychiatrie	Exclusion Duplicate
	Spinale Muskelatrophie – Expertenempfehlungen zur Behandlung von erwachsenen Patienten mit Nusinerse Hagenacker et al. Published on: 2019 Fortschritte Neurologie Psychiatrie	Exclusion Duplicate
	Handlungsempfehlungen zur Gentherapie der spinalen Muskelatrophie mit Onasemnogene Abeparvovec – AVXS-101: Konsensuspapier der deutschen Vertretung der Gesellschaft für Neuropädiatrie (GNP) und der deutschen Behandlungszentren unter Mitwirkung des Medizinisch-Wissenschaftlichen Beirates der Deutschen Gesellschaft für Muskelkranke (DGM) e. V. Ziegler et al. Published on: 2017 Der Nervenarzt	Exclusion Duplicate
Google-Scholar	**Best practice guidelines for molecular analysis in spinal muscular atrophy** Scheffer et al. Published on: 2001 European Journal of Human Genetics	Inclusion

Spinal Muscular Atrophy Prior et al. Published on: 2020 GeneReviews®	Inclusion
Handlungsempfehlungen zur Gentherapie der spinalen Muskelatrophie mit Onasemnogene Abeparvovec – AVXS-101: Konsensuspapier der deutschen Vertretung der Gesellschaft für Neuropädiatrie (GNP) und der deutschen Behandlungszentren unter Mitwirkung des Medizinisch-Wissenschaftlichen Beirates der Deutschen Gesellschaft für Muskelkranke (DGM) e. V. Ziegler et al. Published on: 2017 Der Nervenarzt	Exclusion Duplicate
Recommendations for the diagnosis and management of typical childhood spinal muscular Atrophy Recommandations pour le diagnostic et la prise en charge de l'amyotrophie spinale typique de l'enfant Cuisset et al. Published on: 2012 Revue Neurologique	Inclusion
Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics Finkel et al. Published on: 2018 Neuromuscular Disorder	Exclusion Duplicate
1st Italian SMA Family Association Consensus Meeting: Management and recommendations for respiratory involvement in spinal muscular atrophy (SMA) types I–III Sansone et al. Published on: 2015 Neuromuscular Disorder	Exclusion Duplicate
Revised Recommendations for the Treatment of Infants Diagnosed with Spinal Muscular Atrophy Via Newborn Screening Who Have 4 Copies of SMN2 Glascock et al. Published on: 2020 Journal of Neuromuscular Diseases	Exclusion Duplicate
Management of children with spinal muscular atrophy type 1 in Australia Tassie et al. Published on: 2013 Journal of Pediatrics and Child Health	Exclusion A5, Study type not fulfilled

	Special Considerations in the Respiratory Management of Spinal Muscular Atrophy Schroth et al. Published on: 2009 Pediatrics	Inclusion
	Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening Glascock et al. Published on: 2018 Journal of Neuromuscular Diseases	Inclusion
	Practical guidelines to manage discordant situations of SMN2 copy number in patients with spinal muscular atrophy Cuscó et al. Published on: 2020 Neurology Genetics	Exclusion Duplicate
	Carrier screening for spinal muscular atrophy Prior et al. Published on: 2008 genetics in medicine	Inclusion
	Evidence in focus: Nusinersen use in spinal muscular atrophy Michelson et al. Published on: 2018 Neurology	Exclusion Duplicate
	Consensus Statement for Standard of Care in Spinal Muscular Atrophy Wang et al. Published on: 2007 Sage Open	Exclusion Duplicate
Cochrane Deutschland		No guideline found for the indication SMA.
Pubmed	**Treatment Advances in Spinal Muscular Atrophy** Bharucha-Goebel et al. Published on: 2017 Current neurology and neuroscience reports	Exclusion A5, Study type not fulfilled
	Spinal muscular atrophy care in the COVID-19 pandemic era Veerapandiyan et al. Published on: 2020 Muscle & Nerve	Exclusion A5, Study type not fulfilled

	Spinal muscular atrophy D´Amico et al. Published on: 2011 Orphanet Journal of Rare Diseases	Exclusion A5, Study type not fulfilled
	Recommendations for gene therapy of spinal muscular atrophy with onasemnogene abeparvovec-AVXS-101 : Consensus paper of the German representatives of the Society for Pediatric Neurology (GNP) and the German treatment centers with collaboration of the medical scientific advisory board of the German Society for Muscular Diseases (DGM)] Ziegler et al. Published on: 2020 Der Nervenarzt	Exclusion Duplicate
Selected homepages of German and international professional societies		
NHS - Protocol and Guidelines		No guideline found for the indication SMA.
NICE Guidelines		No guideline found for the indication SMA.
Gesellschaft für Neuropädiatrie	**Diagnosestellung und Behandlung bei SMA Patienten**	Exclusion A5, Study type not fulfilled
Treat-NMD Neuromuscular Network	**Behandlungsstandards für Spinale Muskelatrophie** Wang et al. Journal of Child Neurology Published on: 2007	Inclusion
	Diagnosestellung und Behandlung bei SMA Patienten Translation of Wang et al. by Schwersenz et al.	Exclusion A5, Study type not fulfilled
Deutsche Gesellschaft für Muskelkranke e.V.	**Leitfaden zu den Internationalen Therapiestandards für Spinale Muskelatrophie** Published on: 2017	Exclusion A5, Study type not fulfilled
	Diagnosis and management of spinal muscular atrophy: Part 1:Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care Mercuri et al. Published on: 2018 Neuromuscular Disorders	Exclusion Duplicate
	Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonaryand acute care; medications, supplements and immunizations; other organsystems; and ethics Mercuri et al. Published on: 2018 Neuromuscular Disorders	Exclusion Duplicate

	Management of Neuromuscular Diseases Spinale Muskelathrophie Deutsche Gesellschaft für Muskelkranke e.V. Published on: 2005	Exclusion A5, Study type not fulfilled
Initiative SMA		No guideline found for the indication SMA.
Schweizerischen Muskelgesellschaft		No guideline found for the indication SMA.
Neurologienetz		No guideline found for the indication SMA.
Deutsche Gesellschaft für Humangenetik e.V.		No guideline found for the indication SMA.
Deutsche Gesellschaft für Kinder- und Jugendmedizin e.V.		No guideline found for the indication SMA.
Deutsche Muskelstiftung		No guideline found for the indication SMA.
Deutsche Muskelschwund-Hilfe e.V.		No guideline found for the indication SMA.
Muskeln für Muskeln		No guideline found for the indication SMA.
Patientenstimme SMA		No guideline found for the indication SMA.
SMA Europe	**SPINAL MUSCULAR ATROPHY:PATHOLOGY, DIAGNOSIS,CLINICAL PRESENTATION,THERAPEUTIC STRATEGIES & TREATMENTS** Published on: 11/2020	Exclusion A5, Study type not fulfilled
	Consensus Statement for Standard of Care in Spinal Muscular Atrophy Wang et al. Published on: 2007 Journal of Child Neurology	Exclusion Duplicate
Marathon		No guideline found for the indication SMA.
CTM-austria		No guideline found for the indication SMA.
AFM Telethon		No guideline found for the indication SMA.

Spierziekten Nederland		This website is not available in English or German.
European Neuro Muscular Centre		No guideline found for the indication SMA.
Asami – Associazione per lo Studio delle Atrofie Muscolari Spinali Infantili		This website is not available in English or German.
Muscular Dystrophy UK		No guideline found for the indication SMA.
Cure SMA	**Respiratory muscle function in infants with spinal muscular atrophy type I** Finkel et al. Published on: 2014 Pediatric Pulmonology	Exclusion A5, Study type not fulfilled
	Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care Mecuri et al. Published on: 2018 Neuromuscular Disorders	Exclusion Duplicate
	Assessing the Needs of the SMA Population: Survey Results of Health Care Providers and Families Halanski et al. Published on: 2014 SAGE Open	Exclusion A5, Study type not fulfilled
	The Experience of Families With Children With Spinal Muscular Atrophy Type I Across Health Care Systems Murrell et al. Published on: 2016 Journal of Child Neurology	Exlusion A5, Study type not fulfilled
	Opening the window: The case for carrier and perinatal screening for spinal muscular atrophy Burns et al. Published on: 2016 Neuromuscular Disorders	Exclusion A5, Study type not fulfilled
	What Matters Most: A Perspective From Adult Spinal Muscular Atrophy Patients Hunter et al. Published on: 2016 Journal of Neuromuscular Diseases	Exclusion A5, Study type not fulfilled

	Nutritional Status and Nutrient Intake Challenges in Children With Spinal Muscular Atrophy Metha et al. Published on: 2015 Pediatric Neurology	Exclusion A5, Study type not fulfilled
	Baseline results of the NeuroNEXT spinal muscular atrophy infant biomarker study Kolb et al. Published on: 2016 Annals of Clinical an Translational Neurology	Exclusion A5, Study type not fulfilled
	Understanding the experiences and needs of individuals with Spinal Muscular Atrophy and their parents: a qualitative study Qian et al. Published on: 2015 BMC Neurology	Exclusion A5, Study type not fulfilled
	Responses to Fasting and Glucose Loading in a Cohort of Well Children with Spinal Muscular **Atrophy Type II** Davis et al. Published on: 2015 Journal of pediatrics	Exclusion A5, Study type not fulfilled
	209th ENMC International Workshop: Outcome Measures and Clinical Trial Readiness in Spinal Muscular Atrophy 7-9 November 2014, Heemskerk, The Netherlands Finkel et al. Published on: 2015 Neuromuscular Disorders	Exclusion A5, Study type not fulfilled
	Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics Mecuri et al. Published on: 2018 Neuromuscular Disorders	Exclusion Duplicate
Spinal Muscular Atrophy Foundation **My Care Plus**		No guideline found for the indication SMA. No guideline found for the indication SMA.
World Muscle Society		No guideline found for the indication SMA.

5.4 List of documents viewed in full text and excluded with reason for exclusion (Bibliographic literature research – Guidelines and recommendations)

Table A40: List of guidelines and recommendations viewed in full text and excluded

Ongoing number	Excluded reference	Reason for exclusion
1	Anonym, ADDENDUM: Technical standards and guidelines for spinal muscular atrophy testing. Genet Med 2016:18(7):752.	A5, Study type not fulfilled
2	Anonym, CADTH Canadian Drug Expert Committee Recommendation: Nusinersen (Spinraza — Biogen Canada Inc.): Indication: Treatment of 5q Spinal Muscular Atrophy. CADTH Common Drug Reviews 2017.	A5, Study type not fulfilled
3	Anonym, CADTH Canadian Drug Expert Committee Recommendation: Nusinersen (Spinraza — Biogen Canada Inc.): Indication: Treatment of 5q Spinal Muscular Atrophy. CADTH Com-mon Drug Reviews 2017.	A4, Endpoints not fulfilled
4	Bergin et al. Recommendations to support informal carers of people living with motor neurone disease. Br J Community Nurs 2016:21(10):518-524.	A1, Patient population not fulfilled
5	Deignan et al. Addendum: Technical standards and guidelines for spinal muscular atrophy testing. Genet Med 2020.	A5, Study type not fulfilled
6	Glascock et al. Revised Recommendations for the Treatment of Infants Diagnosed with Spinal Muscular Atrophy Via Newborn Screening Who Have 4 Copies of SMN2.J Neuromuscul Dis 2020:7(2):97-100.	A5, Study type not fulfilled
7	Hagenacker et al. [Spinal Muscular Atrophy - expert recommendations for the use of nusinersen in adult patients]. Fortschr Neurol Psychiatr 2019:87(12):703-710.	A4, Endpoints not fulfilled
8	Harvey et al. ACR Appropriateness Criteria® Movement Disorders and Neurodegenerative Diseases. J Am Coll Radiol 2020:17(5):175-187.	A1, Patient population not fulfilled
9	Mercuri et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord 2018:28(2):103-115.	A5, Study type not fulfilled
10	Anonym, Motor Neurone Disease: Assessment and Management. NICE Guideline 2016:42:1-7.	A1, Patient population not fulfilled
11	Oliver et al. The development of the UK National Institute of Health and Care Excellence evidence-based clinical guidelines on motor neurone disease. Amyotroph Lateral Scler Frontotemporal Degener 2017:18:5-6:313-323.	A1, Patient population not fulfilled
12	Silvinato et al. Spinal muscular atrophy 5Q - Treatment with nusinersen. Rev Assoc Med Bras (1992) 2018:64(6):484-491.	A4, Endpoints not fulfilled
13	Writing Group For Practice Guidelines For et al. [Clinical practice guidelines for spinal muscular atrophy]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi Actions 2020:37(3):263-268	A6, Language

5.5 List of documents viewed in full text and excluded with reason for exclusion (Bibliographic literature research – systematic reviews and Meta-analyses)

Table A41: List of systematic reviews and Meta-analyses viewed in full text and excluded

Ongoing number	Excluded reference	Reason for exclusion
1	Anonym. Global, regional, and national burden of motor neuron diseases 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018:17(12):1083-1097.	A1, Patient population not fulfilled
2	Abati et al. Pregnancy outcomes in women with spinal muscular atrophy: A review. J Neurol Sci 2018:388():50-60.	A1, Patient population not fulfilled
3	Ahmadian-Moghadam et al. Therapeutic potential of stem cells for treatment of neurodegenerative diseases. Biotechnol Lett 2020:42(7):1073-1101.	A5, Study type not fulfilled
4	Alhammoud et al. The impact of scoliosis surgery on pulmonary function in spinal muscular atrophy: a systematic review. Spine Deform 2021.	A4, Endpoints not fulfilled
5	Ali et al. Healthcare utilisation in children with SMA type 1 treated with nusinersen: a single centre retrospective review. BMJ Paediatr Open 2019:3(1):e000572.	A5, Study type not fulfilled
6	Azadinia et al. Can lumbosacral orthoses cause trunk muscle weakness? A systematic review of literature. Spine J 2017:17(4):589-602.	A1, Patient population not fulfilled
7	Bartels et al. Physical exercise training for type 3 spinal muscular atrophy. Cochrane Database of Systematic Reviews 2019: (3).	A1, Patient population not fulfilled
8	Bernardes Neto et al. Weaning from mechanical ventilation in people with neuromuscular disease: protocol for a systematic review. BMJ Open 2019:9(11):e029890.	A1, Patient population not fulfilled
9	Bharucha-Goebel et al. Treatment Advances in Spinal Muscular Atrophy. Curr Neurol Neurosci Rep 2017:17(11):91	A5, Study type not fulfilled
10	Boardman et al. Impairment Experiences, Identity and Attitudes Towards Genetic Screening: the Views of People with Spinal Muscular Atrophy. J Genet Couns 2018:27(1):69-84.	A4, Endpoints not fulfilled
11	Boentert et al. Respiratory involvement in neuromuscular disorders. Curr Opin Neurol 2017:30(5):529-537.	A5, Study type not fulfilled
12	Bowerman et al. Therapeutic strategies for spinal muscular atrophy: SMN and beyond. Dis Model Mech 2017:10(8):943-954.	A5, Study type not fulfilled
13	Bray et al. Preference-based measures of health-related quality of life in congenital mobility impairment: a systematic review of validity and responsiveness. Health Econ Rev. 2020:10(1):9.	A4, Endpoints not fulfilled
14	Butchbach et al. Copy Number Variations in the Survival Motor Neuron Genes: Implications for Spinal Muscular Atrophy and Other Neurodegenerative Diseases. Front Mol Biosci 2016:3():7.	A4, Endpoints not fulfilled
15	Calder et al. Small Molecules in Development for the Treatment of Spinal Muscular Atrophy. J Med Chem 2016:59(22):10067-10083.	A4, Endpoints not fulfilled

16	Castro-Codesal et al. Long-term non-invasive ventilation therapies in children: A scoping review. Sleep Med Rev 2018:37():148-158.	A1, Patient population not fulfilled
17	Chiriboga et al. Nusinersen for the treatment of spinal muscular atrophy. Expert Rev Neurother 2017:17(10):955-962.	A5, Study type not fulfilled
18	Cohen et al. Diffusion MRI of the spinal cord: from structural studies to pathology. NMR Biomed 2017:30(3).	A1, Patient population not fulfilled
19	Dangouloff et al. Systematic literature review of the economic burden of spinal muscular atrophy and economic evaluations of treatments. Orphanet J Rare Dis 2021:16(1):47.	A4, Endpoints not fulfilled
20	Dial et al. The Role of AMPK in Neuromuscular Biology and Disease. Trends Endocrinol Metab 2018:29(5):300-312.	A5, Study type not fulfilled
21	Dubowitz et al. Critical Review Ahead of Publication. Neuromuscul Disord 2019:29(6):412.	A5, Study type not fulfilled
22	Dunaway Young et al. Six-minute walk test is reliable and valid in spinal muscular atrophy. Muscle Nerve 2016:54(5): 836-842.	A1, Patient population not fulfilled
23	Elshafay et al. Efficacy and Safety of Valproic Acid for Spinal Muscular Atrophy: A Systematic Review and Meta-Analysis. CNS Drugs. 2019:33(3):239-250.	A4, Endpoints not fulfilled
24	Finsterer et al. Fasciculations in human hereditary disease. Acta Neurol Belg 2015:115(2):91-95.	A4, Endpoints not fulfilled
25	Göhl et al. [Respiratory Muscle Training: State of the Art]. Pneumologie 2016:70(1):37-48.	A1, Patient population not fulfilled
26	Grayev et al. A Systematic Review of Procedural Complications from Transforaminal Lumbar Puncture for Intrathecal Nusinersen Administration in Patients with Spinal Muscular Atrophy. AJNR Am J Neuroradiol 2021.	A1, Patient population not fulfilled
27	Grotto et al. Type 0 Spinal Muscular Atrophy: Further Delineation of Prenatal and Postnatal Features in 16 Patients. J Neuromuscul Dis 2016:3(4):487-495.	A1, Patient population not fulfilled
28	Grychtol et al. The role of sleep diagnostics and non-invasive ventilation in children with spinal muscular atrophy. Paediatr Respir Rev 2018:28():18-25.	A5, Study type not fulfilled
29	Hensel et al. The Actin Cytoskeleton in SMA and ALS: How Does It Contribute to Motoneuron Degeneration? Neuroscientist 2018:24(1):54-72.	A5, Study type not fulfilled
30	Hu et al. Gene therapeutic strategies and relevant clinical trials in neuromuscular disorder in China. Gene Ther 2020:27(7-8):321-328.	A5, Study type not fulfilled
31	Iftikhar et al. Current and emerging therapies for Duchenne muscular dystrophy and spinal muscular atrophy. Pharmacol Ther 2021:220: 107719.	A5, Study type not fulfilled
32	Jablonka et al. Developmental regulation of SMN expression: pathophysiological implications and perspectives for therapy development in spinal muscular atrophy. Gene Ther 2017:24(9):506-513.	A5, Study type not fulfilled
33	Janoudi et al. Nusinersen for Adolescents and Adults with Spinal Muscular Atrophy: A Review of Clinical Effectiveness. CADTH Rapid Response Reports 2020.	A1, Patient population not fulfilled
34	Kennedy et al. Walking and weakness in children: a narrative review of gait and functional ambulation in paediatric neuromuscular disease. J Foot Ankle Res 2020:13(1):10.	A1, Patient population not fulfilled

36	Kilcher et al. Medical use of cannabis in Switzerland: analysis of approved exceptional licences. Swiss Med Wkly 2017:147():w14463.	A4, Endpoints not fulfilled
36	Kreider et al. Creatine in Health and Disease. Nutrients 2021:13(2).	A4, Endpoints not fulfilled
37	Kremer et al. Transcriptomics: molecular diagnosis of inborn errors of metabolism via RNA-sequencing. J Inherit Metab Dis 2018:41(3):525-532.	A4, Endpoints not fulfilled
38	Lager et al. Pain in adolescents with spinal muscular atrophy and Duchenne and Becker muscular dystrophy. Eur J Paediatr Neurol 2015:19(5):537-546.	A1, Patient population not fulfilled
39	Landfeldt et al. Costs of Illness of Spinal Muscular Atrophy: A Systematic Review. Appl Health Econ Health Policy 2021.	A4, Endpoints not fulfilled
40	Lanigan et al. Comparative Pathology of the Peripheral Nervous System. Vet Pathol 2021:58(1):10-33.	A5, Study type not fulfilled
41	Li et al. The prevalence of spinal muscular atrophy carrier in China: Evidences from epidemiological surveys. Medicine (Baltimore) 2020:99(5):e18975.	A4, Endpoints not fulfilled
42	Lin et al. Molecular Therapies for Muscular Dystrophies. Curr Treat Options Neurol 2018:20(7):27.	A5, Study type not fulfilled
43	Long et al. Genome Editing of Monogenic Neuromuscular Diseases: A Systematic Review. JAMA Neurol 2016:73(11):1349-1355.	A1, Patient population not fulfilled
44	MacDonald et al. The Use of Medical Cannabis with Other Medications: A Review of Safety and Guidelines - An Update. CADTH Rapid Response Reports 2019.	A1, Patient population not fulfilled
45	Magalhães et al. Is transcutaneous electrical muscle stimulation an alternative for preventing acquired muscle weakness in the pediatric intensive care unit? A scoping review. Pediatr Pulmonol 2019:54(8):1108-116.	A1, Patient population not fulfilled
46	Mandarakas et al. Functional outcome measures for infantile Charcot-Marie-Tooth disease: a systematic review. J Peripher Nerv Syst 2018:23(2):99-107.	A4, Endpoints not fulfilled
47	Martin et al. Translating state-of-the-art spinal cord MRI techniques to clinical use: A systematic review of clinical studies utilizing DTI, MT, MWF, MRS, and fMRI. Neuroimage Clin 2016:10():192-238.	A1, Patient population not fulfilled
48	Mensch et al. Instruments for the evaluation of motor abilities for children with severe multiple disabilities: A systematic review of the literature. Res Dev Disabil 2015:47():185-198.	A4, Endpoints not fulfilled
49	Messina et al. A critical review of patient and parent caregiver oriented tools to assess health-related quality of life, activity of daily living and caregiver burden in spinal muscular atrophy. Neuromuscul Disord 2019:29(12):940-950.	A4, Endpoints not fulfilled
50	Miladi et al. Minimally Invasive Surgery for Neuromuscular Scoliosis: Results and Complications in a Series of One Hundred Patients. Spine (Phila Pa 1976) 2018:43(16):E968-E975.	A1, Patient population not fulfilled
51	Nidetz et al. Adeno-associated viral vector-mediated immune responses: Understanding barriers to gene delivery. Pharmacol Ther 2020:207():107453.	A5, Study type not fulfilled
52	O'Sullivan et al. Effect of Lung Volume Recruitment on Pulmonary Function in Progressive Childhood-Onset Neuromuscular Disease: A Systematic Review. Arch Phys Med Rehabil 2020.	A1, Patient population not fulfilled

53	Paganoni et al. Evidence-Based Physiatry: Pediatric Neuromuscular Rehabilitation in the Era of Precision Medicine. Cochrane Database of Systematic Reviews 2018:97(12):920.	A5, Study type not fulfilled
54	Payne et al. Interventions for fatigue and weight loss in adults with advanced progressive illness. Cochrane Database of Systematic Reviews 2017:(4).	A1, Patient population not fulfilled
55	Perez et al. Management of Neuroinflammatory Responses to AAV-Mediated Gene Therapies for Neurodegenerative Diseases. Brain Sci 2020:10(2).	A5, Study type not fulfilled
56	Sansone et al. 1st Italian SMA Family Association Consensus Meeting: Management and recommendations for respiratory involvement in spinal muscular atrophy (SMA) types I-III, Rome, Italy, 30-31 January 2015. Neuromuscul Disord 2015:25(12)979-989.	A5, Study type not fulfilled
57	Silvinato et al. Spinal muscular atrophy 5Q - Treatment with nusinersen.Rev Assoc Med Bras (1992) 2018:64(6):484-491.	A5, Study type not fulfilled
58	Simon et al. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. Cochrane Database of Systematic Reviews 2016:(10).	A1, Patient population not fulfilled
59	Simonds et al. Home Mechanical Ventilation: An Overview. Ann Am Thorac Soc 2016:13(11):2035-2044.	A1, Patient population not fulfilled
60	Tizzano et al. Spinal muscular atrophy: A changing phenotype beyond the clinical trials. Neuromuscul Disord 2017:27(10):883-889.	A1, Patient population not fulfilled
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A2 Relevant variables in SMArtCare Registry

Table A42: Relevant variables in SMArtCARE Registry

CRF	CRF Section	CRF Item	at or before Baseline	after Baseline
Enrolment		Date of consent	x	
		Genetically proven 5q SMA	x	
		Date of Birth	x	
		Gender	x	
Baseline		Date recorded	x	
	Genetic Test Result	SMN2 copy number performed?	x	
		SMN2 copy number	x	
		Was diagnosis made pre-symptomatically?	x	
	Clinical diagnosis	Age at symptom onset	x	
	Motor function	Sitting without support	x	
		Sitting without support: Age gained	x	
		Crawl on hands and knees	x	
		Crawl on hands and knees:	x	

CRF	CRF Section	CRF Item	at or before Baseline	after Baseline
		Age gained		
		Standing without support	x	
		Standing without support: Age gained	x	
		Walking without support	x	
		Walking without support: Age gained	x	
		Climb stairs	x	
		Climb stairs: Age gained	x	
	Registries, clinical trials	Is the patient currently or was previously included in a clinical trial?	x	
		Name of drug	x	
Medical Assessment		Visit date	x	x
		Age at visit	x	x
	Pulmonary	Does the patient receive ventilator support?	x	x
		Type of ventilation		x
		Time of ventilator use	x	x
		Start of ventilator use	x	x

CRF	CRF Section	CRF Item	at or before Baseline	after Baseline
	Nutrition	Does the patient use a gastric or nasal feeding tube?	x	x
		Start of tube feeding	x	x
		Swallowing?		x
		Chewing?		x
	Orthopedics	Does the patient have scolio-sis?		x
		Orthopedic surgery since last visit		x
	Hospitalisation	Planned hospitalisation since last visit (except for treat-ment administration)?		x
		Admission date		x
		Reason for hospitalisation		x
	Medication	Is the patient on any ap-proved medication for SMA?	X	x
		Name of drug	X	x
		Start date	X	x
		Other medication taken on a regular basis?	x	x

CRF	CRF Section	CRF Item	at or before Baseline	after Baseline
		Name of medication	x	x
		Start date	x	x
	Clinical Trial	Is the patient currently in a clinical trial?	x	x
		Name of drug	x	x
		Start Date	x	x
	Motor function	Any changes in motor milestones?	x	x
		Age gained of best motor function	x	x
		Age loss of previous best motor function	x	x
		Best current motor function	x	x
	HINE	Score	x	x
		Head control	x	x
	Clinical examination	Body weight	x	
		Neurology: Symptoms related to SMA	x	
		Are any contractures present?	x	

CRF	CRF Section	CRF Item	at or before Baseline	after Baseline
		Contractures: Type of limitation	x	
	Neurophysiology (optional)	Ulnar CMAP amplitude	x	
Physiotherapeutic Assessment	HFMSE	Date of Evaluation		x
		Score		x
	RULM	Date of Evaluation		x
		Score		x
	CHOP-INTEND	Date of Evaluation	x	x
		Score	x	x
Zolgensma	Admission day	Date of treatment	x	
Nusinersen		Date of treatment	x	x
		Care setting	x	x
Adverse Events		Date recorded		x
		Has there been any adverse event since the last visit?		x
		Has there been unplanned or prolonged hospitalisation?		x
		Type of unexpected event		x
		MedDRA code of acute event		x

CRF	CRF Section	CRF Item	at or before Baseline	after Baseline
		Admission date		x
		Is the adverse event related to drug treatment?		x
		Name of drug		x
		Any unexpected events with-out hospitalisation?		x
		Type of unexpected event		x
		MedDRA code of acute event		x
		Start date		x
		Is the adverse event related to drug treatment?		x
		Name of drug		x
End of data collection		Date recorded		x
		Is the patient deceased?		x
		Date of death		x

Source: SMArtCARE Case Report Form 2021

IQWiG-Berichte – Nr. 1203

Anwendungsbegleitende Datenerhebung zu Onasemnogen-Abeparvovec: Prüfung des Studienprotokolls und des statistischen Analyseplans

Addendum zum Auftrag A20-61

Addendum

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An dem Addendum beteiligte Mitarbeiterinnen und Mitarbeiter des IQWiG

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- Ralf Bender
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Abkürzungsverzeichnis

Abkürzung	Bedeutung
AbD	Anwendungsbegleitende Datenerhebung
AIC	Akaike Information Criterion
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
EFS	Event-free-survival
G-BA	Gemeinsamer Bundesausschuss
GLM	Generalized linear Model (generalisiertes lineares Modell)
GLMM	Generalized linear mixed Model (generalisiertes lineares gemischtes Modell)
HFMSE	Hammersmith Functional Motor Scale Expanded
HINE	Hammersmith Infant Neurological Examination
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
MedDRA	Medical Dictionary for Regulatory Affairs
OS	Overall survival
PICO	Patient, Intervention, Comparator, Outcome
PT	Preferred Term (bevorzugter Begriff)
pU	pharmazeutischer Unternehmer
RULM	Revised Upper Limb Module
SAP	Statistischer Analyseplan
SOC	System Organ Class (Systemorganklasse)
SGB	Sozialgesetzbuch
SMA	spinale Muskelatrophie
SMN	Survival of Motor Neuron
SUE	schwerwiegendes unerwünschtes Ereignis
UE	unerwünschtes Ereignis
WHO	World Health Organisation

1 Hintergrund

Der Gemeinsame Bundesausschuss (G-BA) hat das Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) am 16.08.2021 mit der Prüfung des Studienprotokolls und des statistischen Analyseplans (SAP) zur anwendungsbegleitenden Datenerhebung (AbD) zu Onasemnogen-Abeparvovec beauftragt.

In seiner Sitzung am 04.02.2021 hat der G-BA beschlossen, eine AbD und Auswertungen nach § 35a Absatz 3b Satz 1 SGB V für den Wirkstoff Onasemnogen-Abeparvovec in der Behandlung der spinalen Muskelatrophie zu fordern [1,2]. Dem Beschluss liegt unter anderem das vom IQWiG erstellte Konzept für eine AbD zu Onasemnogen-Abeparvovec zugrunde (Rapid Report A20-61 vom 01.10.2020 [3]).

Zur Prüfung, ob die Anforderungen des G-BA an die AbD und an Auswertungen durch die vom pharmazeutischen Unternehmer (pU) erstellten Unterlagen zum Studienprotokoll und SAP umgesetzt worden sind, hat der G-BA dem IQWiG diese Unterlagen übermittelt [4,5] und mit der Prüfung dieser Unterlagen beauftragt. Neben dem G-BA-Beschluss zur Onasemnogen-Abeparvovec sollen die Inhalte der diesbezüglichen Beratungen des pU zur Studienplanung der AbD (2021-B-190 [6], 2021-B-122 [7]) berücksichtigt werden.

2 Prüfung der Unterlagen zur Planung der AbD von Onasemnogen-Abeparvovec

2.1 Allgemeine Anmerkungen zu den vom pU vorgelegten Unterlagen

2.1.1 Wesentliche Abweichungen vom Beschluss des G-BA

Die Planung des pU für die AbD weicht in wesentlichen Punkten vom zugrundeliegenden Beschluss des G-BA ab [1]. Der pU ändert die Fragestellung, indem er die relevanten Patientenpopulationen anders definiert als der G-BA. Dabei verzichtet er insbesondere auf die Unterteilung der Patientinnen und Patienten nach dem Symptomstatus (prä-symptomatisch vs. Typ-1-SMA vs. Typ-2-SMA, siehe Abschnitt 2.2.1). Darüber hinaus berücksichtigt er den vorgesehenen Hypothesenshift (verschobene Hypothesengrenzen, siehe Abschnitt 2.3.4) nicht, welcher der erhöhten Unsicherheit des für die Bewertung geplanten nicht randomisierten Studiendesigns Rechnung trägt. Außerdem grenzt er die Nutzung der vorhandenen Daten zu Behandlungsverläufen mit Nusinersen und Onasemnogen-Abeparvovec abweichend vom G-BA ein (siehe Abschnitte 2.1.2 und 2.2.3). Diese Abweichungen werden in den folgenden Abschnitten im Detail beschrieben.

2.1.2 Eingeschränkte Nutzung der verfügbaren Daten zu Behandlungsverläufen mit Nusinersen und Onasemnogen-Abeparvovec

Im vorliegenden Fall einer AbD innerhalb einer seltenen Erkrankung stellt die Erhebung von Daten bei einer ausreichenden Zahl von Patientinnen und Patienten eine Herausforderung dar. Der G-BA trägt diesem Umstand Rechnung, indem er neben zeitlich parallel erhobenen Daten auch zeitlich nicht parallel erhobene Daten innerhalb einer Datenquelle für die AbD vorsieht, wenn diese den definierten Anforderungen an die Datenqualität entsprechen. Darüber hinaus sieht der G-BA explizit vor, neben Daten aus dem primär relevanten SMArtCARE-Register auch solche aus weiteren (internationalen) Registern einzuschließen, wenn diese den Anforderungen der AbD entsprechen. Ziel dieser Festlegungen ist es, in einer vertretbaren Zeit möglichst hohe Fallzahlen in die AbD einzuschließen und so die Umsetzung des Ziels der AbD, die Nutzenbewertung nach § 35a SGB V, zu ermöglichen.

Der pU grenzt den Einschluss von Patientinnen und Patienten in die AbD durch eine Reihe von Entscheidungen ein:

- Für die Datenerhebung ist ausschließlich das SMArtCARE-Register vorgesehen. Der Beschluss des G-BA sieht dagegen potenziell die Zusammenführung vergleichender Daten aus verschiedenen Datenquellen (Registern) vor. In den tragenden Gründen des G-BA wird explizit erläutert, wie Daten aus verschiedenen Registern zusammengeführt werden können [2].
- Aus dem SMArtCARE-Register werden ausschließlich Zentren in Deutschland berücksichtigt. Dieser Schritt schließt laut Studienprotokoll 12 Krankenhäuser aus anderen Ländern (in der Mehrzahl aus Österreich), die Daten in SMArtCARE dokumentieren, aus der AbD aus. Der pU begründet diese Entscheidung mit dem bevorstehenden Neugeborenenscreening in Deutschland und den Qualitätsanforderungen

des G-BA an die Anwendung von Onasemnogen-Abeparvovec, die nur in deutschen Zentren greifen.

- Von den deutschen Zentren in SMArtCARE werden nur solche berücksichtigt, die die Qualitätsanforderungen des G-BA für die Anwendung von Onasemnogen-Abeparvovec erfüllen. Damit fallen laut Studienprotokoll 16 von 34 Krankenhäuser in Deutschland, die Daten im SMArtCARE-Register erheben, aus der Datenerhebung heraus. Insgesamt werden nur Behandlungsverläufe aus 18 deutschen Krankenhäusern für die AbD genutzt (zur Einschränkung der Zentren für die Datenerhebung siehe auch Abschnitt 2.2.3).
- Der pU möchte nur optional auf retrospektiv erhobene Daten zu Behandlungsverläufen mit Nusinersen zurückgreifen. Retrospektiv erhobene Daten zu Behandlungsverläufen mit Onasemnogen-Abeparvovec will der pU gar nicht berücksichtigen. Den Ausschluss der retrospektiven Daten zu Onasemnogen-Abeparvovec begründet der pU mit dem Beschluss des G-BA. Es ist unklar, auf welche Passage des Beschlusses er sich dabei bezieht, da eine solche Einschränkung im Beschluss nicht vorgesehen ist (siehe auch Abschnitt 2.2.2).

Durch diese Entscheidungen schränkt der pU die Fallzahlen für die AbD massiv ein. Dadurch werden belastbare Daten für eine Nutzenbewertung von Onasemnogen-Abeparvovec im Vergleich zu Nusinersen voraussichtlich stark verzögert und ggf. nicht in erforderlichem Umfang vorliegen.

2.1.3 Zeitlicher Verlauf der Erstellung des Studienprotokolls und des SAP

Mit Beschluss vom 04.02.2021 hat der G-BA den pU aufgefordert, zum 15.08.2021 finale Entwürfe des Studienprotokolls und des SAP für die AbD zu Onasemnogen-Abeparvovec vorzulegen. Der pU hat am 23.04.2021 und am 15.06.2021 jeweils eine Beratungsanfrage zum Protokoll und SAP an den G-BA gestellt. Die entsprechenden Beratungsgespräche fanden am 29.06.2021 und am 11.08.2021 statt.

Die vom pU eingereichten Entwürfe des Studienprotokolls und des SAP haben ein Versionsdatum vom 05.08.2021. Der pU berücksichtigt damit die Rückmeldungen des G-BA zu seiner zweiten Beratungsanfrage explizit nicht. Dadurch enthalten das vorgelegte Studienprotokoll und der SAP Planungen, zu denen der G-BA dem pU bereits mitgeteilt hat, dass sie sich nicht mit dem Beschluss des G-BA decken (z. B. zur Einschränkung der in die Datenerhebung einzuschließenden Zentren oder der Definition der Patientenpopulationen).

2.2 Anmerkungen zum Studienprotokoll

2.2.1 Fragestellung gemäß PICO

Die Fragestellung des G-BA für die AbD und die anschließende Auswertung der Daten ist im Beschluss mithilfe des PICO-Schemas niedergelegt. Die folgenden Abschnitte beurteilen die Umsetzung des PICO im Studienprotokoll des pU.

Population

Der G-BA hat in seinem Beschluss zur AbD festgelegt, dass der pU vergleichende Daten zur Behandlung mit Onasemnogen-Abeparvovec bzw. Nusinersen für 3 Patientenpopulationen im Anwendungsgebiet erheben und auswerten soll:

- präsymptomatische Patienten mit 5q-assoziierter SMA mit einer biallelischen Mutation im SMN1-Gen und bis 3 Kopien des SMN2-Gens
- symptomatische Patienten mit 5q-assoziierter SMA mit einer biallelischen Mutation im SMN1-Gen und einer klinisch diagnostizierten Typ-1-SMA
- symptomatische Patienten mit 5q-assoziierter SMA mit einer biallelischen Mutation im SMN1-Gen und einer klinisch diagnostizierten Typ-2-SMA und bis 3 Kopien des SMN2-Gens

Dabei sollen in die Erhebung auch Patienten der genannten Patientenpopulation mit einbezogen werden, die zum Zeitpunkt der Gentherapie mit Onasemnogen-Abeparvovec älter als 6 Monate bzw. 6 Wochen sind.

Der pU weicht von dieser Festlegung des G-BA ab. Dabei macht er in verschiedenen Abschnitten des Studienprotokolls inkonsistente Angaben zu den geplanten Patientenpopulationen für die AbD und die Auswertung zur Bewertung des Zusatznutzens von Onasemnogen-Abeparvovec im Vergleich zu Nusinersen.

Der pU sieht im Protokoll in den Abschnitten zum Studiendesign und den Studienzielen eine Population von Patientinnen und Patienten mit einer biallelischen Mutation im SMN1-Gen und bis 3 Kopien des SMN2-Gens vor, ohne den Symptomstatus zu berücksichtigen. Darüber hinaus plant der pU eine Patientenpopulation ausschließlich mit einer Typ-1-SMA. Der pU begründet diese Abweichung vom Beschluss des G-BA in diesen Abschnitten des Studienprotokolls nicht.

In den Einschlusskriterien der Studie bildet der pU dagegen die Populationsdefinitionen des G-BA ab und beschreibt, wie diese Einschlusskriterien aus dem Datensatz des SMArtCARE-Registers ermittelt werden können. Nach diesen Angaben ist der definierte Einschluss der vom G-BA festgelegten Populationen möglich.

Im Abschnitt zur Analyse der Daten beschreibt der pU 2 Auswertungspopulationen, nämlich eine Population mit einer biallelischen Mutation im SMN1-Gen und bis zu 2 Kopien des SMN2-Gens und eine zweite Population mit einer biallelischen Mutation im SMN1-Gen und 3 Kopien des SMN2-Gens. Er berücksichtigt dabei wiederum abweichend von der Festlegung des G-BA den Symptomstatus nicht. Der pU begründet diese Abweichung damit, dass durch die Einführung des Neugeborenenscreenings ab Oktober 2021 der Stellenwert der Anzahl der SMN2-Kopien im Vergleich zum klinischen Phänotyp zunehme und wegen der unmittelbaren

Behandlung nach Diagnose im Screening symptomatische Patientinnen und Patienten eine untergeordnete Rolle spielen würden.

Die folgende Tabelle gibt eine Übersicht über die Populationsdefinitionen des pU im Studienprotokoll (und SAP).

Tabelle 1: Übersicht der Definitionen von Patientenpopulationen im Studienprotokoll des pU

Abschnitt zum Studiendesign Abschnitt zu Studienzielen	**Einschlusskriterien**	**Abschnitt Auswertungspopulationen**
Therapie-naive Patientinnen und Patienten mit ▪ 5q-assoziierter SMA mit einer biallelischen Mutation des SMN1-Gens und bis zu 3 Kopien des SMN2-Gens sowie ▪ symptomatische Patientinnen und Patienten mit 5q-assoziierter Typ-1-SMA die mit Onasemnogen-Abeparvovec oder Nusinersen behandelt werden	▪ Präsymptomatische Patientinnen und Patienten mit 5q-assoziierter SMA mit einer biallelischen Mutation im SMN1-Gen und bis zu 3 Kopien des SMN2-Gens oder ▪ Symptomatische Patientinnen und Patienten mit 5q-assoziierter SMA mit einer biallelischen Mutation im SMN1-Gens und einer klinische diagnostizierten Type-1-SMA oder ▪ Symptomatische Patientinnen und Patienten mit 5q-assoziierter SMA mit einer biallelischen Mutation des SMN1 Gens und einer klinische diagnostizierten Type-2-SMA und bis zu 3 Kopien des SMN2-Gens	▪ Population A: Patientinnen und Patienten mit 5q-assoziierter SMA mit einer biallelischen Mutation im SMN1-Gens und bis zu 2 Kopien des SMN2-Gens ▪ Population B: Patientinnen und Patienten mit 5q-assoziierter SMA mit einer biallelischen Mutation im SMN1-Gens und 3 Kopien des SMN2-Gens

Insgesamt ist die Populationsbeschreibung im Studienprotokoll inkonsistent. Zwar orientiert sich der geplante Einschluss der Patientinnen und Patienten an den Vorgaben des G-BA, die Definition der Fragestellung und die Planung der Analyse weichen aber ab.

Die Definition der Analysepopulationen (und damit der Populationen, für die in einer Bewertung Aussagen zum Zusatznutzen getroffen werden können) beruht auf der Annahme, dass nach Einführung des Neugeborenenscreenings kurzfristig keine symptomatischen Patientinnen und Patienten mehr behandelt werden. Diese Annahme ist spekulativ. Darüber hinaus berücksichtigt diese Planung nicht, dass auch eine relevante Zahl von Behandlungsverläufen für eine retrospektive Datenerhebung zur Verfügung steht. Diese wurden seit Marktzugang von Onasemnogen-Abeparvovec sogar zeitlich parallel zu Nusinersen durchgeführt.

Insgesamt ist die Abweichung des pU von der Populationsdefinition des G-BA nicht adäquat. Der Symptomstatus trägt in Verbindung mit dem Alter zur klinischen Diagnose bei und hat einen relevanten Einfluss auf das Therapieergebnis. Der pU sieht zwar vor, den Symptomstatus bei Therapiebeginn (symptomatisch / prä-symptomatisch) als Confounder und in einer Subgruppenanalyse zu berücksichtigen. Das erscheint wegen der Relevanz dieses Merkmals

und der Anforderungen des G-BA unzureichend. Eine mögliche Effektmodifikation durch den Symptomstatus kann nicht durch eine Berücksichtigung dieses Faktors als Confounder untersucht werden. Subgruppenanalysen dagegen können dafür geeignet sein. Allerdings plant der pU die Analyse von Subgruppen (für Time-to-Event-Endpunkte) nur dann, falls eine statistisch signifikante Interaktion zwischen Behandlung und Subgruppenfaktor besteht. Bei den zu erwartenden geringen Fallzahlen wird die Power für eine statistisch signifikante Interaktion jedoch sehr gering sein. Es sollte entsprechend der Vorgaben des G-BA die Definition der Populationen und die Auswertung der Daten getrennt für prä-symptomatische und symptomatische Patientinnen und Patienten erfolgen.

Intervention und Komparator

Der pU schließt Patientinnen und Patienten, die mit Onasemnogen-Abeparvovec oder Nusinersen gemäß Zulassung behandelt wurden, in die Datenerhebung ein. Dieses Vorgehen ist adäquat.

Endpunkte (Outcomes)

Der pU berücksichtigt die vom G-BA festgelegten Endpunkte wie folgt:

Mortalität und respiratorische Funktion

Der pU plant neben der Mortalität auch die Auswertung eines kombinierten Endpunkts aus Todesfällen und dauerhafter Beatmung. Dieser kombinierte Endpunkt ist in der vorliegenden Indikation adäquat, die Operationalisierung ist sachgerecht. Darüber hinaus sollen auch vergleichende Effekte für die respiratorische Funktion allein charakterisiert werden. Das entspricht den Vorgaben des G-BA. Die vorgesehenen Operationalisierungen sind in der Mehrzahl sachgerecht.

Für den Endpunkt Verbesserung der Notwendigkeit der Beatmung (Improvement in time of ventilator support from baseline) bleibt unklar, wie die zu messenden Verbesserungen in Relation zum Beatmungsstatus zu Studienbeginn (der pU nimmt an, primär prä-symptomatische Patientinnen und Patienten einzuschließen) bzw. mit einer zunächst ggf. erfolgenden Verschlechterung abgebildet werden sollen.

Erreichen motorischer Meilensteine und motorische Funktion

Der pU plant, das Erreichen der Kopfkontrolle (gemessen mit dem HINE) sowie eine Auswahl der motorischen Meilensteine der WHO (sitzen ohne Unterstützung, [Krabbeln], stehen ohne Unterstützung und gehen ohne Unterstützung) zu erfassen. Darüber hinaus plant er, die motorische Funktion mit verschiedenen Instrumenten zu erheben (HFMSE, RULM, CHOP-INTEND, HINE). Diese Planung gewährleistet eine umfassende Charakterisierung der motorischen Entwicklung der Patientinnen und Patienten.

Die folgenden beiden Tabellen fassen die geplanten Endpunkte zur motorischen Entwicklung zusammen. Bezüglich der motorischen Meilenstein bleibt unklar, warum einer der Meilensteine (Krabbeln) nur zum Zeitpunkt des Alters, in dem gesunde Kinder diesen Meilenstein erreichen,

erhoben wird. Bezüglich des Anteil der Patientinnen und Patienten, die ohne Unterstützung sitzen können, erscheint der Zeitpunkt der Erhebung mit 18 Monaten spät. Darüber hinaus erscheint der Erhebung der motorischen Funktion dahin gehend sachgerecht, dass sie das Erreichen der Meilensteine sowie den Erhalt der motorischen Funktion untersucht.

Tabelle 2: Geplante Endpunkte zu motorischen Meilensteinen

Meilenstein	**Anteil der Patientinnen und Patienten, die den Meilenstein zum angegebenen Zeitpunkt erreichen**				**Zeit bis zum ersten Erreichen des Meilensteins**	**Zeit vom ersten Erreichen bis zum Verlust des Meilensteins**
	Monat 8	**Monat 18**	**Monat 24**	**Alter gesunder Kinder**		
Kopfkontrolle	X		X			
Sitzen ohne Unterstützung		X	X	X (9,2 Monate)	X	X
Krabbeln				X (13,5 Monate)		
Stehen ohne Unterstützung			X	X (16,9 Monate)	X	X
Gehen ohne Unterstützung			X	X (17,6 Monate)	X	X

Tabelle 3: Geplante Endpunkte zu Instrumenten zur Erhebung der motorischen Funktion

Instrument	**Erhebungszeitpunkt**
HFMSE	Score im Alter von 36 Monaten
RULM	Score im Alter von 36 Monaten
CHOP-INTEND	Änderung des Scores vom Zeitpunkt der ersten Behandlung bis Monat 6 und 12 nach erster Behandlung
HINE	Änderung des Scores vom Zeitpunkt der ersten Behandlung bis Monat 12 und 24 nach erster Behandlung

Problematisch für eine Bewertung des Zusatznutzens ist die Vielzahl der Endpunkte zur Beschreibung der motorischen Funktion. Diese Multiplizität sollte verringert werden, indem die relevanten Endpunkte selektiert und die Endpunkte insgesamt hierarchisiert werden. Diese Entscheidungen müssen im Studienprotokoll prä-spezifiziert werden.

Der pU nimmt eine gewisse Hierarchisierung vor, indem er die Endpunkte zur Zeit bis zum Auftreten der Meilensteine als explorativ bezeichnet. Die nachgeordnete Betrachtung dieser Endpunkte ist nicht sinnvoll, weil diese Auswertung den gesamten Beobachtungszeitraum abdeckt, der gemäß Beschluss des G-BA 60 Monate betragen soll, während die anderen Endpunkte auf einen Zeitraum von bis zu 24 oder 36 Monate begrenzt sind. Darüber hinaus gehen für die Time-to-Event-Endpunkte alle Patientinnen und Patienten in die Auswertung ein, während für die Endpunkte zu den Anteilen der Patientinnen und Patienten, die den Meilenstein zu einem bestimmten Zeitpunkt erreichen, nur solche relevant sind, die dieses Alter erreicht haben.

Bulbäre Funktion (Schluck- und Sprachfähigkeit, Notwendigkeit nicht oraler Ernährungsunterstützung)

Die bulbäre Funktion bildet der pU Schwierigkeiten beim Schlucken und Kauen und durch die Erhebung nicht oraler Ernährungsunterstützung ab. Von den vom G-BA festgelegten Endpunkten fehlt die Sprachfähigkeit. Bezüglich der Auswertung erscheinen aus den gleichen Gründen, wie bei der motorischen Funktion beschrieben, Zeit-bis-zum-Ereignis-Endpunkte sinnvoller als die Auswertungen zu fixen Zeitpunkten, die vom pU vorgesehen sind.

Weitere Komplikationen der Erkrankung

Der pU plant als Komplikationen der Erkrankung ausschließlich die Erhebung und Auswertung von orthopädischen Komplikationen der Erkrankung (Skoliose und orthopädische Operationen). Er begründet nicht, warum weitere Komplikationen (z. B. Schmerz) nicht zumindest für ältere Patientinnen und Patienten berücksichtigt werden.

Nebenwirkungen (Schwerwiegende unerwünschte Ereignisse [SUE], unerwünschte Ereignisse [UE], die zu Hospitalisierungen führen, spezifische SUE [Hepatotoxizität, Thrombozytopenie, Kardiale Ereignisse, Entzündung der Spinalganglionzellen, renale Toxizität, Hydrocephalus])

Die Planung des pU zur Erhebung von UE weicht von den Festlegungen des G-BA ab. Der pU greift ausschließlich den Endpunkt „UE, die zu Hospitalisierungen führen“ auf und berücksichtigt die SUE und die spezifischen UE nicht.

Der pU begründet den Verzicht auf die Erhebung der spezifischen UE, die aus den jeweiligen Risk-Management-Plänen der EMA für Nusinersen und Onasemnogen-Abeparvovec stammen, damit, dass für diese UE aktuell keine klinisch relevanten Grenzwerte definiert seien. Eine Ergänzung der Datenerhebung sei nach Festlegung dieser Grenzwerte geplant. Diese Verzögerung der Definition von Grenzwerten ist nicht sachgerecht, die Definition der zu erhebenden Daten sollte vor Studienbeginn abgeschlossen sein. Das Fehlen der Erhebung von SUE wird nicht begründet.

Ergänzend ist anzumerken, das auf die Auswertungen von „related“ UE verzichtet werden kann, weil diese Angabe zum Zusammenhang mit der Medikation in der Regel nicht überprüft werden kann. Darüber hinaus ist unklar, warum eine Berichterstattung MedDRA-kodierter Ereignisse nur erfolgen soll, wenn diese bereits im Register dokumentiert sei. Eine MedDRA-Kodierung kann auf Basis des dokumentierten Freitextes eines UE auch nachträglich vorgenommen werden und ist für eine sinnvolle Auswertung zwingend notwendig.

Über die Festlegungen des G-BA hinaus plant der pU folgenden Endpunkt:

Geplante Hospitalisierungen

Der pU ergänzt die vom G-BA festgelegten Endpunkte um einen Endpunkt zu geplanten Hospitalisierungen. Es bleibt unklar, in welchem Zusammenhang diese geplanten Hospitalisierungen mit der durch die SMA verursachte Morbidität stehen und wie sie von den

bereits erhobenen Endpunkten (z. B. zu orthopädischen Operationen) abgegrenzt werden können. Ebenfalls unklar bleibt die Handhabung von Hospitalisierungen zur Medikamentengabe.

2.2.2 Studiendesign

Prospektive / retrospektive Datenerhebung

Bei der AbD handelt es sich um eine vergleichende Studie ohne Randomisierung. Für das Studiendesign sind u. a. die folgenden 2 Fragen relevant:

1) Soll die Studie prospektiv, retrospektiv oder als Kombination von prospektiver und retrospektiver Datenerhebung durchgeführt werden?
2) Sollen im Fall einer retrospektiven Datenerhebung in der Studie ausschließlich zeitlich parallel dokumentierte Daten für die beiden Interventionen berücksichtigt werden oder sollen auch zeitlich nicht parallel dokumentierte Daten genutzt werden?

Der Abschnitt zum Studiendesign im Studienprotokoll des pU klärt diese Fragen nicht.

Zur Frage der prospektiven oder retrospektiven Datenerhebung beschreibt der pU an anderer Stelle im Protokoll im Zusammenhang mit den Ein-/Ausschlusskriterien der Studie, dass er historische Daten (definiert als Daten, die vor dem Beginn der Studie für die AbD dokumentiert wurden, d. h. retrospektiv zu erhebende Daten) ausschließlich für Nusinersen heranziehen will und zwar nur dann, wenn die notwendige Fallzahl nicht allein durch eine prospektive Datenerhebung erreicht werden kann. Er begründet dabei den Ausschluss von retrospektiven Daten zu Onasemnogen-Abeparvovec mit dem Beschluss des G-BA.

Diese Planung ist nicht sachgerecht. Die Nutzung retrospektiv erhobener Daten abhängig von der zukünftigen Rekrutierung von Patientinnen und Patienten ist insbesondere vor dem Hintergrund der Ausführungen des pU zu der erwarteten Rekrutierung unverständlich. Der pU begründet die nur optionale Nutzung von retrospektiven Daten zu Nusinersen mit potenziell geänderten Therapiestandards im Zeitverlauf. Er beschreibt aber nicht, ob und ggf. ab welchem Zeitpunkt solche Änderungen stattgefunden haben und welcher Zeitraum ggf. doch retrospektiv genutzt werden könnte (z. B. mindestens die Daten ab Verfügbarkeit von Onasemnogen-Abeparvovec [zeitlich parallel erhobene Daten]). Gänzlich unverständlich bleibt der Ausschluss der retrospektiven Datenerhebung für Onasemnogen-Abeparvovec. Es ist unklar, aus welchem Abschnitt des Beschlusses des G-BA der pU eine solche Einschränkung ableitet. Ein Ausschluss von retrospektiv zu erhebenden Daten zu Onasemnogen-Abeparvovec bedeutet, dass die zwischen Marktzugang (07/2020) und Beginn der AbD (laut Studienprotokoll: 01/2022) dokumentierten Behandlungsverläufe nicht für die AbD berücksichtigt werden. Diese Behandlungen erfolgten sogar zeitlich parallel mit solchen mit Nusinersen. Dieses Vorgehen ist bei der begrenzten Zahl von Patientinnen und Patienten mit der hier vorliegenden seltenen Erkrankung nicht sachgerecht.

Zur Frage der Nutzung zeitlich nicht parallel erhobener Daten, also solcher Daten zu Nusinersen, die vor Verfügbarkeit von Onasemnogen-Abeparvovec dokumentiert wurden, gibt es im Studienprotokoll keine Angaben. Der pU äußert sich damit nicht zu der vom G-BA eröffneten Option der Nutzung zeitlich nicht parallel erhobener Daten.

Auswahl von Confoundern

Bei einer vergleichenden Studie ohne Randomisierung müssen während der Studienplanung die relevanten Confounder prä-spezifiziert werden. Dieser Schritt ist notwendig, um nach der Datenerhebung in der Analyse durch (prä-spezifizierte) Adjustierung für diese Confounder eine Annäherung an die Strukturgleichheit der Behandlungsgruppen zu erreichen.

Das Vorgehen des pU zur Identifizierung der Confounder durch eine systematische Literaturrecherche und die Einbindung von Expertinnen und Experten ist grundsätzlich sachgerecht. Eine Beurteilung der systematischen Recherche nach Leitlinien und systematischen Reviews / Metaanalysen befindet sich in Anhang A.

Die Liste der Confounder spiegelt allerdings die vom G-BA abweichenden Entscheidungen des pU zu den Patientenpopulationen für die Auswertung und damit für die Nutzenbewertung wider. Diese sollten korrigiert werden und die Auswirkungen dieser Korrektur auf die Liste der Confounder sollte berücksichtigt werden.

So benennt der pU den Symptomstatus zu Studienbeginn als Confounder anstatt in der Fragestellung, wie im Beschluss des G-BA vorgesehen, die Patientenpopulation nach Symptomstatus aufzuteilen. Auf der anderen Seite berücksichtigt er den Confounder „Region“ nicht, weil er u. a. alle Zentren außerhalb von Deutschland aus der Datenerhebung ausschließt, weil sie nicht die Qualitätsanforderungen des G-BA umsetzen. Wie in den Abschnitten 2.1.1 und 2.2.3 beschrieben, sind diese Einschränkungen fraglich. Im Fall einer Korrektur dieser Entscheidungen sollte die Region als Confounder adäquat berücksichtigt werden.

Eine hinreichende Prä-Spezifikation des Vorgehens zur Adjustierung für die Confounder in der Analyse fehlt, die Planung ist damit unzureichend (siehe Abschnitt 2.3.2).

2.2.3 Datenquelle

Der pU wählt das SMArtCARE Register als Datenquelle für die AbD. Das Register ist für die AbD geeignet, da es die notwendigen Qualitätskriterien erfüllt [3], und wurde vom G-BA als primär relevantes Register benannt [1]. Der G-BA weist darüber hinaus auf die Einbindung weiterer Register hin, sofern diese die notwendigen Anforderungen erfüllen.

Der pU nutzt die Möglichkeit der Einbindung weiterer Register nicht. Er beschreibt im Studienprotokoll, dass der Beschluss des G-BA die Datenerhebung innerhalb einer Datenquelle vorsehe. Hier scheint eine Fehlinterpretation des G-BA Beschlusses vorzuliegen. Es ist richtig, dass in den Unterlagen des G-BA beschrieben wird, dass der Vergleich von Onasemnogen-Abeparvovec und Nusinersen mittels paralleler Kontrolle (jeweils) innerhalb einer Datenquelle

durchgeführt werden soll. Diese Angaben beziehen sich jedoch auf das grundsätzliche Studiendesign, nicht auf die ausschließliche Nutzung eines einzigen Registers als Datenquelle. Auf die Möglichkeit der Zusammenführung mehrerer Quellen mittels Metaanalyse wird im Beschluss des G-BA explizit hingewiesen [1,3].

Ein weiteres Register, das potenziell Datensätze für die AbD beitragen könnte, ist das vom pU als Zulassungsauflage selbst geführte RESTORE-Register. Das Register erfüllte zum Zeitpunkt der Konzepterstellung die Anforderungen für eine AbD nicht [3], könnte mit entsprechenden Anpassungen eine weitere geeignete Datenquelle sein. Entsprechende Anpassungen des Registers wären für den pU als Registerverantwortlichem möglich. Der pU hat im Fachgespräch zur Diskussion des IQWiG-Konzepts zur AbD selbst ausgeführt: „Im Prinzip ist es natürlich möglich, aufgrund eines Konzeptes entsprechende Anpassungen oder Planung für RESTORE vorzunehmen, die das aufgreifen, was an wichtiger Diskussion heute besprochen wird.“[8]. Der pU sollte daher die notwendigen Anpassungen vornehmen (insbesondere Harmonisierung der Erhebungszeitpunkte mit SMArtCARE-Vorgaben, Schulung der teilnehmenden Zentren, gleiche Anstrengungen für den Einschluss von Nusinersen-Patienten).

Der pU plant außerdem, nicht die Gesamtheit des SMArtCARE-Registers zu nutzen. Es beschränkt die Zentren, deren Daten er nutzen möchte, vielmehr in zwei Schritten 1) auf deutsche Zentren und 2) innerhalb von Deutschland auf die Zentren, die die Qualitäts-anforderungen des G-BA zur Anwendung von Onasemnogen-Abeparvovec erfüllen. Er begründet diese Planung mit dem Neugeborenenscreening auf SMA, das in Deutschland im Oktober 2021 beginnt, in anderen Ländern aber noch nicht durchgeführt werde. Außerdem befürchtet der pU eine Verzerrung durch unterschiedliche Qualitätsstandards und möchte insbesondere Zentren, die nicht beide Interventionen einsetzen, nicht berücksichtigen.

Der Ausschluss von Zentren außerhalb Deutschlands ist nicht sachgerecht. Studien mit Patientinnen und Patienten mit seltenen Erkrankungen sollten wo immer möglich international durchgeführt werden, um auch bei kleinen Fallzahlen zu zeitgerechten und belastbaren Ergebnissen zu kommen. Das Neugeborenenscreening steht dem Einschluss von Zentren außerhalb Deutschlands nicht entgegen. Der G-BA sieht explizit die Untersuchung von symptomatischen Patientinnen und Patienten vor. Hier könnten insbesondere Zentren außerhalb Deutschlands auch prospektiv relevante Informationen liefern.

Es ist richtig, dass potenzielle Unterschiede der Qualitätsstandards bzw. der Unterschiede in der Versorgung zu berücksichtigen sind. Allerdings sollte die Entscheidung, ob ein Zentrum eingeschlossen wird oder nicht, von der tatsächlich in diesem Zentrum umgesetzten Qualität bzw. Versorgung abhängen. Deshalb könnten auch (internationale) Zentren, die nicht an die Qualitätsanforderungen des G-BA gebunden sind, potenziell eingeschlossen werden. Der Qualitätsstandard wäre jeweils zu überprüfen. In der Anhörung zur Bewertung von Nusinersen wurde diskutiert, dass insbesondere Daten aus an SMA-Studien teilnehmenden internationalen Studienzentren vermutlich verwendet werden könnten [9].

Die Überlegung, Zentren, die nicht beide Interventionen einsetzen, auszuschließen, ist aus methodischen Gründen grundsätzlich nachvollziehbar. Im vorliegenden Fall einer Datenerhebung für eine seltene Erkrankung sollten Daten aus solchen Zentren zunächst jedoch in der Auswertung berücksichtigt werden. Der möglich Einfluss dieser Zentren auf die Ergebnisse sollte zusätzlich in Sensitivitätsanalysen untersucht werden (siehe Abschnitt 2.3.3).

Insgesamt sind die Einschränkungen des pU bezüglich der Datenquellen für die AbD kritisch, da sie die Anzahl der Patientinnen und Patienten, die in die AbD eingeschlossen werden, relevant verringern und so eine zeitgerechte und aussagekräftige Datenerhebung erschweren.

2.2.4 Auswertung der Datenerhebung

Die Angaben zur Auswertung der Datenerhebung im Studienprotokoll werden im Zusammenhang mit den Anmerkungen zum SAP kommentiert.

2.3 Anmerkungen zum SAP

Der pU erfüllt die vom G-BA im Beschluss zur AbD definierten Anforderungen an die Planung der Auswertung der Daten nicht. Die Planung ist teilweise unklar und nicht detailliert genug beschrieben bzw. nicht geeignet. Ein Teil der Anforderungen wird nicht adressiert.

2.3.1 Fallzahlplanung

Der pU beschreibt im Studienprotokoll und im SAP eine detaillierte Fallzahlplanung für die beiden vom pU festgelegten Studienpopulationen A (alle Patientinnen und Patienten mit 5q assoziierter SMA mit einer biallelischen Mutation im SMN1-Gen und bis zu 2 Kopien des SMN2-Gens) und B (alle Patientinnen und Patienten mit 5q assoziierter SMA mit einer biallelischen Mutation im SMN1-Gen und 3 Kopien des SMN2-Gens). Diese Populationen weichen von der Fragestellung des G-BA ab (siehe Abschnitt 2.2.1).

Für die unterschiedenen Endpunkte (OS, EFS, Sitzen ohne Unterstützung zu Monat 18) und die variierten Annahmen (Assoziation zwischen den Faktoren Behandlung und Confounder, Verhältnis der Behandlungsgruppengrößen) werden die benötigten Fallzahlen für eine Power von 90% präsentiert. Die Fallzahlen variieren für beide Studienpopulationen deutlich (für A zwischen 48 und 820, für B zwischen 155 und 10 820). Auf der anderen Seite wird im Studienprotokoll unter 8.3 (Expected Patient Numbers) beschrieben, dass für das SMArtCARE-Register 138 (für A) und 98 (für B) geeignete Kinder zu erwarten sind und wegen des Studiendesigns alle geeigneten Kinder in die Studie eingeschlossen werden. Vor diesem Hintergrund erscheint die vorgelegte Fallzahlplanung wenig hilfreich.

Gemäß Abschnitt 6 des SAP (Planned Analysis) soll nach 18 und 36 Monaten nach Studienbeginn eine Rekalkulation der Fallzahlplanung erfolgen. Durch die Analyse nach 36 Monaten soll entschieden werden, ob der Einschluss von zunächst nur prospektiven Fällen um retrospektive Fälle erweitert wird oder ob die Studie wegen zu geringer Fallzahl sogar vorzeitig beendet wird. Es wird hier immer von „the Sample Size“ gesprochen. Es ist allerdings nicht

klar, welche Fallzahl genau herangezogen wird, da diese von diversen Faktoren (siehe oben) abhängt. Insgesamt verbleibt es unklar, wie die Rekalkulation der Fallzahlplanung im Detail ablaufen soll. Insbesondere durch die Bedeutung der 36-Monats-Analyse ist eine deutlich detailliertere Beschreibung dieser Analysen im SAP angezeigt.

Unter den Annahmen für die Fallzahlplanung wird beschrieben, dass das Maß R^2 zur Beschreibung der Assoziation zwischen den Faktoren Behandlung und Baselineconfounder verwendet wird. Es ist unklar, wie dieses Maß R^2 genau definiert ist und auf welche Analyse es sich bezieht. Vermutlich bezieht es sich auf die logistische Regression zur Berechnung der Propensity-Scores und dient als Goodness-of-Fit-Maß. Die genaue Verwendung dieses Maßes und dessen genaue Definition sollte ergänzt werden. In der Statistik sind bei binären Daten die C-Statistik (Fläche unter der ROC-Kurve [10]) und das AIC (Akaike Information Criterion) allerdings geläufiger und können alternativ in Betracht gezogen werden.

Für seine Population „2 SMN-2-Kopien“ verweist der pU auf einen unpublizierten Vergleich zwischen Onasemnogen-Abeparvovec und Nusinersen, den er für die Fallzahlplanung der AbD durchgeführt habe. Dieser beruht nach Angaben des pU auf einem Vergleich einzelner Studienarme aus den Studien START und STR1VE-US zu Onasemnogen-Abeparvovec mit Studienarmen „der SHINE-Studien“. Eine Darstellung dieses unpublizierten indirekten Vergleichs z. B. im Anhang des Studienprotokolls oder als Anlage zum Studienprotokoll fehlt. Die resultierenden Effekte sind daher nicht überprüfbar. Darüber hinaus zeigt die Dossierbewertung A21-68 zu Onasemnogen-Abeparvovec [11], dass

- weitere Daten zu Onasemnogen-Abeparvovec vorliegen (Studie STR1VE-EU) und
- die vom pU herangezogen Studien zu den beiden Wirkstoffen nicht ausreichend ähnlich sind. Grund hierfür sind zum einen unterschiedliche Ausschlusskriterien (Ausschluss beatmeter Kinder aus den Onasemnogen-Studien) sowie deutliche Unterschiede bezüglich der Krankheitsdauer bei Studieneinschluss.

Die vom pU in seinem unpublizierten Vergleich ermittelten Effekte sind daher potenziell nicht durch die von ihm herangezogenen Daten sachgerecht begründet und ggf. deutlich überschätzt.

Der pU berücksichtigt bei der Fallzahlplanung die verschobenen Hypothesengrenzen für die Beurteilung der Effekte nicht (siehe Abschnitt 2.3.4) [1,3]. Das ist nicht sachgerecht.

2.3.2 Confounderadjustierung

Die adäquat prä-spezifizierte Adjustierung für Confounder ist für die Auswertung von vergleichenden Studien ohne Randomisierung von besonderer Bedeutung. Die Angaben des pU zur Confounderadjustierung in Protokoll und SAP stellen keine adäquate Prä-Spezifikation dar und sind nicht sachgerecht.

Im Zusammenhang mit der Confounderadjustierung definiert der pU 3 „Behandlungsgruppen“ (Seite 42 des SAP):

1) Patienten, die ausschließlich mit Onasemnogen-Abeparvovec behandelt wurden
2) Patienten, die ausschließlich mit Nusinersen behandelt wurden
3) Patienten, die mit Nusinersen behandelt wurden und zu Onasemnogen-Abeparvovec gewechselt haben

Diese Gruppen stellen keine adäquate Aufteilung der Patienten in auswertbare Gruppen dar. Eine adäquate Aufteilung der Patienten muss durch Informationen erfolgen, die zu Studienbeginn vorliegen. Es darf hierzu keine Information verwendet werden, die erst im Studienverlauf vorliegt und somit bereits ein Effekt der Behandlung sein kann (wie z. B das Fehlen oder Auftreten eines Behandlungswechsels).

Der pU gibt an, die Confounderadjustierung zunächst auf Basis einer Propensity-Score-Analyse vornehmen zu wollen. Es bleibt unklar, auf welcher Patienteneinteilung letztlich die Propensity-Score-Analyse beruht. Die Darstellung auf Seite 42 des SAP legt nahe, dass hierzu die obigen Gruppen 1 und 2 verwendet werden sollen und die Patienten aus Gruppe 3 sowohl in Gruppe 1 und Gruppe 2 zugeteilt werden. Dieses Vorgehen wäre in zweifacher Hinsicht inadäquat. Zum einen wird Information verwendet, die erst im Studienverlauf vorliegt und zum anderen werden die Patienten aus Gruppe 3 doppelt verwendet. Das genaue Vorgehen bleibt jedoch unklar. Aber bereits aufgrund der Verwendung von Information, die erst im Studienverlauf vorliegt, ist eine hierauf basierende Propensity-Score-Analyse nicht valide.

Es wird zudem im SAP nicht beschrieben, wie die Güte der Propensity-Score-Analyse überprüft werden soll. Nach dem Rapid Report A19-43 [12] muss eine ausreichende Überlappung und eine ausreichende Balanciertheit der zu vergleichenden Gruppen erreicht worden sein. Es wird zwar angegeben, dass grafische Methoden sowie Permutationstests angewendet werden sollen (Seiten 42-43), weitere wichtige Details hierzu fehlen jedoch. Insbesondere fehlen konkrete Kriterien, was unter einer ausreichenden Überlappung und einer ausreichende Balanciertheit der zu vergleichenden Gruppen verstanden wird.

Ein schwerwiegender Mangel ist der im SAP beschriebene Plan, bei einer nicht ausreichenden Balanciertheit der zu vergleichenden Gruppen nach Anwendung des Propensity Score, ersatzweise ein Regressionsmodell zu verwenden (je nach Messniveau der Zielvariable ein Frailty-Modell bzw. ein generalisiertes lineares gemischtes Modell [GLMM]). Eine nicht ausreichende Überlappung der zu vergleichenden Gruppen kann auch nicht durch die Anwendung eines Regressionsmodells behoben werden. Es ist zwar (außer bei einer völligen Separierung der beiden Gruppen) rein rechnerisch eine Regression durchführbar, das heißt aber nicht, dass die entsprechenden Ergebnisse auch sinnvoll interpretierbar sind. Bei einer nicht ausreichenden Überlappung der zu vergleichenden Gruppen würde ein Regressionsmodell mit

Extrapolationen arbeiten, die nicht valide sind, da Zusammenhänge auf Bereiche übertragen werden, in denen gar keine Beobachtungen vorliegen [13].

Es wird lediglich ein einziges Verfahren für die Anwendung des Propensity Score beschrieben (Fine Stratification), obwohl es hierfür zahlreiche andere Methoden gibt [14,15]. Die übliche Vorgehensweise wäre, ein Verfahren zur Anwendung des Propensity Score zu wählen, sodass eine ausreichende Überlappung und eine ausreichende Balanciertheit der zu vergleichenden Gruppen erreicht wird. Die Beschreibung eines Entscheidungsalgorithmus zur Anpassung der Propensity-Score-Analyse bei fehlender Überlappung und Balanciertheit nach Anwendung des ersten Verfahrens fehlt im SAP. Ebenso fehlt die korrekte Konsequenz daraus, wenn kein Propensity-Score-Verfahren gefunden werden kann, mit dem eine ausreichende Überlappung und eine ausreichende Balanciertheit der zu vergleichenden Gruppen erreicht werden kann. In einem solchen Fall ist der Versuch einer Effektschätzung weder mithilfe von Propensity Scores noch mithilfe von Regressionsmodellen sinnvoll und die untersuchte Fragestellung muss überdacht werden [14].

2.3.3 Analyse der Endpunkte

Im SAP werden in Abhängigkeit des Messniveaus der zu analysierenden Endpunkte (Time-to-Event, binär, stetig, Zähldaten) die Verfahren Cox-Modell mit zeitabhängigen Kovariablen und generalisierte lineare Modelle (GLMs) mit verschiedenen Link-Funktionen genannt, wobei jeweils die Behandlung als fester, zeitabhängiger Effekt behandelt werden soll. Falls keine Confounder-Adjustierung mithilfe der Fine-Stratification-Methode über den Propensity Score vorgenommen wird, sollen stattdessen Frailty-Modelle sowie GLMMs verwendet werden, in denen zusätzlich zum Behandlungseffekt jeweils das Zentrum als zufälliger Effekt und alle Confounder als feste Effekte modelliert werden.

Die genannten übergreifenden Modellklassen in Abhängigkeit des Messniveaus der zu analysierenden Endpunkte sind zwar angemessen, dennoch gibt es bei diesen Modellbeschreibungen inadäquate Teilaspekte sowie Unklarheiten in den Details der Modellierung, sodass die Darstellung der Modelle, mit denen letztlich der Behandlungseffekt geschätzt werden soll, insgesamt unzureichend ist. Wie in Abschnitt 2.3.2 dargestellt, ist es nicht adäquat, ersatzweise ein Regressionsmodell zu verwenden, wenn die Propensity-Score-Analyse nicht zu einer ausreichenden Überlappung und Balanciertheit führt. Wie in Abschnitt 2.3.7 dargestellt, führt außerdem die Modellierung der Behandlung als zeitabhängiger Effekt nicht zu einer validen Effektschätzung.

Des Weiteren ist die Verwendung des Zentrums als zufälliger Effekt in der Modellierung zu hinterfragen. In Anbetracht des begrenzten Stichprobenumfangs sollte hier eher die Annahme getroffen werden, dass das Zentrum keinen relevanten Einfluss hat. Nach der Berücksichtigung von Zentren, die nur eine Intervention einsetzten, ist zudem die Annahme einer zufälligen Verteilung über alle Zentren hinweg nicht plausibel. Daher sollte in die Analyse das Zentrum weder als zufälliger noch als fester Effekt eingehen. In Sensitivitätsanalysen sollte anschließend

ein möglicher Zentrumseffekt untersucht werden, z. B. durch Weglassen der Zentren, die ausschließlich Nusinersen einsetzen, sowie deskriptive Auswertungen innerhalb von Zentren.

Darüber hinaus wird nicht beschrieben, in welcher Form die Confounder als feste Effekte in das jeweilige Endpunkt-Modell eingehen sollen. Gehen die stetigen Confounder in ihrer ursprünglichen Einheit in das Modell ein oder sollen sie vorher transformiert werden? Wird angenommen, dass es überall lineare Zusammenhänge zwischen den Confoundern und dem jeweiligen Endpunkt gibt, oder ist die Betrachtung nicht linearer Zusammenhänge geplant? Ist die Untersuchung von Wechselwirkungen geplant? Diese Modellierungsaspekte sind in einem SAP im Detail zu beschreiben, sodass es eindeutig ist, in welcher Form die Endpunkte zur finalen Effektschätzung analysiert werden. Da diese Angaben fehlen, ist der SAP unvollständig.

Der G-BA sieht in seinem Beschluss vor, dass ggf. neben zeitlich parallel erhobenen Daten auch zeitlich nicht parallel erhobene Daten berücksichtigt werden sollen und fordert, dass beschrieben wird, wie überprüft werden soll, ob solche Daten für gepoolte Analysen herangezogen werden können. Der pU behandelt diese Fragestellung in seinem Protokoll und SAP nicht. Ebenso enthalten Protokoll und SAP keine Angaben zu möglichen gepoolten Analysen aus unterschiedlichen Datenquellen, da der pU die Datenerhebung ausschließlich in einem Teil der Zentren des SMArtCARE-Registers durchführen möchte (siehe Abschnitt 2.2.3).

2.3.4 Berücksichtigung verschobener Hypothesengrenzen

Aus einer nicht randomisierten Studie kann aufgrund potenziell unbekannter Confounder aus den in der Studie beobachteten Effekten erst ab einer bestimmten Effektstärke eine Aussage zum Nutzen oder Schaden einer Intervention abgeleitet werden. Eine (positive oder negative) Aussage zum Nutzen oder Schaden ergibt sich dann, wenn das Konfidenzintervall für den beobachteten Effekt ober- bzw. unterhalb einer zu definierenden Schwelle liegt (Test auf verschobene Nullhypothese). Die konkrete Schwelle ergibt sich durch die Qualität der Daten im Einzelfall, u. a. durch das Wissen über relevante Confounder [3]. Zu dieser Anforderung [1] und deren Implementierung finden sich weder im Studienprotokoll noch in SAP irgendwelche Angaben. Dies sollte ergänzt werden.

2.3.5 Subgruppenanalysen

Im SAP finden sich außer der Auflistung der geplanten Subgruppenfaktoren keine Informationen zur Methodik der Subgruppenanalysen. Lediglich im Studienprotokoll wird die Methodik rudimentär beschrieben. Unter anderem ist geplant, (für Time-to-Event-Endpunkte) Subgruppenanalysen nur bei statistisch signifikanter Interaktion zwischen Behandlung und Subgruppe durchzuführen. Grundsätzlich ist dieser Ansatz methodisch korrekt. Hier muss allerdings die zu erwartende sehr geringe Fallzahl mitberücksichtigt werden. Bei diesen Fallzahlen wird der Interaktionstest keine nennenswerte Power aufweisen. Das hat zur Folge, dass durch diese Anforderung (signifikante Interaktion) vermutlich keine Subgruppenanalysen zu erwarten sind. Das ist insbesondere für den vom pU geplanten Faktor Symptomstatus

relevant, den der pU anstelle der vom G-BA vorgesehenen grundsätzlichen Aufteilung der Patientenpopulation nach Symptomstatus vorsieht. Es steht zu befürchten, dass diese relevante Auswertung getrennt nach prä-symptomatischen und symptomatischen Patientinnen und Patienten nach dieser Methodik gar nicht präsentiert werden. Es wird vorgeschlagen, wegen der zu erwartenden geringen Fallzahlen alle relevanten Subgruppenanalysen ohne die Anforderung einer statistisch signifikanten Interaktion zu rechnen und die entsprechenden Ergebnisse darzustellen.

Der G-BA sieht in seinem Beschluss vor, für die Population der präsymptomatischen Patientinnen und Patienten mit bis zu 3 Kopien des SMN2-Gens Subgruppenanalysen nach Kopienzahl des SMN2-Gens vorzunehmen, um zu überprüfen, ob eine gemeinsame Auswertung sachgerecht ist. Der pU plant jedoch diese Subgruppenanalysen nicht. Er sieht abweichend vom G-BA eine Aufteilung der Population unabhängig vom Symptomstatus anhand der Anzahl der SMN2-Kopien vor (bis zu 2 bzw. 3 Kopien, siehe Abschnitt 2.2.1).

2.3.6 Umgang mit fehlenden Daten

Im SAP finden sich Informationen zum Umgang mit fehlenden Daten. Es wird beschrieben, dass Personen mit fehlenden Daten in den Confoundervariablen aus allen Analysen, die diese Confounder berücksichtigen, ausgeschlossen werden sollen. In Anbetracht der zu erwartenden geringen Fallzahlen erscheint dieses Vorgehen nicht sachgerecht. Es sollte alles unternommen werden, fehlende Informationen zu vermeiden. Verbleibende fehlende Informationen sollten in geeigneter Weise ersetzt werden, um den Verlust an Ergebnissen so gering wie möglich zu halten. Es wird vorgeschlagen, diese fehlenden Werte durch den Ansatz der Multiplen Imputation [16] zu ersetzen.

Im Studienprotokoll und im SAP finden sich keine Informationen dazu, in welchem Umfang und aus welchen Gründen fehlende Daten zu erwarten sind und wie mit unplausiblen Daten und Ausreißern umgegangen werden soll. Diese Informationen sollten im SAP ergänzt werden.

2.3.7 Umgang mit Behandlungswechsel

Der SAP beschreibt die Fragestellung der geplanten Studie als den Vergleich von Onasemnogen-Abeparvovec mit Nusinersen bei therapie-naiven Patientinnen und Patienten mit SMA (5q-assoziierte SMA mit einer biallelischen Mutation im SMN1-Gen und bis zu 3 Kopien des SMN2-Gens sowie symptomatische Patientinnen und Patienten mit SMA Typ 1, zur Problematik der Fragestellung der geplanten Studie siehe Abschnitt 2.2.1). Der pU erwartet einen Behandlungswechsel vor allem von Nusinersen auf Onasemnogen-Abeparvovec und plant deshalb die folgenden 3 „Behandlungsgruppen“:

1) Patienten, die ausschließlich mit Onasemnogen-Abeparvovec behandelt wurden
2) Patienten, die ausschließlich mit Nusinersen behandelt wurden
3) Patienten, die mit Nusinersen behandelt wurden und zu Onasemnogen-Abeparvovec gewechselt haben

Die finale Analyse zur Effektschätzung soll dann auf Basis von Behandlungsepisoden durchgeführt werden und nicht auf Basis von Behandlungsarmen. Hierzu ist die Anwendung des Cox-Modells mit zeitabhängigen Kovariablen geplant, wobei die Behandlung als zeitabhängige Variable berücksichtigt werden soll.

Wie in Abschnitt 2.3.2 dargestellt, ist die obige Aufteilung der Patienten nicht valide. Eine adäquate Aufteilung der Patienten muss durch Informationen erfolgen, die zu Studienbeginn vorliegen. Es darf hierzu keine Information verwendet werden, die erst im Studienverlauf vorliegt und somit bereits ein Effekt der Behandlung sein kann.

Des Weiteren ist das Cox-Modell mit zeitabhängigen Kovariablen keine adäquate Methode zum Umgang mit Behandlungswechseln, da die zeitabhängigen Variablen in diesem Modell nicht durch die Behandlung selbst beeinflusst werden dürfen. Da aber hier die Behandlung selbst die zeitabhängige Variable darstellt, ist diese Annahme trivialerweise verletzt. Ebenso ist bei Behandlungswechseln die Annahme unplausibel, dass der Effekt der zeitabhängigen Variable Behandlung in allen Episoden identisch ist. Es bleibt zudem unklar, wie im finalen Modell damit umgegangen werden soll, dass es nach der Behandlung mit Onasemnogen-Abeparvovec keine Episoden mehr ohne diese Intervention geben kann, da diese Behandlung ja nur einmalig erfolgt und angenommen wird, dass die Wirkungen der Gentherapie andauern. Wie im Arbeitspapier GA14-04 [17] beschrieben, stellt die naive Anwendung des Cox-Modells mit zeitabhängigen Kovariablen in der Regel keine adäquate Methode zum Umgang mit Behandlungswechseln dar.

Das übliche Vorgehen in der pharmakoepidemiologischen Forschung zum Umgang mit Behandlungswechseln stellt das New-User-Design dar, in dem therapienaive Patientinnen und Patienten der Gruppe der jeweiligen Erstbehandlung zugeordnet werden [18]. Analog zum Vorgehen des Intention-to-Treat-Prinzips in randomisierten kontrollierten Studien werden in der Analyse bei der primären Effektschätzung alle nachfolgenden interkurrenten Ereignisse (inklusive Behandlungswechsel) ignoriert. Es wird zunächst auch nicht bei Behandlungswechsel zensiert, da dies eine informative Zensierung darstellt und zu verzerrten Effektschätzungen führen kann. Da bei dem New-User-Design die Randomisierung fehlt, muss hier für Confounding zu Studienbeginn adäquat adjustiert werden, um die Verzerrung durch Confounding so weit wie möglich zu reduzieren. In der Regel werden hierfür Propensity Scores eingesetzt. Es müssen natürlich hierbei die Art und Weise, der Umfang sowie die entsprechenden Zeitpunkte von Behandlungswechseln dargestellt werden, da – analog zum Intention-to-treat-Prinzip – ein hohes Ausmaß von Behandlungswechseln einen relevanten verzerrenden Einfluss auf die Effektschätzung von Onasemnogen-Abeparvovec im Vergleich zu Nusinersen haben kann. Als Sensitivitätsanalyse sollten daher ergänzende Auswertungen mit Zensierungen bei Behandlungswechseln erfolgen, wobei der Zeitpunkt der Zensierung variiert werden sollte, um „Carry-over“-Effekte für die vorherige Behandlung zu berücksichtigen.

Sollte sich herausstellen, dass das Ausmaß von Behandlungswechseln so hoch ist, dass keine valide Effektschätzung von Onasemnogen-Abeparvovec im Vergleich zu Nusinersen mehr möglich erscheint, so ist es mit den verfügbaren Daten nicht möglich, die Ausgangsfrage (Nutzen von Onasemnogen-Abeparvovec im Vergleich zu Nusinersen) zu beantworten. Als Alternative kommt unter Umständen ein Prevalent-New-User-Design infrage [19]. Hiermit wird aber eine andere Fragestellung untersucht, nämlich, z. B. ob Patientinnen und Patienten unter Nusinersen von einem Behandlungswechsel auf Onasemnogen-Abeparvovec profitieren. Ob ein solches Design sinnvoll und möglich ist, muss entschieden werden, wenn Informationen über die Art und Weise, das Ausmaß und die Zeitpunkte von Behandlungswechseln vorliegen.

Um eine höhere Zahl von Behandlungswechseln ggf. adäquat berücksichtigen zu können, sollten Angaben zur Anzahl von Patientinnen und Patienten, die die Behandlung wechseln einschließlich der jeweils vorliegenden Zeiten unter den verschiedenen Behandlungen, Bestandteil der Angaben zum Verlauf der Datenerhebung sein, die regelmäßig dem G-BA vorgelegt werden. Abhängig vom Anteil von Behandlungswechslern kann die Studienplanung ggf. über Protokollamendments angepasst werden.

2.3.8 Geplante Analysen

Der pU beschreibt in Studienprotokoll und SAP 4 deskriptive Analysen, eine Interimsanalyse und eine finale Analyse. Die geplanten Zeitpunkte der Analysen weichen dabei von denen des G-BA ab. Während der G-BA in seinem Beschluss die vorzulegenden Analysen in Relation zum Beschlussdatum (04.02.2021) beschreibt, plant der pU Analysen in Relation zum Studienstart (laut Protokoll Anfang 2022). Die Zeitpunkte für bestimmte Analysen weichen ebenfalls ab; der G-BA sieht eine Überprüfung der Fallzahl nach 18 Monaten vor, der pU erst nach 36. Auch der Zeitpunkt der finalen Analyse wird abweichend vom Beschluss des G-BA vom pU mit 60 Monaten nach der 3. Interimsanalyse angegeben. Gründe für diese Abweichungen bleiben unklar.

Unklar bleibt, ob der Charakter der geplanten Analysen mit dem aus vom Beschluss des G-BA übereinstimmt. Während der G-BA zu verschiedenen Zeitpunkten Zwischenanalysen anfordert, beschreibt der pU deskriptive Analysen und zusätzlich eine Interimsanalyse.

2.4 Übersicht wesentlicher Mängel der vom pU vorgelegten Unterlagen

Die Prüfung des Studienprotokolls und SAP des pU für die AbD zu Onasemnogen-Abeparvovec ergab die folgenden wesentlichen Mängel:

- die Planung des pU entspricht nicht dem Beschluss des G-BA, u. a. plant der pU abweichende Fragestellungen: ausschließliche Trennung der Patientenpopulation nach SMN2-Kopien, keine Trennung zwischen symptomatisch / präsymptomatisch
- die Planung des pU führt potenziell dazu, dass Ergebnisse nicht rechtzeitig oder nicht in ausreichendem Umfang vorliegen
  - Beschränkung auf SMArtCARE in Deutschland
  - Beschränkung auf Zentren, die Qualitätssicherungs-Richtlinie des G-BA erfüllen
  - keine Planung zur Adaptation und Einbindung des vom pU verantworteten RESTORE-Registers erkennbar
  - keine ausreichende Planung zur Einbindung bereits erhobener Daten zu Nusinersen und Onasemnogen-Abeparvovec (aus SMArtCARE oder anderen Registern)
- die Planung der Auswertung ist unzureichend und teilweise nicht adäquat
  - die Planung ist teilweise zu wenig detailliert, um eine ausreichend Prä-Spezifikation der Analysen sicherzustellen (z. B. Confounderadustierung, Modellauswahl und -anpassung für die Endpunktanalysen)
  - es fehlt die Berücksichtigung verschobener Nullhypothesen, um auch bei einem nicht randomisierten Design mit ausreichender Sicherheit auf einen Effekt schließen zu können
  - die vorgeschlagenen Methoden sind teilweise nicht geeignet (z. B. Bildung von Patientengruppen durch Informationen, die sich erst im Studienverlauf ergeben, Verwendung eines Regressionsmodells im Fall einer unzureichenden Überlappung der Gruppen nach Anwendung von Propensity Scores, Berücksichtigung von Behandlungswechseln über ein Cox-Modell mit Behandlung als zeitabhängiger Kovariable).

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Anhang A Prüfung der Informationsbeschaffung zur Identifizierung von Confoundern

Informationsbeschaffung

Zur Identifizierung von relevanten Confoundern führt der pU eine Informationsbeschaffung nach systematischen Übersichten und Leitlinien zu SMA in folgenden Quellen durch:

- bibliografische Recherchen nach Leitlinien und systematischen Übersichten (letzte Suche am 23.03.2021)
- Handsuche auf ausgewählten Webseiten nach Leitlinien (letzte Suche am 23.03.2021)

Kommentar zur Informationsbeschaffung

Für die Identifizierung von systematischen Übersichten und Leitlinien führte der pU eine Recherche in MEDLINE und der Cochrane Database of Systematic Reviews durch. Zudem gibt der pU an, über eine Handsuche weitere Leitlinien identifiziert zu haben.

Die Recherche des pU ist nicht geeignet, die Vollständigkeit des Suchergebnisses sicherzustellen. Dies hat insbesondere folgende Gründe:

- Die bibliografischen Recherchen in MEDLINE enthalten eine zeitliche Limitierung ab 2015 ohne diese in den Ein- und Ausschlusskriterien aufzuführen. Bei der Handsuche hingegen erfolgt keine zeitliche Limitierung, wodurch einige Dokumente eingeschlossenen werden, die vor 2015 veröffentlicht wurden [20-24].
- Die Recherche des pU in der Cochrane Database of Systematic Reviews ist unvollständig, da eine zeitliche Limitierung der Suche auf den Zeitraum Juni 2015 bis Juni 2020 vorgenommen wird. Aktuelle Referenzen nach Juni 2020 werden somit nicht berücksichtigt.

In der Tabelle A25 führt der pU unter den Ausschlusskriterien HTA Reports auf. Dieser Ausschluss ist nicht adäquat.

Zudem ergaben sich bei der Dokumentation der Informationsbeschaffung mehrere Mängel (z. B. eine abschließende Darstellung aller eingeschlossenen Publikationen [z. B. Studienpool u. ä.] fehlt, Darstellung der Ergebnisse der Handsuche im Abschnitt 5.3 ist nicht vollständig).

Zusammenfassung

Die Informationsbeschaffung des pU ist nicht geeignet, die Vollständigkeit der Suchergebnisse sicherzustellen. Die grundsätzliche Vorgehensweise bei der Informationsbeschaffung des pU nach Confoundern ist jedoch als nachvollziehbar und adäquat anzusehen. Es kann daher davon ausgegangen werden, dass eine ausreichend vollständige Liste an potenziell relevanten Confoundern identifiziert wurde.

Anhang B Offenlegung von Beziehungen (externe Sachverständige)

Diese Bewertung wurde unter Einbindung eines externen Sachverständigen (eines biometrisch-fachlichen Beraters) erstellt. Externe Sachverständige, die wissenschaftliche Forschungsaufträge für das Institut bearbeiten, haben gemäß § 139b Abs. 3 Satz 2 SGB V „alle Beziehungen zu Interessenverbänden, Auftragsinstituten, insbesondere der pharmazeutischen Industrie und der Medizinprodukteindustrie, einschließlich Art und Höhe von Zuwendungen“ offenzulegen. Das Institut hat von dem Sachverständigen ein ausgefülltes Formular „Formblatt zur Offenlegung von Beziehungen“ erhalten. Die Angaben wurden durch das speziell für die Beurteilung der Interessenkonflikte eingerichtete Gremium des Instituts bewertet. Es wurden keine Interessenkonflikte festgestellt, die die fachliche Unabhängigkeit im Hinblick auf eine Bearbeitung des vorliegenden Auftrags gefährden.

Im Folgenden sind die Beziehungen des externen Sachverständigen zusammenfassend dargestellt. Alle Informationen beruhen auf Selbstangaben der einzelnen Personen anhand des „Formblatts zur Offenlegung von Beziehungen“ mit Stand 03/2020. Das aktuelle Formblatt ist unter www.iqwig.de abrufbar. Die in diesem Formblatt aufgeführten Fragen finden sich im Anschluss an diese Zusammenfassung.

Name	Frage 1	Frage 2	Frage 3	Frage 4	Frage 5	Frage 6	Frage 7
Stürmer, Til	ja	ja	nein	ja	ja	ja	ja

Im „Formblatt zur Offenlegung von Beziehungen“ (Version 03/2020) wurden folgende 7 Fragen gestellt:

Frage 1: Sind oder waren Sie innerhalb des laufenden Jahres und der 3 Kalenderjahre davor bei einer Einrichtung des Gesundheitswesens (z. B. einer Klinik, einer Einrichtung der Selbstverwaltung, einer Fachgesellschaft, einem Auftragsforschungsinstitut), einem pharmazeutischen Unternehmen, einem Medizinproduktehersteller oder einem industriellen Interessenverband angestellt oder für diese / dieses / diesen selbstständig oder ehrenamtlich tätig bzw. sind oder waren Sie freiberuflich in eigener Praxis tätig?

Frage 2: Beraten Sie oder haben Sie innerhalb des laufenden Jahres und der 3 Kalenderjahre davor eine Einrichtung des Gesundheitswesens (z. B. eine Klinik, eine Einrichtung der Selbstverwaltung, eine Fachgesellschaft, ein Auftragsforschungsinstitut), ein pharmazeutisches Unternehmen, einen Medizinproduktehersteller oder einen industriellen Interessenverband beraten (z. B. als Gutachter/-in, Sachverständige/r, in Zusammenhang mit klinischen Studien als Mitglied eines sogenannten Advisory Boards / eines Data Safety Monitoring Boards [DSMB] oder Steering Committees)?

Frage 3: Haben Sie innerhalb des laufenden Jahres und der 3 Kalenderjahre davor direkt oder indirekt von einer Einrichtung des Gesundheitswesens (z. B. einer Klinik, einer Einrichtung der

Selbstverwaltung, einer Fachgesellschaft, einem Auftragsforschungsinstitut), einem pharmazeutischen Unternehmen, einem Medizinproduktehersteller oder einem industriellen Interessenverband Honorare erhalten (z. B. für Vorträge, Schulungstätigkeiten, Stellungnahmen oder Artikel)?

Frage 4: Haben Sie oder hat Ihr Arbeitgeber bzw. Ihre Praxis oder die Institution, für die Sie ehrenamtlich tätig sind, innerhalb des laufenden Jahres und der 3 Kalenderjahre davor von einer Einrichtung des Gesundheitswesens (z. B. einer Klinik, einer Einrichtung der Selbstverwaltung, einer Fachgesellschaft, einem Auftragsforschungsinstitut), einem pharmazeutischen Unternehmen, einem Medizinproduktehersteller oder einem industriellen Interessenverband sogenannte Drittmittel erhalten (d. h. finanzielle Unterstützung z. B. für Forschungsaktivitäten, die Durchführung klinischer Studien, andere wissenschaftliche Leistungen oder Patentanmeldungen)? Sofern Sie in einer größeren Institution tätig sind, genügen Angaben zu Ihrer Arbeitseinheit, z. B. Klinikabteilung, Forschungsgruppe.

Frage 5: Haben Sie oder hat Ihr Arbeitgeber bzw. Ihre Praxis oder die Institution, für die Sie ehrenamtlich tätig sind, innerhalb des laufenden Jahres und der 3 Kalenderjahre davor sonstige finanzielle oder geldwerte Zuwendungen, z. B. Ausrüstung, Personal, Unterstützung bei der Ausrichtung einer Veranstaltung, Übernahme von Reisekosten oder Teilnahmegebühren für Fortbildungen / Kongresse erhalten von einer Einrichtung des Gesundheitswesens (z. B. einer Klinik, einer Einrichtung der Selbstverwaltung, einer Fachgesellschaft, einem Auftragsforschungsinstitut), einem pharmazeutischen Unternehmen, einem Medizinproduktehersteller oder einem industriellen Interessenverband? Sofern Sie in einer größeren Institution tätig sind, genügen Angaben zu Ihrer Arbeitseinheit, z. B. Klinikabteilung, Forschungsgruppe.

Frage 6: Besitzen Sie Aktien, Optionsscheine oder sonstige Geschäftsanteile einer Einrichtung des Gesundheitswesens (z. B. einer Klinik, einem Auftragsforschungsinstitut), eines pharmazeutischen Unternehmens, eines Medizinproduktherstellers oder eines industriellen Interessenverbands? Besitzen Sie Anteile eines sogenannten Branchenfonds, der auf pharmazeutische Unternehmen oder Medizinproduktehersteller ausgerichtet ist? Besitzen Sie Patente für ein pharmazeutisches Erzeugnis, ein Medizinprodukt, eine medizinische Methode oder Gebrauchsmuster für ein pharmazeutisches Erzeugnis oder ein Medizinprodukt?

Frage 7: Sind oder waren Sie jemals an der Erstellung einer medizinischen Leitlinie oder klinischen Studie beteiligt, die eine mit diesem Projekt vergleichbare Thematik behandelt/e? Gibt es sonstige Umstände, die aus Sicht von unvoreingenommenen Betrachtenden als Interessenkonflikt bewertet werden können, z. B. Aktivitäten in gesundheitsbezogenen Interessengruppierungen bzw. Selbsthilfegruppen, politische, akademische, wissenschaftliche oder persönliche Interessen?

Routine data collection and evaluations of onasemnogene abeparvovec in Germany

Study Protocol

Protocol Number: COAV101A1DE01

Version: 2.02

November 18, 2021

Signature Page

The signatories agree to the content of the final study protocol as presented.

Marketing authorization holder (MAH): *MAH sponsored non-interventional study carried out based on resolution (February 4, 2021) of the G-BA.:* Novartis Gene Therapies EU Ltd. Street: Theresienhöhe 28 City/Zip: 80399 München Country: Germany	DocuSigned by: Hardo Fischer E02204A4C2CA4A9... DocuSigned by: Gunter Harms 9F0278DE432442B... DocuSigned by: Deepa Chand 26CA34D4CA094E7... DocuSigned by: Omar Dabbous FEF6D3467FB0426... DocuSigned by: Sandra P Reyna 50D75DC408144EC... Place, Date, Signature 19-Nov-21 | 7:44:29 PM GMT
Principal Investigator (PI): Prof. Dr. med. Janbernd Kirschner Universitätsklinikum Bonn Zentrum für Kinderheilkunde Abteilung für Neuropädiatrie Street: Venusberg-Campus 1 City/Zip: 53127 Bonn Country: Germany	DocuSigned by: Janbernd Kirschner 105FC14191364E7... Place, Date, Signature 19-Nov-21 | 12:10:40 PM PST
Statistical Analysis: IGES Institut GmbH Berlin Street: Friedrichstraße 180 Zip/State: 10117 Berlin County: Germany	DocuSigned by: Fabian Berkemeier 20E020DB32394BA... Place, Date, Signature 19-Nov-21 | 11:53:43 AM PST

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Content

Figures

Tables

Index of abbreviations and definition of terms

Abbreviation	Term/Definition
AAV	Adeno-associated virus serotype
AbD	Routine Data Collection and Evaluations (Anwendungsbegleitende Datenerhebung)
Abs	absolute
ACT	Appropriate Comparative Therapy
ASO	Antisense oligonucleotide
ATT	Average Treatment Effect on Treated
AWMF	Working Group of the Scientific Medical Societies e.V. (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.)
BO-Ä	Professional Code for Physicians in Germany (Berufsordnung Ärzte)
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CMA Infobase: (CPGs)	Canadian Medical Association Infobase: Clinical Practice Guidelines
CMAP	Compound muscle action potential
COV	Close-Out Visit
CRF	Case report form
CUP	Compassionate use program
DMD	Disease modifying drug
DNA	Deoxyribonucleic acid
EAP	Expanded access program
EFS	Event free survival
EMA	European Medicines Agency
G-BA	Federal Joint Committee (Gemeinsamer Bundesausschuss)
GLMM	Generalized linear mixed model

Abbreviation	Term/Definition
HFMSE	Hammersmith Functional Motor Scale Expanded
HINE	Hammersmith Infant Neurological Examination
HR	Hazard ratio
HRQoL	Health-related quality of life
HSP	Healthcare service provider
ICD	International Statistical Classification of Diseases and Related Health Problems
IPCW	Inverse-probability-of-censoring weighting
IQWiG	Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
ISS	Intronic splice silencing site
ITC	Indirect treatment comparison
ITT	Intention to treat
LTFU	Loss-to-follow-up
MAH	Marketing authorization holder
MAP	Managed access program
MedDRA	Medical Dictionary for Regulatory Affairs
mRNA	Messenger ribonucleic acid
n.a.	Not applicable
NGT	Novartis Gene Therapies
NPP	Named patient program
OS	Overall survival
PICO	Patient-Intervention-Comparator-Outcome
PS	Propensity Score
PT	Preferred term (MedDRA)
RMV	Routine Monitoring Visit

Abbreviation	Term/Definition
RPSFT	Rank Preserving Structural Failure Time Model
RULM	Revised Upper Limb Module
RWE	Real World Evidence
SAP	Statistical analysis plan
SGB V	Social Code Book V (Sozialgesetzbuch V)
SLR	Systematic literature review
SMA	Spinal muscular atrophy
SMD	Standardized mean difference
SMN	Survival motor neuron
SMN1	Survival motor neuron 1 gene
SMN2	Survival motor neuron 2 gene
SmPC	Summary of Product Characteristics
SMRW	Standardized mortality ratio weights
SOC	System Organ Class (MedDRA)
SPI	Single Patient Investigational New Drug
Treat-NMD Neuromuscular Network	Translational Research in Europe for the Assessment and Treatment of Neuromuscular Disease Neuromuscular Network
TRIP Database	Turning Research Into Practice Database
TTE	Time to event
WHO	World Health Organization

Revision History

Version	Date	Revised by	Change made – Reason for the change
0.1	Jul 02, 2021	Fabian Berkemeier (IGES)	Set up protocol
0.2	Jul 16, 2021	Fabian Berkemeier (IGES)	Implementation of feedback from NGT project team
0.3	Jul 21, 2021	Fabian Berkemeier (IGES)	Implementation of feedback from NGT project team
1.0	Aug 04, 2021	Fabian Berkemeier (IGES)	Implementation of feedback from ISRC review
1.01	Aug 05, 2021	Fabian Berkemeier (IGES)	Changed role of Omar Dabbous from Project Management to Project Lead
2.0	Nov 05, 2021	Fabian Berkemeier (IGES)	Implementation of G-BA requests from letter dated 9/28/2021: ▪ Updated synopsis according to changes in protocol ▪ Updated milestones according to G-BA change requests ▪ Added section 1.2 and 1.3 to cover procedural background information ▪ Updated section 2 to cover the two analysis approaches implemented as a consequence of G-BA change requests ▪ Updated section 4 to include safety endpoints requested by G-BA ▪ Updated section 5 to address G-BA change requests on endpoints with a focus on motor function endpoints depicted in section 5.1.2.2 and safety endpoints depicted in section 5.2 ▪ Updated section 6 and added section 6.2 covering G-BA's change request on a utilization of the RESTORE registry ▪ Updated section 6.3 to address G-BA's change request of not applying G-BA quality criteria and dropping restriction to German sites administering both interventions of this study ▪ Updated section 7.1 to eliminate treatment center inclusion criterion ▪ Updated section 7.3 to depict G-BA's change request of utilizing historic data and non-parallel data for nusinersen as well as requiring information on all baseline confounders ▪ Updated section 8.1 to depict NGT and G-BA approach in order to include analysis populations requested by G-BA

Version	Date	Revised by	Change made – Reason for the change
			▪ Updated section 8.2 to include sample size calculations for G-BA analysis populations with different methodologies as requested by G-BA in section 8.2.2 ▪ Updated section 8.2.3 to provide details on sample size recalculations and specifically refer to the methodology defined in the SAP ▪ Updated section 8.3 to include historic data as well as expected patient numbers for G-BA analysis populations ▪ Updated section 8.4 according to G-BA's change requests on utilization of historic and non-parallel data, interim analysis times, and sample size calculations ▪ Updated section 8.5 according to G-BA change request on analysis times and reporting content ▪ Updated section 8.6 to include G-BA analysis populations and definitions of applications per confounder per analysis population ▪ Updated section 0 to define subgroup analysis per analysis population and performance of subgroup analysis irrespective of statistically significant interaction per G-BA change requests ▪ Update section 12 do depict changes made in protocol
2.01	Nov 15, 2021	Fabian Berkemeier (IGES)	Implementation of feedback from NGT project team
2.02	Nov 18, 2021	Fabian Berkemeier (IGES)	Implementation of feedback from ISRC review

Synopsis and Milestones

Table 1: Synopsis

Title	Routine data collection and evaluations of onasemnogene abeparvovec in Germany
Study responsibilities	Marketing authorization holder (MAH) sponsored non-interventional study carried out based on resolution (February 4, 2021) of the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA). SMArtCARE is responsible for patient data collection. Statistical analysis will be performed by IGES Institut GmbH. Source data verification will be performed by CSG (Clinische Studiengesellschaft mbH).
Principal Investigator	Prof. Dr. Janbernd Kirschner Universitätsklinikum Bonn Venusberg-Campus 1 53127 Bonn
Rationale and background	Federal Joint Committee (G-BA) demanded Routine Data Collection and Evaluations for Zolgensma® (onasemnogene abeparvovec) compared to Spinraza® (nusinersen) with its resolution from February 4, 2021. The present study is conducted to fulfill the requirements specified therein. Following an assessment of the study protocol and SAP by IQWiG and G-BA, unresolved differences on major aspects of the study design and analysis methods with regard to their appropriateness in German routine SMA care and feasibility remain. The study thus depicts two design and methodology approaches referred to as “NGT approach” and “G-BA approach”.
Study objective and related endpoints	The objective of this study is to evaluate the overall effectiveness and safety in patients with spinal muscular atrophy (SMA) treated with gene therapy Zolgensma® (onasemnogene abeparvovec) compared to Spinraza® (nusinersen). The following endpoints are subject to investigation in this study: ▪ **Effectiveness** o <u>Survival</u> ▪ Overall survival ▪ Event-free survival o <u>Motor function</u> ▪ Achievement of motor milestones according to age (NGT approach only) ▪ Head control at the age of 8 months (NGT approach only) ▪ Crawl on hands and knees at the age of 18 months (NGT approach only) ▪ Sitting without support at the age of 18 months (NGT approach only) ▪ Standing without support at the age of 24 months (NGT approach only) ▪ Walking without support at the age of 24 months (NGT approach only)

- Sustainability of motor milestones
  - Loss of ability to sit without support
  - Loss of ability to stand without support
  - Loss of ability to walk without support
- CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders)
  - Change from baseline at 6M
  - Change from baseline at 12M
- HINE (Hammersmith Infant Neurological Examination)
  - Change from baseline at 12M
  - Change from baseline at 24M
- Time to sitting without support
- Time to standing without support
- Time to walking without support

o Nutrition
- Difficulties in swallowing
- Difficulties in chewing
- Gastric or nasal feeding tube
  - Any type of tube feeding (supplementary or exclusively)
  - Supplementary (e.g. for fluids)
  - Exclusively

o Orthopedic complications
- Scoliosis or orthopedic surgery
- Scoliosis
- Orthopedic surgery

o Respiratory function
- Time of ventilator use
  - Any ventilator support
  - Ventilator support at night (during sleep)
  - Intermittent ventilator support at day time and continuous at night
  - Permanent ventilator support (>16 hours per day)
  - Intermittent ventilator support with acute illnesses
- Type of ventilator use
  - Non-invasive ventilation
  - Invasive ventilation
- Improvement in time of ventilator support from baseline

o Planned hospitalizations

- Safety

o Adverse events
- Adverse events with or without hospitalization
- Adverse events with or without hospitalization related to treatment
- Adverse events without hospitalization
- Adverse events without hospitalization related to treatment

	○ Serious adverse events ▪ Adverse events with hospitalization ▪ Adverse events with hospitalization related to treatment ▪ Adverse events with hospitalization or death of any cause ▪ Adverse events with hospitalization or death of any cause related to treatment ○ Adverse events of special interest ▪ Hydrocephalus ▪ Hepatotoxicity ▪ Thrombocytopenia ▪ Cardiac events ▪ Dorsal root ganglia cell inflammation ▪ Renal toxicity ▪ Respiratory tract infection ▪ Epileptic seizure ▪ Post lumbar puncture syndrome
Population	Treatment-naïve patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the survival motor neuron 2 (SMN2) gene as well as symptomatic patients with 5q-associated SMA type I treated with onasemnogene abeparvovec or nusinersen Patients will be stratified into two analysis populations for NGT approach and into four analysis populations for G-BA approach: ▪ NGT approach ○ Population NGT-A: Patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 2 copies of the SMN2 gene ○ Population NGT-B: Patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and 3 copies of the SMN2 gene ▪ G-BA approach ○ Population GBA-A: Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 2 copies of the SMN2 gene ○ Population GBA-B: Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA ○ Population GBA-C: Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and 3 copies of the SMN2 gene ○ Population GBA-D: Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene
Inclusion criteria	▪ Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene or

	▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and clinically diagnosed type 1 SMA or ▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene ▪ Treatment initiation with nusinersen (12 mg / 5 ml per administration) or onasemnogene abeparvovec (dosage according to body weight as per summary of product characteristics (SmPC)) ▪ Body weight at treatment initiation ≤ 21 kg ▪ Appropriate consent/assent has been obtained for participation in the study
Exclusion criteria	▪ Pretreatment with an approved disease-modifying therapy (nusinersen, onasemnogene abeparvovec, risdiplam) ▪ Pretreatment with any of the following investigational drugs for the treatment of SMA: albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea ▪ Currently or previously enrolled in an interventional clinical trial involving an investigational product to treat SMA
Study design	Non-interventional, non-randomized data collection using secondary data from the SMArtCARE registry. Upon passing of a corresponding resolution by G-BA, secondary use of data from the RESTORE registry will be implemented via an amendment.
Expected patient numbers	All patients fulfilling inclusion/exclusion criteria during study duration will be included in the study. As the study is conducted in a standard of care setting, the actual numbers of subjects per study population cannot be controlled. Also, as SMA is a rare disease, there is a finite number of patients that can be enrolled. An additional restriction is that included patients need to be stratified into two analysis populations for NGT approach and into four analysis populations for G-BA approach. Based on SMA incidence information derived from the results of pilot newborn screening in Germany, the study is anticipated to enroll up to 599 patients, which will be included both retrospectively and prospectively from the initiation of the SMArtCARE registry in July 2018 to the time of data cut for final analysis on December 31, 2026. Due to required stratification into analysis populations, patient numbers relevant for achieving sufficient

	power per analysis population are significantly lower: ▪ NGT approach ○ Population NGT-A: Up to 377 patients ○ Population NGT-B: Up to 222 patients ▪ G-BA approach ○ Population GBA-A: Up to 157 patients ○ Population GBA-B: Up to 220 patients ○ Population GBA-C: Up to 161 patients ○ Population GBA-D: Up to 61 patients Actual patient numbers eligible for study inclusion are expected to be lower but neither the share of diagnosed and treated patients documented in SMArtCARE nor the share of patients fulfilling eligibility criteria is currently known. A further reduction of patients eligible for analysis is caused by the natural time lag from being diagnosed shortly after birth to assessability of a number of effectiveness endpoints.
Sample Size	Sample size calculations were performed separately for NGT and G-BA approaches due to differences in study populations and methodology. For NGT approach, a standard null hypothesis and alpha = 0.05 was used. For G-BA approach, two different methods of sample size calculations were applied: (1) a shifted null hypothesis requested by IQWiG and (2) a standard null hypothesis with alpha = 0.01 derived from the criteria of a "dramatic effect". The following sample sizes result: ▪ <u>NGT approach</u> ○ Population NGT-A ▪ EFS: 48-68 patients ▪ Sitting: 189-270 patients ○ Population NGT-B ▪ EFS: 256-365 patients ▪ Standing: 155-221 patients ▪ <u>G-BA approach</u> ○ Populations C and D ▪ EFS: 74 patients for "dramatic effect" methodology, 184 patients for shifted null hypothesis ▪ Sitting: 228 patients for "dramatic effect" methodology, 13,862 patients for shifted null hypothesis ○ Populations D and E ▪ EFS: 494 patients for "dramatic effect" methodology, 6,270 patients for shifted null hypothesis ▪ Standing: 228 patients for "dramatic effect" methodology, 13,862 patients for shifted null hypothesis Based on current estimates of patient enrollment the study will be powered for EFS and sitting in study population NGT-A, for standing in population NGT-B, and for EFS in study population GBA-A if the criteria derived from a "dramatic effect" instead of a shifted null hypothesis are applied. For all other endpoints and populations that were included in sample size calculations, expected patient numbers are expected to be insufficient to ensure

	adequate power. Assumptions for sample size calculation will be re-evaluated at first and second interim analysis using actual observed event rates and effect sizes.
Statistical methods	<u>NGT approach</u> All endpoints will be evaluated using a treatment episode design to address the possibility of treatment changes between study in-terventions in this non-interventional study. For time to event (TTE) endpoints, treatment episodes and their durations are considered in the context of a Cox regression with time-dependent covariates. For binary endpoints, scores and count data, weighting with the length of treatment episodes is appropriate within the generalized linear mixed model framework. The comparison of both interventions is carried out descriptively with appropriate statistical methods. Inhomogeneity between treatment episodes with regard to the following baseline confounders will be addressed via an improvement of the structural comparability by propensity score methods (fine stratification weights or standardized mortality ratio weights): ▪ Age at symptom onset ▪ Symptom status at treatment initiation ▪ Age at treatment initiation ▪ Nutrition support ▪ Ventilation support ▪ Contractures ▪ Motoric function: Highest motor milestone ▪ Motoric function: CHOP-INTEND If overlap pre-weighting or balance post-weighting is not sufficient for applying propensity score methods (i.e. >50% of patients for one treatment have a PS < 0.3 and >50% of patients for the other treatment have a PS > 0.7), confounder adjustment will be attempted in the framework of regression models (generalized linear model, Cox-regression). <u>G-BA approach</u> All endpoints will be evaluated based on an allocation to the patient's initial treatment ("new user design"). Per G-BA request, treatment changes will be ignored for main analysis, i.e. no cencoring is performed. The comparison of both interventions is carried out descriptively with appropriate statistical methods. Inhomogeneity between treatment episodes with regard to the following baseline confounders will be addressed via an improvement of the structural comparability by propensity score methods (fine stratification weights or standardized mortality ratio weights): ▪ Age at symptom onset

	▪ Age at treatment initiation ▪ Nutrition support ▪ Ventilation support ▪ Contractures ▪ Motoric function: Highest motor milestone ▪ Motoric function: CHOP-INTEND If patient numbers are too small to allow for interpretable calculation of propensity scores, adjustment for confounders is attempted using a matched-pair approach. If overlap pre-weighting is not sufficient for applying propensity score methods (i.e. >50% of patients for one treatment have a PS < 0.3 and >50% of patients for the other treatment have a PS > 0.7) and a matched-pair approach is not possible (i.e. >50% of confounders or >20% of onasemnogene abeparvovec patients cannot be accounted for), confounder adjustment will not be attempted and a naïve comparison will be performed. <u>Both approaches</u> Potential confounders and patient characteristics are evaluated descriptively: ▪ Continuous characteristics: Measures of position and dispersion (arithmetic. mean with 95% confidence interval, standard deviation, minimum, maximum and quartiles) ▪ Categorical characteristics: absolute and relative frequencies. Time to event (TTE) endpoints are estimated in the context of a Cox regression. For binary endpoints and count data, a generalized linear model is used. Scores will be analyzed using a mixed model for repeated measurement. Survival curves and median survival time as well as hazard ratios are used for the representation of the time-to-event endpoints. Binary endpoints are analyzed using Risk Ratio as effect measure. Scores will be evaluated using mean differences and Hedges' g. Count endpoints will be evaluated using Rate Ratio as effect measure. For all effect measures 95% confidence interval limits are presented. Adverse events are summarized by SOC/PT in terms of absolute and relative frequencies as well as time to first event by treatement episode.
Duration of study	The duration of the study is 60 months prospectively from assumed study start in January 2022 to data cut for final analysis in December 2026. In addition, 42 months of retrospective data is available from the SMArtCARE registry, which started enrolling patients in July 2018. Collectively, a timeframe of 102 months (8.5 years) for patient enrollment results.

Table 2: Milestones

Study milestones	**(Planned) Date**
Submission of study protocol and SAP to G-BA	13 August 2021
Written results of assessment of study protocol	28 September 2021

Study milestones	(Planned) Date
and SAP by G-BA and IQWiG	
Re-submission of study protocol and SAP	24 November 2021
Approval by G-BA or additional change requests	19 January 2022
Study start	If re-submitted protol & SAP are approved: 20 January 2022 If additional changes are requested by G-BA: Expected for March 2022
First status report and interim analysis	Data cut: January 2022 Submission: 4 August 2022
Second status report and interim analysis	Data cut: August 2023 Submission: 4 February 2024
Third status report	Data cut: January 2025 Submission: 4 August 2025
Fourth status report and interim analysis	Data cut: August 2025 Submission: 4 February 2026
Final analysis for benefit assessment	Data cut: 31 December 2026 Submission: 1 July 2027

1. Background

1.1 Spinal muscular atrophy

Spinal muscular atrophy (SMA) is a rare, genetic, neuromuscular disease associated with progressive, irreversible motor neuron loss that results in muscle atrophy leading to progressive muscle weakness and paralysis, impairment of swallowing and breathing, and premature death in its more severe forms (1, 2). SMA is caused by a homozygous absence of the survival motor neuron gene 1 (SMN1), resulting in a lack of survival motor neuron (SMN) protein (1, 2). The SMN protein is also encoded by the survival motor neuron 2 (SMN2) back-up gene that is closely homologous to SMN1; however, only 10–15% of the protein produced by SMN2 is a full-length, functional SMN protein (3–6). SMA is historically classified into five clinical types (0 through 4) based on the age at symptom onset and highest motor milestone achievement. SMN2 copy number is inversely associated with disease severity and is correlated with SMA type; 97% of infants with two SMN2 copies will develop type 1, and infants with three copies of SMN2 have a 7% chance of developing SMA type 1 and 83% chance of developing SMA type 2 (7–9).

Although infants with SMA type 1 are alert and aware, they lose the ability to swallow and safely feed by mouth, never gain developmental milestones after initial presentation and develop progressive skeletal muscle weakness and atrophy, and suffer from chronic ventilatory failure (10–15). SMA type 2 is defined by the maximum motor ability to be able to sit unsupported, which is achieved at the average age of 1 year (16–20). SMA type 3 is distinguished from SMA type 2 by the ability to walk independently (20). While infants with a later age of onset have better functional ability initially, their condition deteriorates over time and often results in severe disability, regardless of SMA type.

The main cause of mortality is respiratory failure (21, 22). Infants experience rapid, significant, and progressive muscle weakness, leading to the inability to breathe or swallow and ultimate death, typically following a severe respiratory illness (11). Without intensive respiratory and nutritional intervention and disease-modifying treatment, the life expectancy of infants with SMA type 1 is typically <2 years (23). The findings from various neurophysiological and animal studies have shown an early loss of motor neurons in the embryonic and early postnatal periods (24–26).

Until recently, the mainstay of treatment for these patients was supportive medical care. However, advances in medical treatment focusing on gene replacement, modulation of splicing, motor neuron protection and muscle enhancement are continually changing the management and prognosis of these patients.

1.2 Benefit assessments for onasemnogene abeparvovec

Onasemnogene abeparvovec (Zolgensma®) is a gene therapy medicinal product that expresses the human SMN protein. It is delivered by a one-time intravenous infusion.

Onasemnogene abeparvovec was approved by the European Commission on 18 May 2020 for the following indication:

- Patients with 5q SMA with a biallelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or
- Patients with 5q SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.

According to § 35a of the German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) evaluates the additional benefit of reimbursable medicinal products with new active ingredients, and pharmaceutical companies are obliged to submit a dossier on product benefit when a new product is launched on the German market or authorized for new indications. The purpose of early benefit assessment in Germany is to compare newly authorized drugs to an appropriate comparative therapy (ACT) in order to establish a ruling on their additional benefit, which serves as the basis for price negotiations between the manufacturer and the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband).

Novartis Gene Therapies EU Ltd. initially submitted a dossier for the benefit assessment on 1 July 2020 and submitted for a renewed benefit assessment according to § 35a section 1 sentence 12 on 15 May 2021 as per the requirement of G-BA. G-BA determined nusinersen as ACT for the renewed benefit assessment and ruled on 4 November 2021 that an additional benefit is not demonstrated (27).

1.3 Routine Data Collection and Evaluations for onasemnogene abeparvovec

1.3.1 G-BA resolutions and procedures

On 4 February 2021 G-BA requested the first-ever Routine Data Collection and Evaluations according to § 35a paragraph 3b SGB V for onasemnogene abeparvovec (28). The resolution was preceded by a G-BA resolution of 16 July 2020 (29), which initiated the procedure as well as a concept development by the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) of 1 October 2020 (30).

Along with the resolution mandating the Routine data Collection and Evaluations, G-BA passed a resolution restricting reimbursement of onasemnogene abeparvovec to physicians participating in the Routine Data Collection and Evaluations on 4 February 2021 (31). G-BA also passed a resolution on quality criteria for the application of onasemnogene abeparvovec on 20 November 2020 (32). This resolution includes quality aspects specifically aimed at ensuring a high validity and comparability of the data collected for the Routine data Collection and Evaluations (e.g. experience and training of physicians and physical therapists).

Prior to the initiation of the specific procedures mandating the Routine Data Collection and Evaluations for onasemnogene abeparvovec, IQWiG was commissioned to develop methodological guidance for this new form of evidence generation, which was published as a Rapid Report in January 2020 (33).

As required by the G-BA code of procedure, all but one G-BA resolution on onesemnogene abeparvovec included a public consultation procedure allowing for a participation of stakeholders, including clinical SMA experts. Table 3 summarizes the relevant G-BA procedures as well as their public consultations.

Table 3: Relevant G-BA procedures concerning the Routine Data Collection and Evaluations for onasemnogene abeparvovec

G-BA procedure	Resolution date	Public consultation
Initiatation of a procedure to request Routine Data Collection and Evaluations for onasemnogene abeparvovec	16 July 2020	None
Quality criteria for onasemnogene abeparvovec	20 November 2020	11 August 2020: Consultation on the written statements 22 September 2020: Oral hearing
Requirement of Routine Data Collection and Evaluations	4 February 2021	Written statements on IQWiG concept development: 30 October 2020 Exchange of expertise on IQWiG concept development: 23 November 2020
Restriction of the Authority to Supply Care	4 February 2021	6 January 2021: Consultation on the written statements 11 January 2021: Oral hearing

Source: (34), (35), (36), (37)

The G-BA resolution from 4 February 2021 defined a number of aspects for the Routine Data Collection and Evaluations for onasemnogene abeparvovec. The population to be included in the study as well as intervention, comparator, and outcomes are defined by a PICO scheme depicted in Table 4.

Table 4: PICO scheme for Routine Data Collection and Evaluations for onasemnogene abeparvovec

Population	▪ Pre-symptomatic patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene ▪ Symptomatic patients with 5q spinal muscular atrophy (SMA) with a biallelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1 ▪ Symptomatic patients with 5q spinal muscular atrophy (SMA) with a biallelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 2 and up to 3 copies of the SMN2 gene The survey should also include patients in the above patient population who are older than 6 months or 6 weeks at the time of gene therapy with onasemnogene abeparvovec.
Intervention	▪ Onasemnogene abeparvovec The marketing authorisation and the dosage information in the product information of the active ingredients must be taken into account.
Comparator	▪ Nusinersen The marketing authorisation and the dosage information in the product information of the active ingredients must be taken into account.
Outcome	Mortality ▪ Deaths Morbidity ▪ Motor functioning (surveyed with age-appropriate instruments) and ▪ Achievement of motor development milestones of the WHO and ▪ Respiratory functioning (need for [continuous] ventilation) and ▪ Bulbar functioning (ability to swallow and speak, need for non-oral nutritional support) and ▪ Further complications of the disease (e.g. pain, orthopaedic complications) Side effects ▪ Serious adverse events (SAE) ▪ Adverse events leading to hospitalization ▪ Serious specific adverse events: Hepatotoxicity, thrombocytopenia, cardiac events, inflammation of spinal ganglion cells, renal toxicity, hydrocephalus

Source: (28)

In addition to the PICO scheme, G-BA defined that the SMArtCARE registry is to be used as the primary registry provided that the quality criteria mentioned in Table 5 are fulfilled. G-BA also defined that “it is also possible to integrate other registries, taking into consideration all the data source requirements” depicted in Table 5.

The G-BA resolution of 4 February 2021 further required Novartis Gene Therapies to submit a study protocol and SAP to G-BA by 15 August 2021, in which information on a number of aspects depicted in Table 5 is to be provided.

Table 5: Requirements on data source, study protocol, and SAP per G-BA resolution

Aspect	Requirments of G-BA resolution
Data Source	Use of indication registries as a data source that meet the requirements for the routine data collection and fulfil at least the following quality criteria: ▪ Detailed registry description (protocol) ▪ Exact definition or operationalisation of exposures (type and duration of medicinal therapy and other concomitant therapies), clinical events, endpoints, and confounders ▪ Use of standard classifications and terminologies ▪ Use of validated standard survey instruments (questionnaires, scales, tests) ▪ Training on data collection and recording ▪ Implementation of an approved disease-specific core data set ▪ Use of exact dates for the patient, the disease, important examinations, and treatments/interventions ▪ Clearly defined inclusion and exclusion criteria for registry patients ▪ Strategies to avoid unwanted selections during patient inclusion in order to achieve representativeness ▪ Specifications to ensure completeness of data per survey date and completeness of survey dates ▪ Source data verification for 100% of patients per survey centre for the primary endpoint and for at least 10% of randomly selected patients per survey centre for all other endpoints over the period since the start of data collection ▪ Assurance of scientific independence and transparency of the registry Use of an indication registry in which spinal muscular atrophy is treated in accordance with everyday care in Germany or is sufficiently similar to care in Germany.
Protocol & SAP	The pharmaceutical company shall prepare a study protocol and a statistical analysis plan before carrying out the routine data collection and evaluations. In this context, it shall, in particular, provide the following information in advance with regard to the evaluation of the data: ▪ Information on the statistical methods and models used as well as naming of the procedures and the criteria used in model selection and fitting Information on the expected scope and reasons for missing data as well as measures to avoid missing data and evaluation strategies to deal with missing data ▪ Information on dealing with implausible data and outliers ▪ Information on planned sensitivity analyses ▪ Information on the identification and adequate pre-specified adjustment for confounders ▪ Information on the investigation of potential effect modifiers

Aspect	Requirments of G-BA resolution
	▪ Information on subgroup analyses based on the copy number of the SMN2 gene for pre-symptomatic patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene for the purpose of verifying whether a joint evaluation is appropriate ▪ Information on the extent to which the data on nusinersen collected in parallel and not collected in parallel are suitable for a pooled analysis ▪ Information on the extent to which data, if any, comparing onasemnogene abeparvovec and nusinersen from different data sources are suitable for a pooled analysis ▪ Information on dealing with patients who change their medicinal therapy or receive combination therapy ▪ Information on interim analyses taking into account the requirements defined in the G-BA resolution ▪ Information on discontinuation criteria because of futility

Source: (28)

1.3.2 Written change requests from G-BA based on IQWiG assessment of study protocol and SAP

In accordance with the G-BA resolution from 4 February 2021, Novartis Gene Therapies submitted a study protocol and SAP to G-BA on 13 August 2021. The G-BA justification (Tragende Gründe) of the 4 February 2021 resolution defined that "G-BA, with the involvement of the IQWiG, will review the study protocol and the statistical analysis plan and send the pharmaceutical company the result in writing within 4 to 6 weeks. If, after review by the Subcommittee on Medicinal Products of the G-BA, there is no need to adapt the study protocol and the statistical analysis plan submitted by the pharmaceutical company, the pharmaceutical company shall be informed of the result in writing. If, after examination by the Subcommittee on Medicinal Products of the G-BA, there is a need for adjustments, the G-BA will pass a resolution regarding the adjustments deemed necessary."

With a letter dated 28 September 2021, G-BA's Subcommittee on Medicinal Products informed Novartis Gene Therapies of 22 change requests (38) based on an assessment of the submitted study protocol and SAP by IQWiG (39). In contrast to the provisions of the justification of the 4 February 2021 resolution, no G-BA resolution was passed on these change requests. Accordingly, no public consultation took place and the change requests match the content and order of the IQWiG assessment of protocol and SAP. The 22 change requests are depicted in Table 6.

Seven change requests concern study design aspects, for which Novartis Gene Therapies deviated from the provisions of the G-BA resolution of 4 February 2021 (No. 1, 3-5, 15, 16, 22, Table 6). Novartis Gene Therapies had provided rationales

for these deviations, of which many were performed on the explicit recommendation of six advising German clinical SMA experts named in the protocol.

Three change requests (No. 6-8, Table 6) concern the data sources. In its 4 February resolution and its justification, G-BA defined SMArtCARE as the primary registry and required the "use of an indication register in which spinal muscular atrophy is treated in accordance with everyday care in Germany or is sufficiently similar to care in Germany". The integration of other registries was defined as "possible" – not mandatory – if the quality criteria depicted in Table 5 were fulfilled. It was also explained that "if there are relevant differences in the standard of care in another country, registry data from this country should not be used for the present routine data collection and evaluations". As part of the change request depicted in the 28 September 2021 letter, G-BA has requested to include the RESTORE registry (change request No. 6, Table 6), study sites outside of Germany (change request No. 7, Table 6), and study sites within Germany not fulfilling G-BA quality criteria and thus not able to offer both interventions of this study (change request No. 8, Table 6).

The remaining 12 change requests (No. 2, 9-15, 17-21, Table 6) cover details on the methods of statistical analysis. None of these aspects were depicted in the 4 February 2021 ruling, as Novartis Gene Therapies was mandated by G-BA to develop methodological approaches for aspects depicted in Table 5 without guidance as to which methods should be used.

Table 6: G-BA requests

No.	Topic	G-BA Request	Depicted in 4 February 2021 resolution
1	Question according to PICO: patient population	The definition of the patient population and the evaluation of the data should be carried out separately for pre-symptomatic and symptomatic patients according to the specifications of the G-BA.	Yes
2	Question according to PICO: Outcome (morbidity)	The multiplicity created by the number of endpoints describing motor function should be reduced by selecting the relevant endpoints and hierarchizing the endpoints overall. These decisions must be prespecified in the study protocol. Primarily, endpoints covering the entire relevant observation period should be used.	No
3	Question according to PICO: Outcome (side effects)	The thresholds for the collection of the specific AEs referred to in the decision should be defined and prespecified before the start of the study. As an approach to collecting SAEs, a combined endpoint of AEs leading to death and AEs leading to hospitalization should be evaluated.	Yes

No.	Topic	G-BA Request	Depicted in 4 February 2021 resolution
4	Study design: prospective / retrospective data collection	The use of already collected data on nusinersen and onasemnogene abeparvovec (from the SMArtCARE registry and possibly other registries) should be planned for the registry study, provided that they meet the stated data quality requirements in the AbD (Routine Data Collection and Evaluations) decision on onasemnogene abeparvovec.	Yes
5	Study design: selection of confounders	The list of confounders should be adapted to the patient populations mentioned in the decision and to the data sources used for the registry study.	Yes
6	Data source	The pharmaceutical company should make the necessary adjustments to the self-managed RESTORE registry in accordance with the final study protocol and SAP for the AbD in order to be able to use evaluations based on the RESTORE registry together with the present registry study, e.g. in the form of a meta-analysis for the AbD.	No
7	Data source	SMArtCARE centers outside Germany should not be excluded as a data source in principle, since they can also provide prospective data for symptomatic patients.	No
8	Data source	There should be no exclusive restriction to centers that fulfil the quality assurance guideline of the G-BA for the use of onasemnogene abeparvovec. Rather, the decision whether or not to include a center should depend on the quality or care actually implemented in that center.	No
9	Evaluation of the data collection; planning of the number of cases	The description of the recalculation of the case number planning (36-month analysis) in the SAP should be much more detailed; in addition, the exact use of the measure $R^2$and its precise definition should be added. The description of the recalculation should be based on a shifted hypothesis boundary for the assessment of the effects.	No
10	Evaluation of the data collection: Confounder adjustment	The division of patients into the proposed "treatment groups" for confounder adjustment should be changed. A division of patients must be made by information available at the beginning of the study.	No
11	Evaluation of the data collection: Confounder adjustment	Missing details for the propensity score analysis should be added (verification of goodness, concrete criteria for sufficient overlap and balance).	No

No.	Topic	G-BA Request	Depicted in 4 February 2021 resolution
12	Evaluation of the data collection: Confounder adjustment	A description of a decision algorithm to adjust the propensity score analysis in case of missing overlap and balance after application of the first procedure should be added. Likewise, the correct consequence should be named if no propensity score procedure can be found. A definition should be given with which a sufficient overlap and a sufficient balance of the groups to be compared can be achieved. In such a case, it makes no sense to attempt to estimate the effect using either propensity scores or regression models.	No
13	Evaluation of the data collection: Analysis of the endpoints	The models for effect estimation should be presented in detail. The center effect should not be included in the analysis as either a random or a fixed effect. A possible center effect should be investigated in a sensitivity analysis.	No
14	Evaluation of the data collection: Analysis of the endpoints	The SAP should describe in detail the form in which the confounders are to be included as fixed effects in the respective endpoint model.	No
15	Evaluation of the data collection: Analysis of the endpoints	Information on how to check whether temporally parallel and non-parallel data or data from different data sources can be used for pooled analyses is missing and should be added.	Yes
16	Evaluation of data collection: consideration of shifted hypothesis boundaries	The consideration of a shifted hypothesis boundary in the evaluation of the data is missing and should be supplemented. These additions could be made, for example, in the (previously missing) formulation of a hypothesis.	Yes
17	Evaluation of data collection: subgroup analyses	Due to the expected small number of cases, it is proposed to calculate and present all relevant subgroup analyses without the requirement of a statistically significant interaction.	No
18	Evaluation of the data collection: Dealing with	For the consideration of data, the corresponding registers/data sets should in principle contain information on all relevant baseline confounders. However, an exclusion of individual patients with remaining missing	No

No.	Topic	G-BA Request	Depicted in 4 February 2021 resolution
	missing confounders	data from all analyses that take these confounders into account does not appear appropriate in view of the small number of cases. It is suggested that remaining missing values for individual patients be replaced by the multiple imputation approach. In addition, information on the extent to which or the reasons for which missing data are to be expected and information on how to deal with implausible data or outliers should be added. Furthermore, a description of the proportions of missing data should be provided.	
19	Evaluation of data collection: dealing with changes in treatment	The division of patients into the proposed "treatment groups" should be changed, as an adequate division of patients must be made by information available at the beginning of the study.	No
20	Evaluation of data collection: dealing with changes in treatment	A Cox model with time-dependent covariates is not considered an adequate method for dealing with treatment changes in the present case. An allocation of treatment-naïve patients to the respective initial treatment (new-user design) is recommended. As a sensitivity analysis, supplementary evaluations should be performed with censoring in the case of treatment changes, whereby the time of censoring should be varied in order to take into account "carry-over" effects for the previous treatment. If the initial question can no longer be answered due to a high proportion of treatment changes, a prevalent-new-user design can be used as an alternative for the evaluation. Whether this option should be used can be decided in each case after data on the course of AbD (see following point) have been submitted to the G-BA and implemented in an amendment to the protocol and SAP.	No
21	Evaluation of data collection: dealing with changes in treatment	Information on the number of patients changing treatment, including the respective times under the different treatments, should be part of the information on the course of AbD to be submitted regularly to the G-BA.	No
22	Evaluation of data collection: Planned	The planned dates for the interim and final analyses differ from those set out in the decision. The analyses to be submitted should be planned in relation to the date of the decision, not in relation to the	Yes

No.	Topic	G-BA Request	Depicted in 4 February 2021 resolution
	analyses	start of the study, and should be carried out as specified in the decision. A futility check should also be performed for each interim analysis.	

Source: (38)

1.3.3 Depiction of change requests in study protocol and SAP

In the context of a non-randomized, non-interventional trial, the exact statistical methodology used for analysis is of critical importance both for the feasibility of the study as well as its ability to generate valid results in light of the specific framework of routine care in Germany for the relevant indication. Accordingly, the German parliamentaty health committee pointed out that "G-BA has to define as specifically as possible the form in which the data collection should be carried out" as part of its rationale and report on the law for more safety in the supply of medicines (Gesetz für mehr Sicherheit in der Arzneimittelversorgung - GSAV), which provides the legal basis for the Routine Data Collection and Evaluations[1]. This is also reflected in § 35a section 3b sentence 4 SGB V, which mandates that G-BA to especially define methodological aspects of the study.

In line with these legal requirements, G-BA code of procedure mandates that the concept for the Routine Data Collection and Evaluations is to include requirements on the "methodology of the data collection" (G-BA Code of Procedure, Chapter 5, § 56, section 1 No. 3). Accordingly, the G-BA resolution mandating a Routine Data Collection and Evaluations is to include "requirements for the data collection and for evaluations on the basis of the concept" (G-BA Code of Procedure, Chapter 5, § 58, section 1 No. 1). This procedure would allow for relevant stakeholders (e.g. medical societies and the pharmaceutical entrepreneurs) to weigh in on methodological aspects of the Routine Data Collection and Evaluations as part of a public consultation procedure (G-BA Code of Procedure, Chapter 5, § 57, section 1).

Neither the IQWiG concept nor the 4 February 2021 G-BA resolution include methodological requirements on key study design aspects (e.g. handling of treatment switches, handling of missing and unplausable data, eligibility of non-parallel data). An inclusion of methodological aspects in the resolution mandating the study according to § 35a section 3b sentence 4 would have allowed for a public consultation procedure to also address key questions on the methodology of the study as well as the impact of methodological aspects on study feasibility. By also

[1] Deutscher Bundestag. Beschlussempfehlung und Bericht from June 5 2019, Drucksache 19/10681, Ausschuss für Gesundheit (14. Ausschuss); 2019 [cited: 2021 Nov 5]. Available from: https://dserver.bundestag.de/btd/19/106/1910681.pdf.

shifting the methodological aspects from a resolution-making procedure to a letter, a public consultation did not take place, although such a consultation would have been very valuable precisely in view of the absolute novelty of the procedure and the methodological principles.

Novartis Gene Therapies believes that the Routine Data Collection and Evaluations would have benefited from a dialog and involvement of medical societies on methodological questions – especially in light of the pilot character of this particular study. Proposals on dialog formats, e.g. via an expert workshop to address methodological questions not covered in the IQWIG concept and G-BA resolution, were put forward both during G-BA advice meetings and in writing by Novartis Gene Therapies but not pursued by G-BA.

With this protocol version, Novartis Gene Therapies includes methodological requests from G-BA in the study concept. Key aspects of the study design could not be consented between G-BA and Novartis Gene Therapies. As a consequence, Novartis Gene Therapies will also conduct statistical analysis according the originally submitted study design, which was developed to incorporate the recommendations of German SMA clinical experts.

Both approaches are depicted in this protocol version and will be submitted to G-BA at each interim analysis as well as with the value dossier scheduled for submission on 1 July, 2027. While an exchange on methodological questions including clinical SMA experts was not possible in the procedure on these Routine Data Collection and Evauations, full transparency on different methodological approaches as well as their influence on the study feasibility and outcomes will support the process of utilizing the best available evidence in a benefit assessment in 2027.

2. Overview of study design and study schematic

2.1 Pre-specification of two analysis approaches

The study is a non-interventional, non-randomized, registry-based data collection. The study is based on secondary use of data from the SMArtCARE registry (40). Upon passing of a corresponding resolution by G-BA, the study will be amended to include secondary use of data from the RESTORE registry (section 6.2) (41).

Participants are enrolled when they first meet the inclusion and exclusion criteria of the study (sections 7.1, 7.2) and are observed until the date of data cut for final analysis or loss to follow-up.

It was not possible to reach an alignment on key aspects of the the study methodology between Novartis Gene Therapies and G-BA/IQWiG incorporating recommendations from medical societies and clinical SMA experts (section 1.3.2, 1.3.3). The study concept depicted in the revised versions of protocol and SAP thus includes two approaches: (1) a methodology developed by Novartis Gene Therapies based on a broad involvement of external clinical and methodological experts (hereafter: “NGT approach”) and (2) the methodology requested by G-BA based on IQWiG’s assessment of study protocol and SAP (hereafter: “G-BA approach”). Table 7 gives an overview of key study design aspects for both approaches.

Table 7: Overview of key similarities and differences between NGT approach and G-BA approach

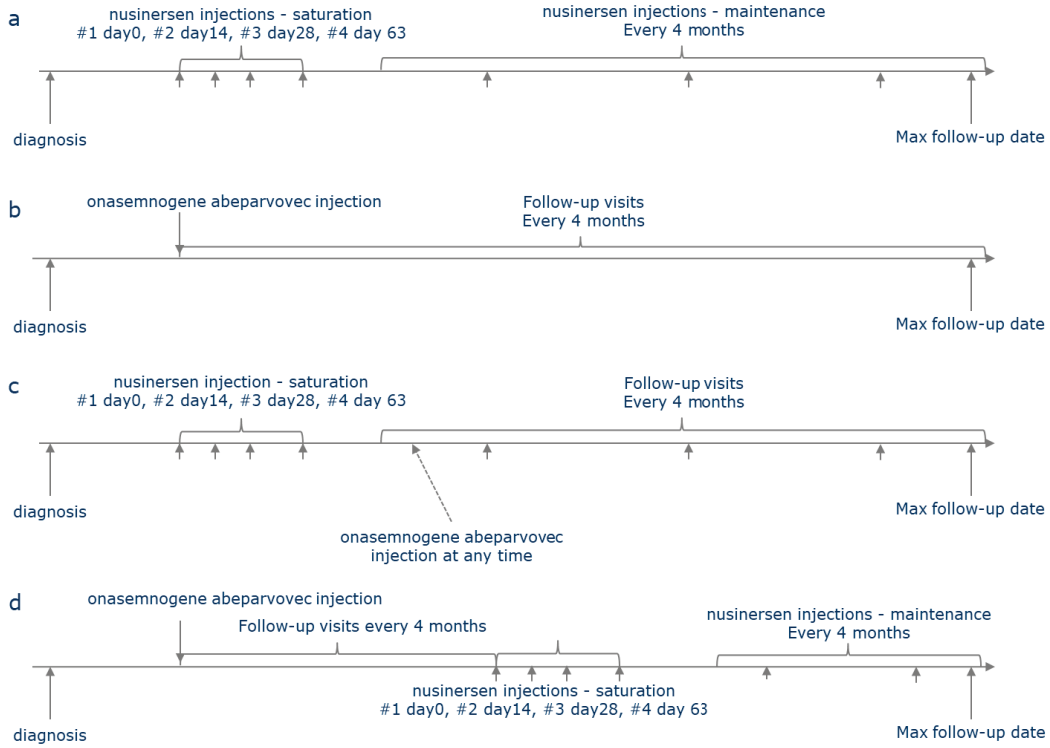
Study design aspect	NGT approach	G-BA approach
Inclusion and exclusion criteria	Key inclusion criteria: ▪ Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene OR ▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA OR ▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene ▪ Treatment initiation with nusinersen (12 mg / 5 ml per administration) or onasemnogene abeparvovec (dosage according to body weight as per SmPC) ▪ Body weight at treatment initiation ≤ 21 kg Key exclusion criteria: ▪ Pretreatment with disease-modifying therapy (nusinersen, onasemnogene abeparvovec, risdiplam) ▪ Pretreatment with any of the following investigational drugs for the treatment of SMA: albuterol/salbutamol,	

Study design aspect	NGT approach	G-BA approach
	riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea	
Analysis populations	▪ NGT-A: Patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 2 copies of the SMN2 gene ▪ NGT-B: Patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and 3 copies of the SMN2 gene	▪ GBA-A: Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 2 copies of the SMN2 gene ▪ GBA-B: Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA ▪ GBA-C: Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and 3 copies of the SMN2 gene ▪ GBA-D: Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene
Handling of treatment switches	Treatment episodes, censoring for treatment switches to risdiplam	Allocation to initial treatment, no censoring for treatment switches
Confounder adjustment	Propensity score methods or conditional regression based on the best suitability for the actual data available	Propensity score methods or matched-pair approach in case of low patient numbers (due to stratification into 4 analysis populations)
Sensitivity analyses	Comparative analysis of treatment patterns: ▪ Nusinersen monotherapy ▪ Onasemnogene abeparvovec monotherapy ▪ Treatment switch from nusinersen to onasemnogene abeparvovec ▪ Add-on therapy of nusinersen after onasemnogene abeparvovec (few to no patients	Censoring for treatment switches Pooled analysis of populations GBA-A and GBA-B (2 copy SMN2) as well as populations GBA-C and GBA-D (3 copy SMN2)

Study design aspect	NGT approach	G-BA approach
	expected)	
Utilization of parallel retrospective data, i.e. collected after availability of onasemnogene abeparvovec	Yes	
Utilization of non-parallel retrospective data, i.e. collected before availability of onasemnogene abeparvovec	If overlap criteria pre-weighting are fulfilled	
Data sources	Primary: SMArtCARE Secondary: RESTORE upon passing of a corresponding resolution by G-BA via amendment	
Study sites	SMArtCARE: Germany and Austria RESTORE (if mandated via G-BA resolution): De novo sites Any registry: ▪ Experience with drug therapy for SMA: use of approved drugs (nusinersen, onasemnogene abeparvovec, risdiplam) in ≥ 15 patients under 18 years of age and ≥ 10 patients under 10 years within 3 years o At study start and for retrospective data: 2018-2020 period o Annual review thereafter to see if new sites are added. No exclusion of sites once included. ▪ Performance of standardized motor function tests for diagnosis by physical therapists with at least two years of experience in physical therapy diagnosis and treatment of children with neuromuscular diseases and training in the performance of standardized, disease-specific muscle function tests.	
Sample size calculation	Standard null-hypothesis	Shifted null-hypothesis and methodology derived from "dramatic effect"
Interim analysis and status reports	18, 36, 54, and 60 months after G-BA resolution from 4 February 2021	

Four types of treatment patterns regarding onasemnogene abeparvovec and nusinersen are possible (Figure 1), of which three are expected in the registry data. In addition to subjects who are (a) treated exclusively with nusinersen or (b) with onasemnogene abeparvovec according to the SmPC, there will also be (c) patients who switch from nusinersen to onasemnogene abeparvovec at a given time point. Patients (d) treated with nusinersen after receiving onasemnogene abeparvovec are theoretically possible, but expected to not occur at all or in very limited numbers because combination therapy is not routinely reimbursed by the Statutory Health Insurance in Germany.

Figure 1: Expected treatment schemes



2.2 NGT approach

Due to the non-interventional nature of Routine Data Collection and Evaluations, it is not possible to regulate therapy changes within the study protocol. Novartis Gene Therapies expects that a significant number of patients included in this study will be characterized by a treatment switch, especially from nusinersen to onasemnogene abeparvovec or risdiplam. No methodological approach exists, which can completely exclude possible bias of treatment effects due to therapy changes.

In an effort to generate best possible evidence in a situation with high patient shares with treatment switches, a treatment episode design is used for main analysis. Patients without treatment switches are characterized by only one treatment episode for the single treatment they have received from inclusion in the study to end of observation. Patients switching from nusinersen to onasemnogene abeparvovec (group c) or receiving nusinersen after onasemnogene abeparvovec (group d) are characterized by two treatment episodes and are is analyzed in terms of treatment episodes under each treatment (section 7.3 of SAP). A treatment episode starts with the day of first administration and ends with the first administration of the respective follow-up intervention or the date of analysis.

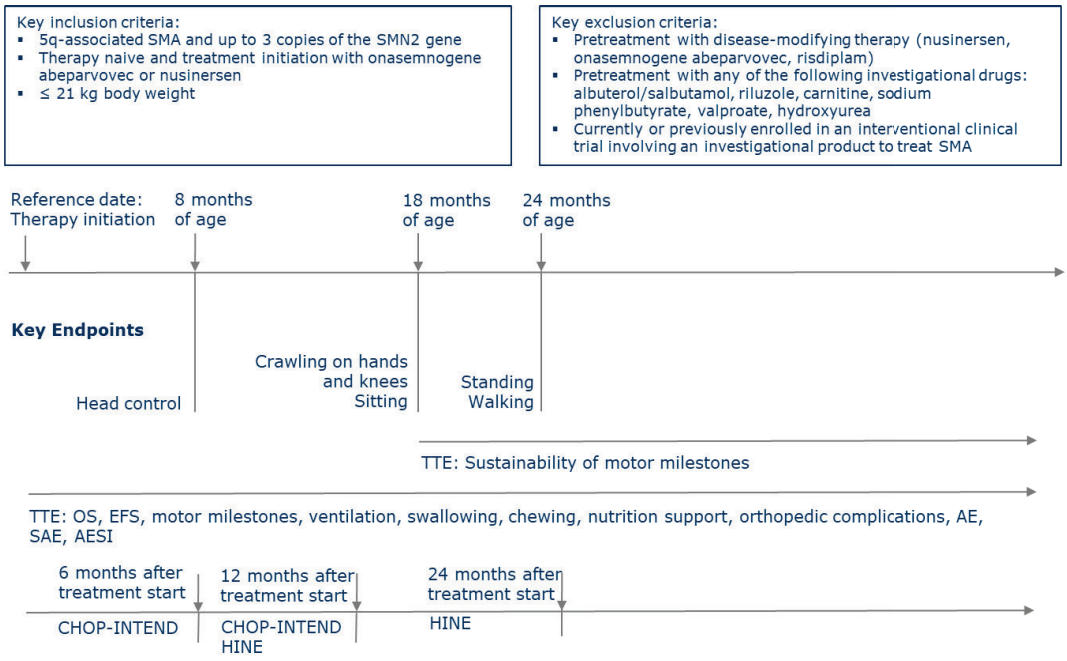
Furthermore, switches from nusinersen to risdiplam and risdiplam to onasemnogene abeparvovec as well as combination therapy of onasemnogene abeparvovec and risdiplam are expected. These will not be investigated, as only nusinersen was defined as the comparator for this study (28). Subjects switching from risdiplam to onasemnogene abeparvovec violate the inclusion criteria of this study. Subjects switching from nusinersen or onasemnogene abeparvovec to risdiplam will be censored at the time of the switch.

In case of substantial number of patients switching from nusinersen to other therapies suggesting a potential deterioration under treatment that might not have been reflected yet into the key study outcomes, missing data handling approaches that consider patients as missing not at random (MNAR) would be considered via an amendment and discussed with G-BA to ensure that appropriate methodology to handle such patients is defined.

For sensitivity analysis, comparative analysis of treatment patterns (a-d) will be performed (section 8.5.1 of SAP). Interpretation of results, especially on the effects of treatment switching, will be based on both the main analysis (treatment episodes) as well as the sensitivity analysis (comparative analysis of treatment patterns).

Fehler! Verweisquelle konnte nicht gefunden werden. Figure 2 shows an overview of the study design.

Figure 2: Overview study design: NGT approach



2.3 G-BA approach

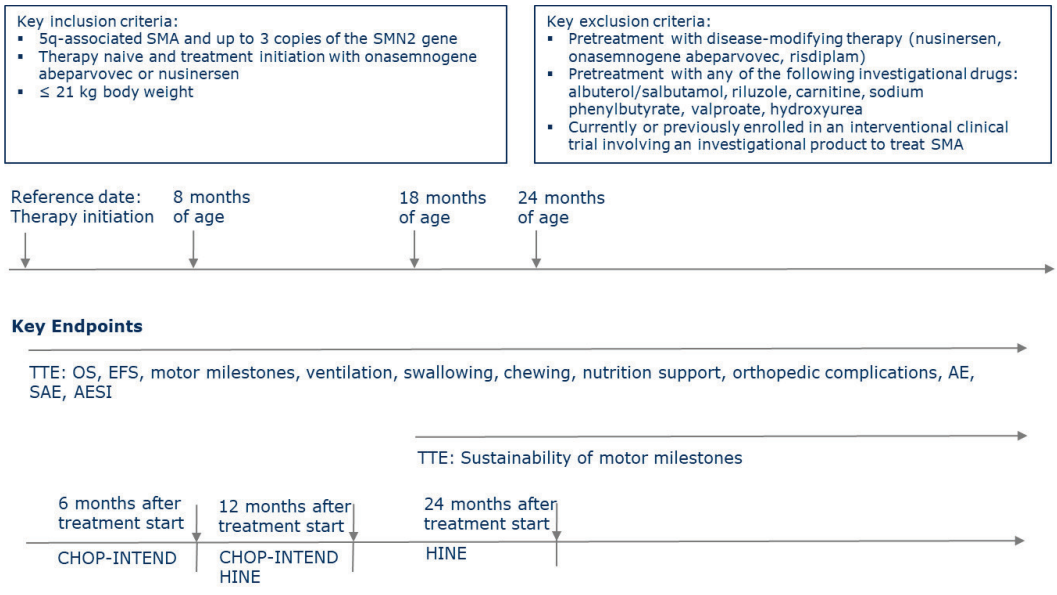
As per change requests No. 10, 19, 20, and 21 (Table 6), main analysis will allocate patients into two treatment arms depending on their initial treatment: 1) nusinersen or 2) onasemnogene abeparvovec. Patients initially treated with risdiplam and switched to nusinersen or onasemnogene abeparvovec violate the inclusion and eclusion criteria of this study (sections 7.1, 7.2) and are thus not allocated to any treatment arm.

Treatment switches from nusinersen to onasemnogene abeparvocec or risdiplam as well as combination therapies of nusinersen or risdiplam after onasemnogene abeparvovec are ignored for main analysis of treatment effects. Accordingly, no censoring, exclusion or any other type of methodological handling of treatment switches is performed.

For sensitivity analysis, patients switching from nusinersen to onasemnogene abeparvocec or risdiplam as well as combination therapies of nusinersen or risdiplam after onasemnogene abeparvovec will be censored (section 8.5.2 of SAP).

Figure 3 shows an overview of the study design.

Figure 3: Overview study design: G-BA approach



3. Compared therapies

3.1 Onasemnogene abeparvovec

3.1.1 Mechanism of action

Onasemnogene abeparvovec is a gene therapy medicinal product that expresses the human SMN protein. It is designed to introduce a functional copy of the SMN1 gene in the transduced cells to address the monogenic root cause of SMA. By providing an alternative source of SMN protein expression in motor neurons, it is expected to promote the survival and function of transduced motor neurons (42).

Onasemnogene abeparvovec is a non-replicating recombinant adeno-associated virus serotype (AAV) vector that utilizes AAV9 capsid to deliver a stable, fully functional human SMN transgene. The SMN1 gene present in onasemnogene abeparvovec is designed to reside as episomal deoxyribonucleic acid (DNA) in the nucleus of transduced cells and is expected to be stably expressed for an extended period of time in post-mitotic cells. The transgene is introduced to target cells as a self-complementary double-stranded molecule. Expression of the transgene is driven by a constitutive promoter (cytomegalovirus enhanced chicken-β-actin-hybrid), which results in continuous and sustained SMN protein expression (42).

3.1.2 Method of administration and dosage

Onasemnogene abeparvovec is administered as a single-dose intravenous infusion. It should be administered with a syringe pump as a single intravenous infusion with a slow infusion of approximately 60 minutes. It must not be administered as an intravenous push or bolus (42).

It is recommended to initiate an immunomodulatory regimen with oral prednisolone starting 24 hours prior to infusion of onasemnogene abeparvovec and continue for 30 days post infusion (including the day of infusion). The further immunomodulatory therapy with gradually lower doses lasts 28 days and can be conducted with oral prednisolone or systemic corticosteroids, depending on the patient´s liver function (42).

The SmPC recommends a dose of nominal 1.1 x 10^{14} vg/kg onasemnogene abeparvovec and determines the total volume by patient body weight (32).

3.2 Nusinersen

3.2.1 Mechanism of action

Nusinersen acts to enhance the amount of functional SMN protein in infants/children and adults with SMA. It replaces the SMN protein deficit which causes SMA, by increasing the splicing efficiency of the SMN2 pre-messenger ribonucleic acid.

More specifically, nusinersen is an antisense oligonucleotide (ASO) which increases the proportion of exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts by binding to an intronic splice silencing site (ISS-N1) found in intron 7 of the SMN2 pre-mRNA. By binding, the ASO displaces splicing factors, which normally suppress splicing. Displacement of these factors leads to retention of exon 7 in the SMN2 mRNA and hence when SMN2 mRNA is produced, it can be translated into the functional full length SMN protein (43).

3.2.2 Method of administration and dosage

Nusinersen is for intrathecal use by lumbar puncture. It is administered as an intrathecal bolus injection over 1 to 3 minutes, using a spinal anesthesia needle. Sedation may be required for administration, as indicated by the clinical condition of the patient. Ultrasound (or other imaging techniques) may be considered to guide intrathecal administration of nusinersen, particularly in younger patients and in patients with scoliosis (43).

The recommended dosage is 12 mg (5 ml) per administration. Nusinersen treatment should be initiated as early as possible after diagnosis with 4 loading doses on Days 0, 14, 28 and 63. A maintenance dose should be administered once every 4 months thereafter (43).

A recent study on nusinersen (DEVOTE) is currently investigating the clinical efficacy and safety of higher doses of nusinersen in a different regimen (44). For example, in deviation from the approved dose, treatment-naïve patients with SMA receive 50 mg nusinersen on days 0 and 14 as a loading dose followed by a maintenance dose of 28 mg after 4-5 months. Patients who have already received the maintenance dose of 12 mg nusinersen for one year will receive 50 mg once 4 months after their last dose and 28 mg every 4 months thereafter.

In case of a positive benefit-risk ratio of the results of the DEVOTE study, a corresponding adjustment of the approval is conceivable. In this case, an amendment of the protocol and SAP of this study will be initiated to depict the exact changes of nusinersen's marketing authorization that may arise.

4. Objectives

The objective of this study is to evaluate the overall effectiveness and safety in therapy-naïve patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene as well as symptomatic patients with 5q-associated SMA type I treated with gene therapy Zolgensma® (onasemnogene abeparvovec) compared to Spinraza® (nusinersen).

The effectiveness and safety will be assessed based on patient-relevant endpoints, which are derived from the G-BA resolution mandating this study (28).

Effectiveness covers the following:

- Survival
- Motor function
- Nutrition
- Orthopedic complications
- Respiratory function
- Planned hospitalizations

Safety covers the following:

- Adverse events (AE)
- Serious adverse events (SAE)
- Adverse events of special interest (AESI)

The outcomes of this study are to be used in a future benefit assessment according to § 35a SGB V in Germany.

5. Endpoints

Due to the non-interventional nature of this real world data collection, the definition of endpoints as primary or secondary is omitted formally. This is in line with the general methods of the German benefit assessment according to § 35a SGB V, which requires the assessment of patient relevant endpoints irrespective of their character as primary vs. secondary in a specific study (45, 46). An endpoint is considered patient relevant if it depicts how a patient feels, can perform his or her functions and activities, or whether he or she survives (46).

The endpoints depicted in this study are based on the Patient-Intervention-Comparator-Outcome (PICO)-Scheme included in the G-BA resolution mandating this study (28). As per the justification to the resolution, mortality and at least one endpoint per morbidity category depicted in the PICO-Scheme is covered in this study:

"In particular, deaths (mortality category) and at least one endpoint from each of the following patient-relevant morbidity categories should be surveyed: Motor functioning (surveyed with age-appropriate instruments), achievement of motor development milestones of the WHO, respiratory function (need for [continuous] ventilation), bulbar function (e.g. ability to swallow and speak), need for oral nutritional support), and further complications of the disease (e.g. pain, orthopedic complications)." (36).

All endpoints and in particular their definitions were coordinated and validated with clinical experts as well as representatives from the SMArtCARE registry. The endpoints event free survival (EFS) / ventilatory support and motor milestones are considered key endpoints and provide reliable results independent of the age of the treated children. They were thus used for initial sample size calculations (section 8.2).

In addition to the endpoints mandated by G-BA, planned hospitalizations are included upon recommendation by clinical experts. Reasons for planned hospitalizations may include – but are not limited to – the administration of disease modifying therapies, the placement of a gastric tube, or orthopedic complications. This combined endpoint thus depicts a patient relevant burden of the disease and its therapy. This is in line with IQWiG's general methods, which clarify that "the intervention- and disease-related effort of the treatment can be taken into account" in assessing the additional benefit of an intervention (46).

The following sections list endpoints and definitions used for the comparison. G-BA requested that endpoints on motor function are reduced and put into a hierarchy to reduce multiplicity (change request No. 2, Table 6). Novartis Gene Therapies aknowledges the issue of multiplicity but regards it as a secondary issue to the more serious challenge of limited power of the study. Novartis Gene Therapies has proposed a study design with only two study populations and linking the time of outcome analysis to reaching sample size required for sufficient power. G-BA has rejected this approach and mandated a design with four analysis populations and

fixed times for outcome analysis irrespective of reaching required sample sizes. As a consequence, it is significantly less likely that sufficient power will be reached in the G-BA approach. Irrespective of these concerns, a reduced list of motor function endpoints used for G-BA mandated analyses (G-BA approach) is depicted in section 5.1.2.2. All other endpoints will be applied for both NGT and G-BA approaches.

Health-related quality of life (HRQoL) is not surveyed in German routine care and not included in the SMArtCARE registry. HRQoL thus cannot be depicted in this registry-based, non-interventional study.

5.1 Effectiveness

5.1.1 Survival

Table 8: Effectiveness endpoints: Survival

Endpoint	Definition	Fields of SMArtCARE CRF (47)
Overall Survival (OS)	Time from the date of first treatment to the date of death due to any cause	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ End of data collection: Date of death ▪ Medical assessment: Visit date
Event Free Survival (EFS)	Time from the date of first treatment to the date of death due to any cause or first of two consecutive documentations of permanent ventilation of at least 16 hours per day	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ End of data collection: Date of death ▪ Medical assessment: Visit date ▪ Medical assessment: Time of ventilator use = Continuous (>16h/day)

5.1.2 Motor function

5.1.2.1 NGT approach

Table 9: Effectiveness endpoints: Motor function (NGT approach)

Endpoint	Definition	Fields of SMArtCARE CRF (47)
Achievement of motor milestones according to age	Proportion of patients achieving motor milestone as appropriate to their age at the time of outcome analysis Age limits per milestone	▪ Medical assessment: Best current motor function ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled)

Endpoint	Definition	Fields of SMArtCARE CRF (47)
	(based on WHO (48)) ▪ Sitting without support: 9.2 months ▪ Crawl on hands and knees: 13.5 months ▪ Standing without support: 16.9 months ▪ Walking without support: 17.6 months	▪ *Note: SMArtCARE refers to the WHO performance criteria (49) as guidance.*
Head control at the age of 8 months	Proportion of patients achieving a score of 2 for head control according to HINE until reaching 8 months of age	▪ Medical assessment: Age at visit ▪ Medical Assessment: HINE: Head control
Crawl on hands and knees at the age of 18 months	Proportion of patients achieving the motor milestone of crawling on hands and knees at or before the age of 18 months	▪ Medical assessment: Best current motor function = Crawl on hands and knees or higher motor milestone (Standing without support, Walking without support, or Climb stairs) ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled) ▪ *Note: SMArtCARE refers to the WHO performance criteria (49) as guidance: "Child alternately moves forward or backward on hands and knees. The stomach does not touch the dupporting surface. There are continuous and consecutive movements, at least three in a row."*
Sitting without support at the age of 18 months	Proportion of patients achieving the motor milestone of sitting without support at or before the age of 18 months	▪ Medical assessment: Best current motor function = Sitting without support or higher motor milestone (Crawl on hands and knees, Standing without support, Walking without support, or Climb stairs) ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled) *Note: SMArtCARE refers to the WHO performance criteria (49) as guidance:*

Endpoint	Definition	Fields of SMArtCARE CRF (47)
		"Child sits up straight with the head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position."
Standing without support at the age of 24 months	Proportion of patients achieving the motor milestone of standing without support at or before the age of 24 months	▪ Medical assessment: Best current motor function = Standing without support or higher motor milestone (Walking without support or Climb stairs) ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled) *Note: SMArtCARE refers to the WHO performance criteria (49) as guidance: "Child stands in upright position on both feet (not on the toes) with the back straight. The legs support 100% of the child's weight. There is no contact with a person or object. Child stands alone for at least 10 seconds."*
Walking without support at the age of 24 months	Proportion of patients achieving the motor milestone of walking without support at or before the age of 24 months	▪ Medical assessment: Best current motor function = Walking without support or higher motor milestone (Climb stairs) ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled) *Note: SMArtCARE refers to the WHO performance criteria (49) as guidance: "Child takes at least five steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object."*
Sustainability of motor milestones	Time from gaining motor milestone to permanent loss of milestone ability ▪ Loss of the ability to sit without support ▪ Loss of the ability to stand without support ▪ Loss of the ability to walk without support	▪ Medical assessment: Visit date ▪ Medical assessment: Best current motor function ▪ Medical assessment: Changes in motor milestones ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age lost of previous motor milestone

Endpoint	Definition	Fields of SMArtCARE CRF (47)
	Documentation of the new (worsened) highest motor milestone at 2 consecutive visits is required.	▪ Baseline: Sitting without support (if gained: Age gained) ▪ Baseline: Standing without support (if gained: Age gained) ▪ Baseline: Walking without support (if gained: Age gained)
CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders): Change from baseline	Change in CHOP-INTEND score from baseline at ▪ 6 months after initial treatment ▪ 12 months after initial treatment *Note: Endpoint of exploratory nature due to uncertainties regarding experience, training, and certification of physical therapists in using the scoring instrument*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ CHOP-INTEND: Date of evaluation ▪ CHOP-INTEND: Score
HINE (Hammersmith Infant Neurological Examination): Change from baseline	Change in HINE score from baseline at ▪ 12 months after initial treatment ▪ 24 months after initial treatment *Note: Endpoint of exploratory nature due to uncertainties regarding experience, training, and certification of physical therapists in using the scoring instrument*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical Assessment: HINE: Visit date ▪ Medical Assessment: HINE: Score
Time to sitting without support	Time from the age at first treatment to the age at reaching motor milestone of sitting without support *Note: Endpoint of exploratory nature due to uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed)*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Best current motor function = Sitting without support or higher motor milestone (Crawl on hands and knees, Standing without support, Walking without support, or Climb stairs) ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled) *Note: SMArtCARE refers to the WHO*

Endpoint	Definition	Fields of SMArtCARE CRF (47)
		performance criteria (49) as guidance: "Child sits up straight with the head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position."
Time to standing without support	Time from the age at first treatment to the age at reaching motor milestone of standing without support *Note: Endpoint of exploratory nature due to uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed)*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Best current motor function = Standing without support or higher motor milestone (Walking without support or Climb stairs) ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled) *Note: SMArtCARE refers to the WHO performance criteria (49) as guidance: "Child stands in upright position on both feet (not on the toes) with the back straight. The legs support 100% of the child's weight. There is no contact with a person or object. Child stands alone for at least 10 seconds."*
Time to walking without support	Time from the age at first treatment to the age at reaching motor milestone of walking without support *Note: Endpoint of exploratory nature due to uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed)*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Best current motor function = Walking without support or higher motor milestone (Climb stairs) ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled) *Note: SMArtCARE refers to the WHO performance criteria (49) as guidance: "Child takes at least five steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object."*

For TTE analyses of motor milestones, there are uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed) as well as potential bias from different frequencies of visits between the study interventions.

5.1.2.2 G-BA approach

Table 10: Effectiveness endpoints: Motor function (G-BA approach)

Endpoint	Definition	Fields of SMArtCARE CRF (47)
Time to sitting without support	Time from the age at first treatment to the age at reaching motor milestone of sitting without support	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Best current motor function = Sitting without support or higher motor milestone (Crawl on hands and knees, Standing without support, Walking without support, or Climb stairs) ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled) ▪ *Note: SMArtCARE refers to the WHO performance criteria (49) as guidance: "Child sits up straight with the head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position."*
Time to standing without support	Time from the age at first treatment to the age at reaching motor milestone of standing without support	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Best current motor function = Standing without support or higher motor milestone (Walking without support or Climb stairs) ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled) ▪ *Note: SMArtCARE refers to the WHO performance criteria (49) as guidance: "Child stands in upright position on both feet (not on the toes) with the back straight. The legs support 100% of the child's weight. There is no contact with a*

Endpoint	Definition	Fields of SMArtCARE CRF (47)
		person or object. Child stands alone for at least 10 seconds."
Time to walking without support	Time from the age at first treatment to the age at reaching motor milestone of walking without support	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Best current motor function = Walking without support or higher motor milestone (Climb stairs) ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age at visit (if age gained of new motor milestone not filled) ▪ *Note: SMArtCARE refers to the WHO performance criteria (49) as guidance: "Child takes at least five steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object."*
Sustainability of motor milestones	Time from gaining motor milestone to permanent loss of milestone ability ▪ Loss of the ability to sit without support ▪ Loss of the ability to stand without support ▪ Loss of the ability to walk without support Documentation of the new (worsened) highest motor milestone at 2 consecutive visits is required.	▪ Medical assessment: Visit date ▪ Medical assessment: Best current motor function ▪ Medical assessment: Changes in motor milestones ▪ Medical assessment: Age gained of new motor milestone ▪ Medical assessment: Age lost of previous motor milestone ▪ Baseline: Sitting without support (if gained: Age gained) ▪ Baseline: Standing without support (if gained: Age gained) ▪ Baseline: Walking without support (if gained: Age gained)
CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders): Change from baseline	Change in CHOP-INTEND score from baseline at ▪ 6 months after initial treatment ▪ 12 months after initial treatment	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ CHOP-INTEND: Date of evaluation ▪ CHOP-INTEND: Score
HINE (Hammersmith Infant Neurological Examination): Change from baseline	Change in HINE score from baseline at ▪ 12 months after initial treatment ▪ 24 months after initial	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical Assessment: HINE: Visit date ▪ Medical Assessment: HINE: Score

Endpoint	Definition	Fields of SMArtCARE CRF (47)
	treatment	

For TTE analyses of motor milestones, there are uncertainties regarding the method of reporting age at reaching milestone (parent-reported vs. neuropediatrician confirmed) as well as potential bias from different frequencies of visits between the study interventions.

5.1.3 Nutrition

Table 11: Effectiveness endpoints: Nutrition

Endpoint	Definition	Fields of SMArtCARE CRF (47)
Difficulties in swallowing	Time from the date of first reatment to the first documented difficulties in swallowing	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Visit date ▪ Medical assessment: Swallowing? = With difficulties
Difficulties in chewing	Time from the date of first reatment to the first documented difficulties in chewing	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Visit date ▪ Medical assessment: Chewing? = With difficulties
Gastric or nasal feeding tube	Time from the date of first treatment to the start date of first tube feeding of two consecutive documentations ▪ Any type of tube feeding (supplementary or exclusively) ▪ Supplementary (e.g. for fluids) ▪ Exclusively	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes - exclusively fed by tube ▪ Medical assessment: Does the patient use a gastric or nasal feeding tube? = Yes – supplementary e.g. for fluids ▪ Medical assessment: Start of tube feeding (date) ▪ Medical assessment: Visit date (if start date of feeding tube not filled)

5.1.4 Orthopedic complications

Table 12: Effectiveness endpoints: Orthopedic complications

Endpoint	Definition	Fields of SMArtCARE CRF (47)
Scoliosis or orthopedic surgery	Time from the date of first treatment to first documentation of scoliosis or orthopedic surgery	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Visit date ▪ Medical assessment: Does the patient have scoliosis? ▪ Medical assessment: Orthopedic surgery since last visit?
Scoliosis	Time from the date of first treatment to first documentation of scoliosis	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Visit date ▪ Medical assessment: Does the patient have scoliosis?
Orthopedic surgery	Time from the date of first treatment to first documentation of orthopedic surgery	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Visit date ▪ Medical assessment: Orthopedic surgery since last visit?

5.1.5 Respiratory function

Table 13: Effectiveness endpoints: Respiratory function

Endpoint	Definition	Fields of SMArtCARE CRF (47)
Time of ventilator use	Time from the date of first treatment to the first of two consecutive documentations of ▪ Any ventilator support ▪ Ventilator support at night (during sleep) ▪ Intermittent ventilator support at day time and continuous at night ▪ Permanent ventilator support (>16 hours per day) ▪ Intermittent ventilator support with acute illnesses Documentation of same or higher ventilator support time required at 2 consecutive visits.	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Visit date ▪ Medical assessment: Does the patient receive ventilator support? ▪ Medical assessment: Time of ventilator use ○ Night (during sleep) ○ Intermittent day time and continuous at night ○ Continuous (>16h/day) ○ Intermittent with acute illnesses

Endpoint	Definition	Fields of SMArtCARE CRF (47)
Type of ventilator use	Time from the date of first treatment to the first of two consecutive documentations of (each separately) ▪ Non-invasive ventilation ▪ Invasive ventilation Documentation of same or higher ventilator support type required at 2 consecutive visits.	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Visit date ▪ Medical assessment: Does the patient receive ventilator support? ▪ Medical assessment: Type of ventilation o Non-invasive o Invasive
Improvement in time of ventilator support from baseline	Time from the date of first treatment to the first of two consecutive documentations of an improvement in time of ventilator use. An improvement is defined as any of the following ▪ Change from permanent ventilator support (>16 hours per day) to ventilator support at night (during sleep) or intermittent ventilator support at day time and continuous at night or no ventilator support OR ▪ Change from intermittent ventilator support at day time and continuous at night to ventilator support at night (during sleep) or no ventilator support OR ▪ Change from ventilator support at night (during sleep) to no ventilator support	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Visit date ▪ Medical assessment: Does the patient receive ventilator support? ▪ Medical assessment: Time of ventilator use o Night (during sleep) o Intermittent day time and continuous at night o Continuous (>16h/day)

5.1.6 Planned hospitalizations

Table 14: Effectiveness endpoints: Planned hospitalizations

Endpoint	Definition	Fields of SMArtCARE CRF (47)
Planned hospitalizations	Cumulative number of planned hospitalizations across all patients per pa-	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Medical assessment: Visit date ▪ Medical assessment:

Endpoint	Definition	Fields of SMArtCARE CRF (47)
	tient-year of being at risk including planned hospitalizations for administration of SMA treatments	Planned hospitalisation since last visit (except for treatment administration)? ▪ Medical assessment: Reason for hospitalisation ▪ Nusinersen/Zolgensma: Care Setting = Inpatient (overnight) *Note: Onasemnogene abeparvovec is exclusively administered in an inpatient setting in Germany. SMArtCARE SAP accordingly refers to the hospitalization for treatment. One planned hospitalization is counted for each patient receiving onasemnogene abeparvovec at the date of treatment.*

5.2 Safety

5.2.1 Adverse events

Table 15: Safety endpoints: Adverse events

Endpoint	Definition	Fields of SMArtCARE CRF (47)
Adverse events	Cumulative number of patients with and number of adverse events with or without hospitalization across all patients per patient-year of being at risk *Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Any unexpected events without hospitalisation? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: MedDRA code of acute event ▪ Adverse events: Type of unexpected event ▪ Adverse events: Start date ▪ Adverse events: Date recorded (in case start date is not filled) ▪ Adverse events: name of drug
Adverse events releted to treatment	Cumulative number of patients with and number of adverse events related to treatment (yes/possibly) with or without hospitalization across all patients per	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Any unexpected

Endpoint	Definition	Fields of SMArtCARE CRF (47)
	patient-year of being at risk *Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.*	events without hospitalisation? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: MedDRA code of acute event ▪ Adverse events: Type of unexpected event ▪ Adverse events: Start date ▪ Adverse events: Date recorded (in case start date is not filled) ▪ Adverse events: Is the adverse event related to drug treatment? ▪ Adverse events: name of drug
Adverse events without hospitalization	Cumulative number of patients with and number of adverse events without hospitalization across all patients per patient-year of being at risk *Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Any unexpected events without hospitalisation? ▪ Adverse events: MedDRA code of acute event ▪ Adverse events: Start date ▪ Adverse events: name of drug
Adverse events without hospitalization related to treatment	Cumulative number of patients with and number of adverse events related to treatment (yes/possibly) without hospitalization across all patients per patient-year of being at risk *Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Any unexpected events without hospitalisation? ▪ Adverse events: MedDRA code of acute event ▪ Adverse events: Start date ▪ Adverse events: Is the adverse event related to drug treatment? ▪ Adverse events: name of drug

5.2.2 Serious adverse events

Serious adverse events (SAE) are not directly documented in SMArtCARE (50). SMArtCARE supports documenting adverse events that lead to unplanned or prolonged hospitalization, which is considered the most common criterion for an adverse event being classified as serious in SMA by clinical SMA experts. SMArtCARE does not, however, document the following, remaining criteria for serious adverse events:

- Adverse events leading to death
- Life-threatening adverse events
- Adverse events leading to permanent or serious disability or invalidity
- Development of a congenital anomaly or birth defect

It is assumed that most – if not all – life-threatening adverse events as well as those leading to permanent or serious disability or invalidity will coincide with an unplanned or prolonged hospitalization and would thus be captured. Developments of a congenital anomaly or birth defect is not expected to play a role for the study population of infants and young children.

To approximate serious adverse in this study, endpoints for adverse events leading to hospitalization as well as for adverse events leading to hospitalization or death of any cause are defined. Death of any cause is used for the endpoint definition as no data is captured in SMArtCARE on adverse events leading to death.

Table 16: Safety endpoints: Serious adverse events

Endpoint	Definition	Fields of SMArtCARE CRF (47)
Adverse events with hospitalization	Cumulative number of patients with and number of adverse events with hospitalization across all patients per patient-year of being at risk *Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: MedDRA code of acute event ▪ Adverse events: Start date ▪ Adverse events: name of drug
Adverse events with hospitalization related to treatment	Cumulative number of patients with and number of adverse events related to treatment (yes/possibly) with hospitalization across all patients per patient-year of being at risk *Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: MedDRA code of acute event ▪ Adverse events: Start date ▪ Adverse events: Is the adverse event related to drug treatment? ▪ Adverse events: name of drug

Endpoint	Definition	Fields of SMArtCARE CRF (47)
Adverse events with hospitalization or death of any cause	Cumulative number of patients with and number of adverse events with hospitalization or death of any cause across all patients per patient-year of being at risk *Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: MedDRA code of acute event ▪ Adverse events: Start date ▪ Adverse events: name of drug ▪ End of data collection: Date of death
Adverse events with hospitalization or death of any cause related to treatment	Cumulative number of patients with and number of adverse events related to treatment (yes/possibly) with hospitalization or death of any cause across all patients per patient-year of being at risk *Reporting by MedDRA (SOC/PT). Coding from free text documentation if no MedDRA code was documented.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: MedDRA code of acute event ▪ Adverse events: Start date ▪ Adverse events: Is the adverse event related to drug treatment? ▪ Adverse events: name of drug ▪ End of data collection: Date of death

5.2.3 Adverse events of special interest

According to the G-BA resolution and justification of resolution mandating this study, serious specific unwanted side effects identified on the basis of the information provided in the Risk Management Plan and the European Public Assessment Report (EPAR) of the intervention onasemnogene abeparvovec and the comparator nusinersen should be surveyed. This should include hepatotoxicity, thrombocytopenia, cardiac events, dorsal root ganglia cell inflammation, renal toxicity, and hydrocephalus (36).

This requirement was discussed with clinical experts as well as representatives from the SMArtCARE registry to evaluate if there are generally accepted clinical thresholds or criteria that can be applied. This is currently not the case and Novartis Gene Therapies had considered it sufficient to cover these adverse events of special interest in the MedDRA-based reporting of adverse events that is planned for this study.

SMArtCARE has documented the following specific adverse events and adverse events with hospitalization using specific checkboxes from its initiation, which were based on specific reporting needs for nusinersen:

- Respiratory tract infection
- Hydrocephalus
- Epileptic seizure
- Post lumbar puncture syndrome

Based on G-BA change request No. 3 (Table 6), SMArtCARE will add checkboxes for the following adverse events and adverse events with hospitalization to its CRF:

- Hepatotoxicity
- Thrombocytopenia
- Cardiac events
- Dorsal root ganglia cell inflammation
- Renal toxicity

In general, SMArtCARE requires documented adverse events if, in the investigator's opinion, they are considered clinically significant. Clinical significance is defined as any abnormality that causes a deviation from standard care (e.g., additional tests or measures).

Table 17: Safety endpoints: Adverse events of special interest

Endpoint	Definition	Fields of SMArtCARE CRF (47)
Hydrocephalus with or without hospitalization	Cumulative number of patients with and number of adverse events of hydrocephalus per patient-year of being at risk *Analysis based on specific checkbox in SMArtCARE CRF pre- and post CRF update.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: Any unexpected events without hospitalisation? ▪ Adverse events: Type of unexpected event = Hydrocephalus ▪ Adverse events: Start date ▪ Adverse events: name of drug
Hydrocephalus with hospitalization	Cumulative number of patients with and number of adverse events of hydrocephalus per patient-year of being at risk	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last

Endpoint	Definition	Fields of SMArtCARE CRF (47)
	Analysis based on specific checkbox in SMArtCARE CRF pre- and post CRF update.	visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: Type of unexpected event = Hydrocephalus ▪ Adverse events: Start date ▪ Adverse events: name of drug
Hepatotoxicity with or without hospitalization	Cumulative number of patients with and number of adverse events of hepatotoxicity per patient-year of being at risk *Analysis based on specific checkbox in SMArtCARE CRF post CRF update.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: Any unexpected events without hospitalisation? ▪ Adverse events: Type of unexpected event = Hepatotoxicity ▪ Adverse events: Start date ▪ Adverse events: name of drug
Hepatotoxicity with hospitalization	Cumulative number of patients with and number of adverse events of hepatotoxicity per patient-year of being at risk *Analysis based on specific checkbox in SMArtCARE CRF post CRF update.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: Type of unexpected event = Hepatotoxicity ▪ Adverse events: Start date ▪ Adverse events: name of drug
Thrombocytopenia with or without hospitalization	Cumulative number of patients with and number of adverse events of thrombocytopenia per patient-year of being at risk *Analysis based on specific checkbox in SMArtCARE CRF post CRF update.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: Any unexpected events without hospitalisation? ▪ Adverse events: Type of unexpected event = Thrombocytopenia ▪ Adverse events: Start date

Endpoint	Definition	Fields of SMArtCARE CRF (47)
		▪ Adverse events: name of drug
Thrombocytopenia with hospitalization	Cumulative number of patients with and number of adverse events of thrombocytopenia per patient-year of being at risk *Analysis based on specific checkbox in SMArtCARE CRF post CRF update.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: Type of unexpected event = Thrombocytopenia ▪ Adverse events: Start date ▪ Adverse events: name of drug
Cardiac events with or without hospitalization	Cumulative number of patients with and number of cardiac adverse events per patient-year of being at risk *Analysis based on specific checkbox in SMArtCARE CRF post CRF update.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: Any unexpected events without hospitalisation? ▪ Adverse events: Type of unexpected event = Cardiac events ▪ Adverse events: Start date ▪ Adverse events: name of drug
Cardiac events with hospitalization	Cumulative number of patients with and number of cardiac adverse events per patient-year of being at risk *Analysis based on specific checkbox in SMArtCARE CRF post CRF update.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: Type of unexpected event = Cardiac events ▪ Adverse events: Start date ▪ Adverse events: name of drug
Dorsal root ganglia cell inflammation with or without hospitalization	Cumulative number of patients with and number of adverse events of dorsal root ganglia cell inflammation per patient-year of being at risk	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been

Endpoint	Definition	Fields of SMArtCARE CRF (47)
	Analysis based on specific checkbox in SMArtCARE CRF post CRF update.	unplanned or prolonged hospitalisation? ▪ Adverse events: Any unexpected events without hospitalisation? ▪ Adverse events: Type of unexpected event = Dorsal root ganglia cell inflammation ▪ Adverse events: Start date ▪ Adverse events: name of drug
Dorsal root ganglia cell inflammation with hospitalization	Cumulative number of patients with and number of adverse events of dorsal root ganglia cell inflammation per patient-year of being at risk *Analysis based on specific checkbox in SMArtCARE CRF post CRF update.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: Type of unexpected event = Dorsal root ganglia cell inflammation ▪ Adverse events: Start date ▪ Adverse events: name of drug
Renal toxicity with or without hospitalization	Cumulative number of patients with and number of adverse events of renal toxicity per patient-year of being at risk *Analysis based on specific checkbox in SMArtCARE CRF post CRF update.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: Any unexpected events without hospitalisation? ▪ Adverse events: Type of unexpected event = Renal toxicity ▪ Adverse events: Start date ▪ Adverse events: name of drug
Renal toxicity with hospitalization	Cumulative number of patients with and number of adverse events of renal toxicity per patient-year of being at risk *Analysis based on specific checkbox in SMArtCARE CRF post CRF update.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: Type of unexpected event = Renal toxicity ▪ Adverse events: Start date

Endpoint	Definition	Fields of SMArtCARE CRF (47)
		▪ Adverse events: name of drug
Respiratory tract infection with or without hospitalization	Cumulative number of patients with and number of adverse events of respiratory tract infection per patient-year of being at risk *Analysis based on specific checkbox in SMArtCARE CRF pre- and post CRF update.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: Any unexpected events without hospitalisation? ▪ Adverse events: Type of unexpected event = Respiratory tract infection ▪ Adverse events: Start date ▪ Adverse events: name of drug
Respiratory tract infection with hospitalization	Cumulative number of patients with and number of adverse events of respiratory tract infection per patient-year of being at risk *Analysis based on specific checkbox in SMArtCARE CRF pre- and post CRF update.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: Type of unexpected event = Respiratory tract infection ▪ Adverse events: Start date ▪ Adverse events: name of drug
Epileptic seizure with or without hospitalization	Cumulative number of patients with and number of adverse events of epileptic seizure per patient-year of being at risk *Analysis based on specific checkbox in SMArtCARE CRF pre- and post CRF update.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: Any unexpected events without hospitalisation? ▪ Adverse events: Type of unexpected event = Epileptic seizure ▪ Adverse events: Start date ▪ Adverse events: name of drug
Epileptic seizure with hospitalization	Cumulative number of patients with and number of adverse events of epileptic	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded

Endpoint	Definition	Fields of SMArtCARE CRF (47)
	seizure per patient-year of being at risk *Analysis based on specific checkbox in SMArtCARE CRF pre- and post CRF update.*	▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: Type of unexpected event = Epileptic seizure ▪ Adverse events: Start date ▪ Adverse events: name of drug
Post lumbar puncture syndrome with or without hospitalization	Cumulative number of patients with and number of adverse events of post lumbar puncture syndrome per patient-year of being at risk *Analysis based on specific checkbox in SMArtCARE CRF pre- and post CRF update.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: Any unexpected events without hospitalisation? ▪ Adverse events: Type of unexpected event = Post lumbar puncture syndrome ▪ Adverse events: Start date ▪ Adverse events: name of drug
Post lumbar puncture syndrome with hospitalization	Cumulative number of patients with and number of adverse events of post lumbar puncture syndrome per patient-year of being at risk *Analysis based on specific checkbox in SMArtCARE CRF pre- and post CRF update.*	▪ Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Adverse events: Date recorded ▪ Adverse events: Has there been any adverse event since the last visit? ▪ Adverse events: Has there been unplanned or prolonged hospitalisation? ▪ Adverse events: Type of unexpected event = Post lumbar puncture syndrome ▪ Adverse events: Start date ▪ Adverse events: name of drug

The specific documentation of hepatotoxicity, thrombocytopenia, cardiac events, dorsal root ganglia cell inflammation, and renal toxicity in SMArtCARE can only be applied prospectively following the update of SMArtCARE's CRF. All adverse events possibly relating to the five AESIs mandated by G-BA that require an update of SMArtCARE's CRF generally covered retrospectively in the MedDRA-based reporting of AEs (section 5.2.2, 5.2.2).

6. Data sources

IQWiG identified the RESTORE registry (41), the German Patient SMA registry (as part of the Global TREAT-NMD SMA Global Registry (51–53) and the SMArtCARE registry (40) as potentially suitable registries via literature research (30). Their suitability for the present Routine Data Collection and Evaluations was evaluated in detail.

The German Patient SMA registry (as part of the Global TREAT-NMD SMA Registry) does not collect longitudinal data, i.e. no data on effectiveness, and is therefore not eligible as data source (30).

According to IQWiG, the RESTORE registry bears risk of selection bias as there are differences in the completeness of patients treated with onasemnogene abeparvovec and nusinersen. Moreover, the recruiting centers that collect patient-level data on both interventions ("de novo sites") are exclusively located in the United States of America, whereas there are no such recruiting centers exist in Germany so far (30). As such, differences in standard of care between the United States and Germany are expected to manifest in the RESTORE data.

In its 4 February 2021 G-BA resolution and its justification, G-BA thus defined SMArtCARE as the primary registry and required the "use of an indication register in which spinal muscular atrophy is treated in accordance with everyday care in Germany or is sufficiently similar to care in Germany" (28). The integration of other registries was defined as possible – not mandatory – if the quality criteria depicted in Table 5 were fulfilled. It was also noted that "if there are relevant differences in the standard of care in another country, registry data from this country should not be used for the present routine data collection and evaluations". This concern was also put forward by the Drug Commission of the German Medical Association, which expressed concern that an inclusion of non-national registries might induce bias due to different national regulations of reimbursement (54).

Based on the conclusions of the IQWiG concept as well as the provisions of the G-BA resolution mandating this study, Novartis Gene Therapies had defined SMArtCARE as the exclusive data source for this study and further restricted to data from study sites in Germany that fulfil the quality criteria defined by G-BA for the use of onasemnogene abeparvovec (55).

Irrespective of these provisions, G-BA has requested that "the pharmaceutical company should make the necessary adjustments to the self-managed RESTORE registry in accordance with the final study protocol and SAP for the Routine Data Collection and Evaluations in order to be able to use evaluations based on the RESTORE registry together with the present registry study, e.g. in the form of a meta-analysis for the Routine Data Collection and Evaluations." (Change request No. 6, Table 6).

Since G-BA did not pass a resolution on the change requests, there was no public consultation procedure and there is no justification that would allow for further interpretation of these requests. Although Novartis Gene Therapies understands

and shares G-BA's motivation to increase patient numbers for the Routine Data Collection and Evaluations, it remains unclear how the three above-mentioned change requests are compatible to the provisions of the 4 February 2021 G-BA resolution and its justification regarding the requirement that "if there are relevant differences in the standard of care in another country, registry data from this country should not be used for the present routine data collection and evaluations".

Routine care of patients treated with onasemnogene abeparvovec in Germany is regulated by G-BA and characterized by two important provisions: First, nationwide newborn screening is in place since October 2021 (56). While G-BA communicated doubts that nationwide newborn screening will actually be implemented quickly according to its resolution during the advice meeting on 11 August 2021, it will certainly be fully implemented by 2027, when the transferability of any study results to the German standard of care will be discussed in a benefit assessment. Second, patients in Germany may only be treated with onasemnogene abeparvovec at sites fulfilling the quality assurance guideline passed by G-BA (32).

Study sites in RESTORE providing individual-level data eligible for the purposes of this study ("de novo sites") are exclusively located in the United States of America. Consortia sites located in other geographies to dot provide patient-level data but only aggregated data on nusinersen into RESTORE. In contrast to routine care in Germany, there is no currently nationwide newborn screening in the United States. While passed by the federal government, it has to be implemented on a state level, with different initiatives being in different stages of implementation (57). Reimbursement of SMA therapies is also very different from Germany with a segmented healthcare market (private payers, Medicaid), prior authorization, individual payers' decisions on formularies, coverage and reimbursement of combination therapy, as well as a general absence of universal health insurance.

Novartis Gene Therapies cannot influence that healthcare systems and reimbursement situations differ significantly between the United States of America and Germany. A decision on the inclusion of RESTORE is thus a consideration between increasing patient numbers of this study on the one hand and introducing potential bias from differences and transferability of treatment and reimbursement landscapes on the other hand.

Should G-BA decide to accept the potential bias from differences in treatment and reimbursement landscape and include results from the RESTORE registry in its benefit assessment of onasemnogene apeparvovec based on the results of the Routine Data Collection and Evaluations, Novartis Gene Therapies will will prespecify all alayses in the RESTORE registry that can be depicted based on the available data. This would be limited to data from sites providing patient-level data on both nusinersen and onasemnogene abeparvovec as consortia data provided from other geographies only include aggregated data on nusinersen.

The addition of all analyses in RESTORE will be performed via an amendment to the study protocol and SAP following a corresponding resolution changing the

provisions of the 4 February resolution by G-BA. If requested, the amendment will pre-specify all analyses to be performed in the eligible RESTORE data in addition to SMArtCARE. Analyses will be conducted within each data source and presented to G-BA. If the results meet homogeneity criteria, meta-analysis will be performed. To support this decision process, information on the RESTORE registry is provided in Table 20.

6.1 SMArtCARE registry

The SMArtCARE registry is a joined initiative of academic institutions and patient organizations and supported by pharmaceutical industry. The contractual framework is set up in a way that the academic network has full data ownership and publication rights. SMArtCARE does not transfer patient level data to pharmaceutical companies. If data analysis is needed for regulatory purposes, this is done via an independent third party. All studies and data analysis require prior approval of the SMArtCARE steering committee.

Data for the SMArtCARE registry is collected mainly in German centers and includes information on potential confounders. Data quality is ensured by standardized data collection, staff training at the participating centers, plausibility checks and queries. Physiotherapeutic evaluation is performed by appropriately trained physiotherapists and according to WHO criteria (50). Source data verification will be implemented as described in section 10.2 of this protocol. IQWiG concludes that the SMArtCARE registry sufficiently meets the quality criteria and qualifies as data source for the mandated Routine Data Collection and Evaluations (30).

Details of IQWiG's assessment of SMArtCARE are listed in Table 18.

Table 18: Fulfillment of quality criteria by SMArtCARE Registry (30)

No.	Quality criterion	Fulfillment by SMArtCARE
	Consistent systematics	
1	Detailed description of registry (registry protocol)	yes
	Standardization	
2	Exact definition/ operationalization of expositions, clinical events, endpoints and confounders	yes
3	Current data plan/ coding list	yes
4	Use of standard classifications (e.g. ICD-10) and terminologies (e.g. MedDRA)	yes
5	Use of validated standard assessment instruments (questionnaires, scales, tests)	yes, but no assessment of health-related quality of life
6	Training on data collection and - acquisition	yes
7	Implementation of a disease-specific core data set	yes

No.	Quality criterion	Fulfillment by SMArtCARE
8	Use of exact patient-specific dates (e.g. birth, death, pregnancy)	yes
9	Use of exact dates in medical history (e.g. diagnosis, clinical relevant events)	yes
10	Use of exact dates of important medical assessments	yes
11	Use of exact dates for treatments and interventions (e.g. start/stop, dosage, dosage adjustment)	yes, with limitations (no documentation of nusinersen dosage)
	Achievement of recruitment target/sample collection	
12	Clearly defined inclusion/exclusion criteria for registry population	yes
13	Completeness of registry patients (complete registration or representative sample)	unclear
14	Strategies to avoid unintentional recruitment bias to attain representative status	yes (consecutive inclusion)
	Validity of data collection	
15	Completeness of data per assessment	shall be assured through standards
16	Completeness of assessments (loss to follow-up, drop outs)	shall be assured through standards
17	Accuracy of data	limited as there is actually no source data verification[a]
18	Consistency of data over time	yes
19	Source data verification (e.g. for 10% randomly selected patients per participating center)	No[a]
20	Internal audits	no
21	External audits	no
22	Quality management system (with regular evaluation of quality indicators, where appropriate)	yes
23	Standard Operating Procedures regarding data collection	yes
	Superordinate quality criteria	
24	Transparency of the registry (including funding, decision-making, conflict of interest, amongst others)	yes
25	Scientific independence	yes
26	Secured funding (for planned study period)	yes

No.	Quality criterion	Fulfillment by SMArtCARE
27	Steering committee	yes
28	Up-to-date registry documents (e.g. protocol, data plan, statistical analysis plan, informed consent etc.)	yes
29	Protection of patients´ rights and data protection, consideration of ethical aspects	yes
30	Timeliness (current status/quick availability/timeliness of requested results)	yes
31	Flexibility and adaptability (e.g. implementation of trials, further assessments, changing medical care situation)	yes
32	Documentation trail - documentation of all changes to processes and definitions	yes
33	Audit trail - documentation and attribution of all data transactions	yes
34	Interconnect ability with other data sources	planned
	Further possible criteria from a regulatory point of view	
46	Assessment and handling of adverse events (AE) in accordance with regulatory requirements	yes

[a)] Source Data Verification will be implemented in the course of this study as described in section 10.2 of this protocol.

6.2 RESTORE registry

The RESTORE registry is a prospective, multicenter, non-interventional disease registry for SMA. The registry is sponsored by Novartis Gene Therapies and goverened by an international steering committee of SMA experts, who are committed to ensuring the quality of the data and to sharing findings through publication. Clinical care is not dictated by a research protocol and no additional visits or investigations are be performed beyond those consistent with normal clinical practice. Patients will be enrolled over a 5-year period and followed for 15 years, or until death (41).

The RESTORE registry is part of the requirements in the EMA's Risk Management Plan for onasemnogene abeparvovec (58). A minimum of 500 subjects will be recruited. Recruitment started in September 2018. Table 19 depicts RESTORE inclusion and exclusion criteria.

Table 19: RESTORE eligibility criteria

Inclusion Criteria	Exclusion criteria
▪ Patients not treated with AVXS-101 with SMA genetically confirmed on or after 24 May 2018 OR ▪ Patients treated with AVXS-101 with SMA genetically confirmed regardless of the date of diagnosis AND ▪ Appropriate consent/assent has been obtained for participation in the registry.	▪ Currently enrolled in an interventional clinical trial involving an investigational product to treat SMA.
Note: patients that are participating in a CUP for AVXS-101 (Zolgensma) such as a MAP, an EAP, SPI or NPP are eligible to enroll in the registry regardless of the date of genetic confirmation of SMA. Patients that are participating in long-term follow-up studies of Zolgensma (such as LT-001 or LT-002) are not eligible to enroll in the registry. However, patients who have completed clinical trials and are not participating in the long-term follow up studies may enroll in this registry.	

Source: (59)

RESTORE data is sourced both from de novo study sites and consortia. From de novo sites, patient level data on both onasemnogene abeparvovec and nusinersen is available and could generally be used for the Routine data Collection and Evaluations. Consortia are study groups or other international SMA registries that contractually agreed to share their data in the RESTORE registry. While some consortia agreed to provide patient level data for onasemnogene abeparvovec, no consortia partner has agreed to also sharing patient level data on nusinersen. Since only aggregated data on nusinersen is thus available from consortia, only data from de novo RESTORE sites is eligible for the Routine Data Collection and Evaluations. All de novo sites are currently located in the United States of America.

Novartis Gene Therapies will add all operationalizations and analyses – as far as they are depictable – in the RESTORE restistry via an amendment following a corresponding resolution changing the provisions of the 4 February resolution by G-BA. All analyses will pe performed within a data source, i.e. within RESTORE in addition to the analyses within SMArtCARE. If homogeneity of results is sufficient for aggregated meta-analysis, meta-analysis will pe performed and also reported to G-BA. To support this decision process, information on the RESTORE registry is provided in Table 20.

Table 20: Fulfillment of quality criteria by RESTORE Registry

No.	Quality criterion	Fulfillment by RESTORE
	Consistent systematics	
1	Detailed description of registry (registry protocol)	Yes

No.	Quality criterion	Fulfillment by RESTORE
	Standardization	
2	Exact definition/ operationalization of expositions, clinical events, endpoints and confounders	Yes
3	Current data plan/ coding list	Yes
4	Use of standard classifications (e.g. ICD-10) and terminologies (e.g. MedDRA)	Yes
5	Use of validated standard assessment instruments (questionnaires, scales, tests)	Yes
6	Training on data collection and - acquisition	Yes
7	Implementation of a disease-specific core data set	Yes
8	Use of exact patient-specific dates (e.g. birth, death, pregnancy)	Yes
9	Use of exact dates in medical history (e.g. diagnosis, clinical relevant events)	Yes
10	Use of exact dates of important medical assessments	Yes
11	Use of exact dates for treatments and interventions (e.g. start/stop, dosage, dosage adjustment)	Yes, with limitations (no documentation of treatment start for nusinersen if it occurred prior to enrollment)
	Achievement of recruitment target/sample collection	
12	Clearly defined inclusion/exclusion criteria for registry population	Yes
13	Completeness of registry patients (complete registration or representative sample)	Zolgensma: yes (completeness intended) Nusinersen: unclear (no completeness, representativeness unclear)
14	Strategies to avoid unintentional recruitment bias to attain representative status	Yes (open for inclusion of patients with any intervention at de novo sites)
	Validity of data collection	
15	Completeness of data per assessment	shall be assured through standards
16	Completeness of assessments (loss to follow-up, drop outs)	shall be assured through standards
17	Accuracy of data	Ensured by automated quality checks and possibility of audits
18	Consistency of data over time	Yes

No.	Quality criterion	Fulfillment by RESTORE
19	Source data verification (e.g. for 10% randomly selected patients per participating center)	No
20	Internal audits	Yes
21	External audits	Yes
22	Quality management system (with regular evaluation of quality indicators, where appropriate)	Yes
23	Standard Operating Procedures regarding data collection	Yes
	Superordinate quality criteria	
24	Transparency of the registry (including funding, decision-making, conflict of interest, amongst others)	yes
25	Scientific independence	Yes (steering committee with charter)
26	Secured funding (for planned study period)	Yes
27	Steering committee (SC)	*Yes (listed below) :* ▪ ***Richard Finkel, (SC Chair)*** *MD - St. Jude Children's Research - Memphis, TN, USA* ▪ ***Laurent Servais (SC Co-Chair),*** *MD, PhD, MDUK Oxford Neuromuscular Centre, Oxford, UK* ▪ ***John Day,*** *MD, PhD Stanford University Medical Center Palo Alto, CA, USA* ▪ ***Isabelle Desguerre,*** *MD, PhD - Assistance Publique, Hôpitaux de Paris –APHP -Paris, France* ▪ ***Darryl De Vivo,*** *MD-Columbia University Medical Center - New York, NY, USA* ▪ ***Nicole Gusset,*** *PhD- Patient Representative - SMA Europe, Switzerland* ▪ ***Janbernd Kirschner,*** *MD - Universität Bonn-Bonn, Germany* ▪ ***Eugenio Mercuri,*** *MD, PhD-Università Cattolica del Sacro Cuore - Roma, Italy* ▪ ***Francesco Muntoni,*** *MD Univeristy College - London, UK* ▪ ***Crystal Proud****, MD, Children's Hospital of The King's Daughters, Norfolk, VA, USA*

No.	Quality criterion	Fulfillment by RESTORE
		▪ ***Susana Quijano-Roy**, MD, PhD, University Hôpital Raymond Poincaré, Paris, France* ▪ ***Kayoko Saito,** MD, Tokyo's Women's Medical University School of Medicine, Tokyo, Japan* ▪ ***Perry Shieh,** MD, PhD, Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA* ▪ ***Eduardo Tizzano,** MD, PhD, Hospital Valle Hebron, Barcelona, Spain)*
28	Up-to-date registry documents (e.g. protocol, data plan, statistical analysis plan, informed consent etc.)	Yes
29	Protection of patients´ rights and data protection, consideration of ethical aspects	Yes
30	Timeliness (current status/quick availability/timeliness of requested results)	Yes
31	Flexibility and adaptability (e.g. implementation of trials, further assessments, changing medical care situation)	Yes
32	Documentation trail - documentation of all changes to processes and definitions	Yes
33	Audit trail - documentation and attribution of all data transactions	Yes
34	Interconnect ability with other data sources	Yes
	Further possible criteria from a regulatory point of view	
46	Assessment and handling of adverse events (AE) in accordance with regulatory requirements	Yes

6.3 Study sites

Due to the design of a registry-based, non-interventional study, available data in the SMArtCARE registry is provided by all HSPs participating in the registry. According to public information, 53 entities of 46 hospitals are currently participating in the SMArtCARE registry, of which 41 entities of 34 hospitals are located within Germany and 9 entities of 8 hospitals are located in Austria (60). Two hospitals located in Spain and one hospital located in Switzerland are also listed on the SMArtCARE website. However, SMArtCARE informed Novartis Gene Therapies that these sites only use the documentation forms and database design of SMArtCARE and do not

actually provide data to SMArtCARE. Thus, centers located in Germany and Austria can be included in this study and are depicted in Table 22.

Novartis Gene Therapies had restricted study sites to centers that meet the quality criteria of the G-BA resolution of November 20, 2020 for the use of onasemnogene abeparvovec (32). This approach would have ensured a minimization of potential bias from different infrastructure, treatment, and documentation standards between HSPs. It would have also avoided using data from HSPs that use only one of the two study interventions and whose specific standards of care are therefore not reflected in the effects for both study interventions. While IQWiG confirmed the potential of bias introduced by including other centers (39), it was requested that "there should be no exclusive restriction to centers that fulfil the quality assurance guideline of the G-BA for the use of onasemnogene abeparvovec. Rather, the decision whether or not to include a center should depend on the quality or care actually implemented in that center" (change request No. 8, Table 6).

The quality criteria of the G-BA resolution of 20 November 2020 for the use of onasemnogene abeparvovec (32) explicitly includes provisions aimed at ensuring data quality for the Routine Data Collection and Evaluations (section 13 paragraph 2). While it is possible for G-BA to monitor the fulfilment of its directive in Germany, Novartis Gene Therapies has no mandate to comprehensively define quality criteria nor any ability to monitor or enforce the fulfillment and compliance with quality criteria. The request to include centers based on their level of quality or care actually implemented without any specification as to what constitutes an acceptable level of quality or care based on data that is accessable to Novartis Gene Therapies is thus very challenging to implement, especially in the contect of a non-interventional study.

In an attempt to address G-BA's change request irrespective of the described challenges, the criteria depicted in Table 21 will be applied that are possible for Novartis Gene Therapies to evaluate based on data of the SMArtCARE registry as well as individual surveying and contracting activities with SMArtCARE sites located in Germany and Austria. They are derived from the quality criteria put forward in the G-BA resolution of 20 November 2020 but explicitly defined to allow for significantly more nusinersen patients to be included in the study than the criteria previously proposed by Novartis Gene Therapies.

Table 21: SMArtCARE center inclusion criteria

#	Center inclusion criterion	Rationale
1	Experience with drug therapy for SMA: Use of approved drugs (nusinersen, zolgensma, risdiplam) in ≥ 10 patients under 18 years of age and ≥ 5 patients under 10 years of age within 3 years ▪ For study start and retrospective data: 2019-2021 period ▪ Annual review thereafter to	G-BA quality criteria for onasemnogene abeparvovec require at least 15 patients treated with an approved SMA therapy within 3 years (§ 3 section 2). In addition, G-BA requires at least 5 SMA treatments of patients less than one year of age within the last 3 years. However, this criterion is explicitly dropped for follow-up care after one year (§ 10 section 2). In

#	Center inclusion criterion	Rationale
	check if new centers are added. No exclusion of centers once included.	order to ensure a uniform pool of centers for treatment and follow-up and at the same time to maximize patient numbers as much as possible, the additional criterion for initial treatment is dropped. In an effort to fulfill G-BA requests to maximize patient numbers for this study, the minimum patient number was reduced from 15 to 10. The G-BA quality criteria also consistently focus on neuropediatrics. Unlike G-BA, Novartis Gene Therapies cannot verify the qualifications of the treating physicians in detail. While the fulfillment of the G-BA quality criteria separately requires certain minimum quantities as well as the neuropediatric qualification, the separate verification of the latter is not possible for Novartis Gene Therapies. Therefore, the required minimum quantities are applied to the age group of under 18-year-olds. The inclusion criteria of ≤ 21kg for this study effectively limits initial treatment to patients less than 5 years of age. Given a follow-up period of 5 years, it can be assumed that the included patients will be under 10 years of age. An additional experience criterion of ≥ 5 patients under 10 years of age was thus applied to ensure adequate experience and routine, especially regarding the performance of motor function tests.
2	Performance of standardized motor function tests for diagnosis by physical therapists with at least two years of experience in physical therapy diagnosis and treatment of children with neuromuscular diseases and training in the performance of standardized, disease-specific muscle function tests.	In its justification of the quality criteria for onasemnogene abeparvovec, G-BA explicitly regulates experience and training requirements for physiotherapeutic staff in order to ensure the validity of the AbD: *"In order to ensure that data collection is uniform and comparable and that valid follow-up with comparably collected baseline values can be performed across treatment facilities, it is important that the physicians and physiotherapists collecting the findings are appropriately trained. Therefore, the requirements for physiotherapeutic care apply in accordance with § 6 paragraph 2 sentences 1 and 2. Reference*

#	Center inclusion criterion	Rationale
		is made to the comments on § 6 paragraph 2 sentences 1 and 2." The referenced criteria of § 6 section 2 sentences 1 and 2 define: "*In the treatment facilities within the meaning of this resolution, it must be ensured that the performance of standardized motor function tests for diagnosis is carried out by physiotherapists with at least two years of experience in the physiotherapeutic diagnosis and treatment of children with neuromuscular diseases. They must be trained in the performance of standardized, disease-specific muscle function tests (e.g., CHOP-INTEND, HFMSE, RULM, 6MWT)."* The restriction to centers that meet the appropriate experience and training requirements is therefore consistent with the G-BA's resolutions and justifications. Novartis Gene Therapies will survey fulfillment of this criterion SMArtCARE.

Table 22 lists all German and Austrian HSPs participating in SMArtCARE. Centers fulfilling the quality criteria depicted in Table 21 will be included in the study. Based on the data in SMArtCARE as of November 2021, 22 HSPs would be included in the study, of which 19 are located in Germany and 3 are located in Austruia. It is expected that additional HSPs can be included in the study after systematically evaluationg backlog of paper-CRFs and supporting sites in addressing backlog for this study (section 10.3).

Table 22: Participating German and Austrian HSPs in SMArtCARE and current fulfillment of patient number inclusion criterion

Country	City	HSP	Fulfillment of patient number inclusion criterion (as of 11/2021)
Germany	Augsburg	Universitätsklinikum Augsburg ▪ Klinik für Kinder und Jugendliche / Mutter-Kind-Zentrum Schwaben	No
	Berlin	Charité Universitätsmedizin Berlin: Campus Virchow Klinikum ▪ Sozialpädiatrisches Zentrum Neuropädiatrie	Yes

Country	City	HSP	Fulfillment of patient number inclusion criterion (as of 11/2021)
	Berlin	DRK Kliniken Berlin Westend ▪ Klinik für Kinder- und Jugendmedizin Epilepsiezentrum / Neuropädiatrie	Yes
	Bochum	Ruhruniversität Bochum im St. Josef Hospital ▪ Klinik für Kinder- und Jugendmedizin: Neuropädiatrie	Yes
	Bonn	Universitätsklinikum Bonn ▪ Zentrum für Kinderheilkunde Abteilung Neuropädiatrie	Yes
	Dresden	Universitätsklinikum Carl Gustav Carus Dresden an der Technischen Universität Dresden ▪ Klinik und Poliklinik für Neurologie ▪ Neuropädiatrie Klinik und Poliklinik für Kinder- und Jugendmedizin	Yes
	Erlangen	Universitätsklinikum Erlangen ▪ Neurologische Klinik ▪ Kinder und Jugendklinik Neuropädiatrie	Yes
	Essen	Universitätsklinikum Essen ▪ Neurologische Klinik und Poliklinik ▪ Klinik für Kinderheilkunde Neuropädiatrie	Yes
	Freiburg	Universitätsklinikum Freiburg ▪ Klinik für Neuropädiatrie und Muskelerkrankungen	Yes
	Gießen	Universitätsklinikum Gießen und Marburg GmbH - Klinikum der Justus-Liebig-Universität ▪ Zentrum für Kinderheilkunde und Jugendmedizin. Abteilung für Kinderneurologie, Sozialpädiatrie und Epileptologie	Yes
	Göttingen	Universitätsmedizin Göttingen ▪ Klinik für Neurologie ▪ Klinik für Kinder- und Jugendmedizin Sozialpädiatrisches	Yes

Country	City	HSP	Fulfillment of patient number inclusion criterion (as of 11/2021)
		Zentrum	
	Halle	Universitätsklinikum Halle ▪ Klinik und Poliklinik für Neurologie	No
	Hamburg	Asklepios Klinik Nord Hamburg ▪ Neuropädiatrie	No
	Hamburg	Universitätsklinikum Hamburg-Eppendorf Zentrum für Geburtshilfe, Kinder- und Jugendmedizin ▪ Klinik und Poliklinik für Kinder- und Jugendmedizin	Yes
	Hannover	Medizinische Hochschule Hannover ▪ Klinik für Neurologie ▪ Zentrum für Kinderheilkunde u. Jugendmedizin	Yes
	Heidelberg	Universitätsklinikum Heidelberg ▪ Neurologische Klinik ▪ Zentrum für Kinder- und Jugendmedizin	Yes
	Homburg	Universitätsklinikum des Saarlandes ▪ Klinik für Allgemeine Pädiatrie und Neonatologie	Yes
	Jena	Universitätsklinikum Jena ▪ Neurologische Klinik und Poliklinik ▪ Klinik für Neuropädiatrie Sozialpädiatrisches Zentrum	Yes
	Kassel	Klinikum Kassel ▪ Neuropädiatrie	Yes
	Kiel	Universitätsklinikum Schleswig-Holstein ▪ Klinik für Neurologie	No
	Cologne	Kliniken der Stadt Köln GmbH Kinderkrankenhaus ▪ Sozialpädiatrisches Zentrum	No
	Leipzig	Universitätsmedizin Leipzig ▪ Klinik und Poliklinik für Neurologie	No

Country	City	HSP	Fulfillment of patient number inclusion criterion (as of 11/2021)
	Mannheim	Universitätsmedizin Mannheim ▪ Neurologische Klinik	No
	Munich	Klinikum der Universität München ▪ Friedrich-Baur-Institut	No
	Munich	Dr. von Haunersches Kinderspital ▪ Kinderklinik und Kinderpoliklinik der Ludwig Maximilian Universität München	Yes
	Munich	Technische Universität München Klinikum rechts der Isar ▪ Klinik und Poliklinik für Neurologie	No
	Münster	Universitätsklinikum Münster ▪ Klinik und Poliklinik für Kinder- und Jugendmedizin Allgemeine Pädiatrie - Neuropädiatrie	Yes
	Oldenburg	Klinik und Poliklinik für Kinder- und Jugendmedizin Allgemeine Pädiatrie – Neuropädiatrie ▪ Klinik für neurologische Intensiv- medizin und Frührehabilitation	No
	Rostock	Universitätsklinikum Rostock ▪ Klinik und Poliklinik für Neurologie Zentrum für Nervenheilkunde	No
	Stuttgart	Klinikum Stuttgart Olgaspital ▪ Päd. Neurologie, Psychosomatik und Schmerztherapie	No
	Tübingen	Universitätsklinikum Tübingen ▪ Kinderklink Abteilung III	Yes
	Ulm	Universitätsklinikum Ulm ▪ Sektion Sozialpädiatrisches Zentrum und Pädiatrische Neurologie / Stoffwechsel	No
	Wiesbaden	DKD Helios Klinik Wiesbaden ▪ FB Neurologie und Klin. Neurophysiologie	No

Country	City	HSP	Fulfillment of patient number inclusion criterion (as of 11/2021)
	Würzburg	Universitätsklinikum Würzburg ▪ Kinderklinik und Poliklinik Sozialpädiatrisches Zentrum Neuropädiatrie ▪ Neurologische Klinik und Poliklinik	No
Austria	Bregenz	Landeskrankenhaus Bregenz Kinder und Jugendheilkunde Neuropädiatrie	No
	Graz	Universitätsklinikum Graz Universitätsklinik für Kinder- und Jugendheilkunde, Klinik für Neuropädiatrie und angeborene Stoffwechselkrankheiten	Yes
	Innsbruck	Tirol Kliniken Universitätsklinik für Pädiatrie I Department für Kinder - und Jugendheilkunde	Yes
	Klagenfurt	Klinikum Klagenfurt am Wörthersee ▪ Abteilung für Neurologie Abteilung für Kinder- und Jugendmedizin	No
	Linz	Kepler Universitätsklinikum Linz Universitätsklinikum für Kinder- und Jugendheilkunde	No
	Linz	Ordensklinikum Linz GmbH Barmherzige Schwestern Kinder- und Jugendheilkunde Neuropädiatrische Ambulanz	No
	Mödling	Landesklinikum Baden-Mödling Abteilung für Kinder- und Jugendheilkunde	No
	Wels	Klinikum Wels-Grieskirchen Abteilung für Kinder- und Jugendheilkunde	No
	Wien	Kaiser-Franz-Josef Spital mit G.v. Preyersches Kinderspital Abteilung für Kinder- und Jugendheilkunde	Yes

Source: SMArtCARE (60)

7. Population Selection

This analysis will use individual patient data from patients included in SMArtCARE registry which are treated with onasemnogene abeparvovec or nusinersen and fulfill the inclusion and exclusion criteria.

7.1 Inclusion Criteria

Patients included in the study need to fulfill the criteria listed in Table 23.

Table 23: Inclusion criteria and operationalization in SMArtCARE registry

#	Inclusion criteria	Definition in SMArtCARE (47)
1	Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene OR	▪ Enrolment: Genetically proven 5q SMA AND ▪ Baseline: Was diagnosis made pre-symptomatically? = yes AND ▪ Baseline: SMN2 copy number ≤ 3
	Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA OR	▪ Enrolment: Genetically proven 5q SMA AND ▪ Baseline: Was diagnosis made pre-symptomatically? = no AND ▪ Baseline: Age at symptom onset < 6 months
	Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene	▪ Enrolment: Genetically proven 5q SMA AND ▪ Baseline: Was diagnosis made pre-symptomatically? = no AND ▪ Baseline: SMN2 copy number ≤ 3 AND ▪ Baseline: Age at symptom onset ≥ 6 months AND ▪ Baseline: Age at symptom onset < 18 months
2	Treatment initiation with nusinersen (12 mg / 5 ml per administration) or onasemnogene abeparvovec (dosage according to body weight as per SmPC)	▪ Medical Assessment: Is the patient on any approved medication for SMA? = no for all visits

#	Inclusion criteria	Definition in SMArtCARE (47)
		before Nusinersen/Zolgensma: MIN(Date of treatment) ▪ Name of drug = onasemnogene abeparvovec/Zolgensma OR nusinersen/Spinraza ▪ Nusinersen/Zolgensma: MIN(Date of treatment) ≥ study start date (not applied to nusinersen if historic data is used, see section 8.4)
3	Body weight at treatment initiation ≤ 21 kg	▪ Medical assessment: Body weight (kg) ≤ 21 AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treatment)
4	Appropriate consent/assent has been obtained for participation in the study	▪ Enrolment: Date of consent <> “”

The first inclusion criterion depicted in Table 23 depicts the population mandated for this study by G-BA (28).

The second criterion depicted in Table 23 ensures compliance with the concept of “emulation of target trial” set forth by IQWiG. The IQWiG methodological framework for RWE application in the benefit assessment (33) and the IQWiG concept for Routine Data Collection and Evaluations for onasemnogene abeparvovec (30) recommend the explicit emulation of the planning of randomized trials for planning of non-randomized Real World Evidence (RWE) studies for the benefit assessment ("emulation of target trial"). Within the components of the emulation of the target trial from a non-randomized data set, a "new user design" is required:

"Patients who meet the inclusion/exclusion criteria are assigned to the intervention they received at the beginning of their treatment for the disease or indication under investigation". (33).

To implement these requirements, only therapy-naïve patients will be included in the study.

The third criterion depicted in Table 23 is introduced to ensure that only patients eligible for treatment with both interventions of this study are included. While the EU marketing authorization for onasemnogene abeparvovec does not recommend an age limit, the use of onasemnogene abeparvovec is expected to be almost exclusive to newborns and infants. This is also reflected in the G-BA's quality criteria for the use of onasemnogene abeparvovec (32). Onasemnogene abeparvovec is administered by intravenous infusion. Patients receive a dosage based on body

weight. The SmPC specifies a recommended dosage for patients with a body weight up to 21.0 kg body weight (42). For this reason, only patients ≤21 kg body weight are included in the in-use data collection to ensure the best possible comparability of the patient populations for both interventions.

The fourth criterion depicted in Table 23 serves to ensure compliance with all legal requirements of this study (see section 11).

7.2 Exclusion Criteria

Patients characterized by any of the criteria listed in Table 24 will not be included in the study.

Table 24: Exclusion criteria and operationalization in SMArtCARE registry

#	Exclusion criteria	Fields in SMArtCARE CRF (47)
1	Pretreatment with disease-modifying therapy (nusinersen, onasemnogene abeparvovec, risdiplam)	▪ Medical Assessment: Is the patient on any approved medication for SMA? = yes for any visit before Nusinersen/Zolgensma: MIN(Date of treatment)
2	Pretreatment with any of the following investigational drugs for the treatment of SMA: albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea	▪ Medical Assessment: Other medication taken on a regular basis? = yes AND ▪ Medical Assessment: Name of medication (other medication) includes albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, or hydroxyurea AND ▪ Medical Assessment: Start Date (other medication) ≤ Nusinersen/Zolgensma: MIN(Date of treatment)
3	Currently or previously enrolled in an interventional clinical trial involving an investigational product to treat SMA	▪ Baseline: Is the patient currently or was previously included in a clinical trial? = Yes OR ▪ Medical assessment: Is the patient currently in a clinical trial? = Yes for any visit before Nusinersen/Zolgensma: MIN(Date of treatment)

The first criterion depicted in Table 24 serves to ensure patients are not pre-treated with any authorized disease modifying drug (DMD) prior to their inclusion in the study.

The second and third criteria depicted in Table 24 ensures that patients are not treated with any DMD not authorized but investigated for use in SMA prior to their inclusion in the study.

7.3 Criteria for historic data

The SMArtCARE registry has been enrolling patients since July 2018 (30) and prospectively collected data for patients treated with nusinersen since then. Onasemnogene apeparvovec has been authorized in Germany since July 2020, i.e. two years later than nusinersen. However, a limited number of patients has been treated with onasemnogene abeparvovec in Germany prior to marketing authorization and may have been documented in SMArtCARE. As per G-BA request No. 4 (Table 6), historical data, i.e. data prospectively captured in SMArtCARE prior to the start of this study, will be utilized in this study.

The use of data that was collected at different times per intervention generally results in a relevant potential for bias. Even if significant confounders are mapped and data was collected at the time of treatment, it cannot be ruled out that non-measurable confounders, e.g. in the form of changes in the standard of care over time, may have an impact on the results. Data on nusinersen collected in SMArtCARE before the first onasemnogene abeparvovec patient fulfilling eligibility criteria of this study (sections 7.1, 7.2) was treated and documented in SMArtCARE will thus be used only if their inclusion does not lead to a violation of the overlap criterion depicted in section 8.1.1 of the SAP.

As per G-BA's position in the G-BA advice meeting of 11 August 2021, all historical data must meet the following criteria in addition to fulfilling the inclusion and exclusion criteria depicted in sections 7.1 and 7.2 (61):

1. Information must be available on all baseline confounders depicted in section 8.6.1.
2. Information on key endpoints of the study must be available, which are used for sample size calculation. This includes event-free survival and motor milestones. Should other endpoints be used for final sample size calculations, which is possible and explicitly allowed by the G-BA resolution (28), information on these endpoints needs to be available.
3. The data on baseline confounders and endpoints used to calculate treatment effects must be quality assured retrospectively by 100% source data verification (section 10.2). As such, informed consent from living patients must have been obtained (section 11.2).

Fulfillment of all criteria required for inclusion of historic nusinersen patients will be assessed to determine the number of eligible historic patients treated with

nusinersen. The results regarding criteria 1 and 2 can be included in the first status report submitted to G-BA (section 12). As informed consent has to be obtained for all patients in order to allow for source data verification, information on the third criterion will be included in the second status report submitted to G-BA (section 12).

8. Study Design & Methods: Statistical Considerations

8.1 Analysis Populations

In the resolution of February 4, 2021, the G-BA defined the following patient groups within the PICO-scheme for the Routine Data Collection and Evaluations for inclusion (28):

- Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene
- Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and clinically diagnosed type 1 SMA
- Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene

Patients who are older than 6 months or 6 weeks at the time of gene therapy with onasemnogene abeparvovec are to be included. As part of the G-BA advice meeting on 29 June 2021, G-BA further specified that pre-symptomatic patients should be stratified by SMN2 copy number (62).

The stratification of patients within the study has been subject to intense exchange with clinical experts. The unanimous assessment of the external experts was that stratification of the study population according to symptom status at the start of treatment is common and feasible in clinical trials in SMA, but not in the Routine Data Collection and Evaluations in German/Austrian routine care based on the SMArtCARE registry.

Novartis Gene Therapies has explained the reasons for a stratification based solely on the copy number of the SMN2 gene with corresponding control for the characteristic of the symptom status at the start of treatment in the context of the confounder adjustment in the G-BA advice meeting of 11 August 2021:

- As a consequence of early detection and immediate treatment, the importance of the copy number of the SMN2 gene versus the clinical phenotype of the disease is increasing from a clinical perspective (9, 8).
- Due to the introduction of nationwide newborn screening (56) and the results on the proportion of patients treated with disease-modifying therapy immediately after diagnosis from the pilot screening (63), it can be assumed that hardly any symptomatic diagnoses and therapy initiations will be observed in Germany prospectively. Stratification based on symptom status at the start of treatment thus effectively prevents the inclusion of historic data to increase patient numbers within study populations. If stratified by symptom status at treatment initiation, it can be assumed that the vast majority of historic data would be depicted in the study populations of symptomatic patients. In contrast, the vast majority

of prospectively collected data will be attributable to the study populations of presymptomatic patients because of newborn screening.

- Furthermore, stratification into four instead of two study populations leads to a substantial increase in the required patient numbers for the study. For statistical significance, only the number of cases within a study population is relevant, which is why IQWiG's orienting case number calculation of 106-548 patients (30) applies per study population. Using the mean of the four IQWiG scenarios (282 patients), the required total number of approximately 500 patients would be understandable in case of a stratification into two study populations. Stratification into four study populations, on the other hand, would result in a required total number of more than 1,000 patients, which does not seem feasible given the epidemiological and temporal framework.
- Dichotomous assignment of syptom status, as would be required for stratification of the study population, is not clinically present in patients with SMA. Instead, clinical symptomatology manifests as a continuum. In the context of clinical trials, a stratification based on symptom status has been performed in the past, but due to the continuum character of clinical symptomatology based on predefined thresholds of specialized diagnostic procedures (esp. compound muscle action potential - CMAP). Contrary to the usual procedure for checking inclusion and exclusion criteria in the context of clinical trials, there is no comparable and systematic survey of symptom status in German routine care using specialized diagnostic procedures such as the measurement of specific CMAP amplitudes.

Irrespective of these challenges communicated by Novartis Gene Therapies, G-BA has requested that “the definition of the patient population and the evaluation of the data should be carried out separately for pre-symptomatic and symptomatic patients” (change request No. 1, Table 6). While G-BA did not provide any further information on this change request, IQWIG noted that “a relevant number of patients are also available for retrospective data collection” and that “symptom status, in conjunction with age, contributes to clinical diagnosis and has a relevant impact on treatment outcome” (39).

Novartis Gene Therapies agrees that syptom status at treatment initiation is an important prognostic factor in SMA and had thus proposed to include it as a confounder for adjustment in statistical analysis. However, neither G-BA nor IQWiG speak to the practical challenges, e.g. the impossibility of characterizing symptom status by means of diagnostic information available in German routine care outside of clinical trials or the effective prevention of historic data to increase patient numbers within study populations. As a consequence, both the stratification approach proposed by Novartis Gene Therapies based on recommendations of clinical experts as well as the one requested by G-BA are implemented in this study.

8.1.1 NGT approach

In the setting of care for this study, it is appropriate to only stratify study populations based on the copy number of the SMN2 gene. Control of the influence of the symptom status at treatment initiation is achieved via adequate adjustment methods for confounders (section 8.6). In addition, possible effect modification in symptomatic patients will be investigated in the planned subgroup analyses for all confounders (section 0).

Patients with 5q-associated SMA with biallelic mutation in the SMN1 gene will thus be stratified by number of copies of the SMN2 gene: up to 2 copies vs. 3 copies. Therefore, the following study populations are defined for analyses:

- Population NGT-A: Patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 2 copies of the SMN2 gene
- Population NGT-B: Patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and 3 copies of the SMN2 gene

All patients in each population are targeted for effectiveness and safety analyses. The analysis will not be performed on the combined overall population of A and B.

8.1.2 G-BA approach

Per change request No. 1 (Table 6), analyses will also be stratified into the four populations requested by G-BA:

- Population GBA-A: Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 2 copies of the SMN2 gene
- Population GBA-B: Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA
- Population GBA-C: Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and 3 copies of the SMN2 gene
- Population GBA-D: Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene

All patients in each population are targeted for effectiveness and safety analyses.

For sensitivity analysis, populations GBA-A and GBA-B as well as populations GBA-C and GBA-D will be pooled. Sensitivity analysis will be performed with and without censoring for treatment switches (section 8.5 of SAP)

The analysis will not be performed on the combined overall population of GBA-A, GBA-B, GBA-C, and GBA-D.

8.2 Sample Size

Due to the non-interventional design of this study, Novartis Gene Therapies has no control over enrollment in the study. All patients fulfilling the inclusion and exclusion criteria (section 7) will be included in the study.

As SMA is a rare disease, there is a finite number of patients that can be enrolled with the additional restriction that the study needs to be stratified into two analysis subsets for the NGT approach and four analysis subsets for the G-BA approach (section 8.1). Despite these limitations, sample size calculation and fulfillment of minimum patient numbers is essential to ensure that there will be sufficient numbers of patients to generate interpretable results. If patient numbers are too low compared to required sample size, statistically insignificant results are to be expected irrespective of the true treatment effect.

8.2.1 NGT approach

Within the scope of the study planning, sample size calculations based on the best available evidence are performed. For a sample size estimation in non-interventional studies, assumptions on effect measure are required as well as assumptions on the available number of patients per treatment and the degree of association between treatment and confounders. The latter point is important because at the time of planning it cannot be assumed that structural comparability can be established using PS methods and confounders must be controlled for using regression based methods.

In models with more than one covariate, the influence of the covariates on the power of the test can be taken into account by using a correction factor. This factor depends on the proportion R^2 of the variance of the treatment explained by the regression relationship with the confounders. If N is the sample size considering treatment alone, then the sample size in a setting with additional covariates is $N' = N/(1 - R^2)$. This correction has been proposed by Hsieh, Bloch et al. (64) and is implemented in G*Power (65).

8.2.1.1 Assumptions of effect measures and event rates

Population NGT-A

To derive an estimate for effect measures for population NGT-A, an adjusted indirect comparison of nusinersen and onasemnogene abeparvovec in patients with SMA type I was performed by Novartis Gene Therapy (30). This was based on the START and STR1VE-US studies for onasemnogene abeparvovec and SHINE for nusinersen. Sample size calculations for study population NGT-A are thus based on unpublished results of an ITC of study results from START, STR1VE-US, and SHINE trials, which was performed by Novartis Gene Therapies and used for the purpose of planning this study (30). Adjustments were made for the confounders CHOP-INTEND and ventilatory support at baseline; additional confounders could

not be considered due to lack of convergence of the statistical models. The results are shown in Table 25.

Table 25: Effect measures and event rates: SMA type I used for population NGT-A

Endpoint	Type	Effect measure [95% CI]	Overall event rate for patient ratio 1:1
EFS until month 18	TTE	HR: 0.19 [0.07-0.54]	35.2%
Sitting without support to month 18	binary	OR: 2.88 [0.95-8.73]	41.6%

Source: (30)

Population NGT-B

For population NGT-B, no results from indirect comparisons are available, which could be used as a basis for a sample size calculation. Against this background, sample size estimates were performed based on very rough assumptions.

Because of the generally slower disease progression in patients with 3 copies of the SMN2 gene, a reduction in event rates for EFS is expected and the event rate for EFS is assumed to be 20% (vs. 35.2% in SMA type I).

Based on the mechanism of action of nusinersen, which modulates alternative splicing of the SMN2 gene, it is hypothesized that nusinersen will show relatively better effectiveness in patients with 3 copies of SNM2 than in patients with 2 copies of SNM2. For this reason, the assumed effect measure in TTE endpoints of onasemnogene abeparvovec versus nusinersen in patients with 3 copies of the SMN2 gene was reduced by a factor of approximately two compared with the assumptions for population NGT-A derived from the indirect comparison of patients with type I SMA.

Because of the high proportion of patients with 3 copies of the SMN2 gene who achieve unassisted sitting and the low proportion of patients who require permanent ventilation at a young age, other endpoints (e.g. standing, walking, or motor function in HFMSE & RULM) are more likely to show relevant differences. Because no evidence or assumptions are currently available for these endpoints, it was assumed that event rates and effect size for independent standing may be comparable to those observed for independent sitting in SMA type I. The resulting assumptions on effect measures and event rates are shown in Table 26.

Table 26: Assumed effect measures and event rates: Population NGT-B

Endpoint	Type	Assumend effect measure [95% CI]	Assumend average event rate for patient ratio 1:1
EFS until month 18	TTE	HR: 0.38	20%
Standing without support to month 18	binary	OR: 2.88 [0.95-8.73]	41.6%

8.2.1.2 Further assumptions and methods of case number calculation

Sample size calculations were performed for both TTE and binary endpoints. Due to unknown patient proportions in the non-interventional setting, calculations in SAP-Version 1 were performed for both a 1:1 ratio and a 1:2 ratio. Based on IQWiG's assessment of protocol and SAP and its suggestion to reduce scenarios and results of sample size estimations (39), only a patient ratio of 1:1 is used for the purposes of sample size estimation. While unlikely in the prospective part of this study, the utilization of non-parallel nusinersen patients requested by G-BA (change request No. 4) makes an even distribution of patient shares more likely.

The assumed association between treatment and baseline confounders after adjustment in terms of R^2 was assumed at two possible levels: 0 (perfect balance, "RCT-like") and 30% (strong association). The following assumptions were used for both types of endpoints:

- Alpha: 0.05 two-sided
- Power: 0.9
- Drop-out/loss-to-follow-up (LTFU): 20% (e.g., due to censoring when changing treatment to risdiplam).

For TTE endpoints, it was additionally assumed:

- Effect measure: HR
- Method for estimating sample size: Cox regression (66)

For binary endpoints, it was additionally assumed:

- Effect measure: OR
- Method for estimating sample size: logistic regression - binomial distribution, enumeration procedure (67) if N < 100.000

8.2.1.3 Results of the sample size calculations

Population NGT-A

Based on the assumptions presented, for patients with up to 2 copies of the SMN2 gene (population NGT-A), the sample sizes presented in Table 27 result.

Table 27: Required total sample size for patients with up to 2 copies of the SMN2 gene

Endpoint	Input	R^2 between confounders and treatment	Patient ratio 1:1
EFS until month 18	HR=0.2, event rate = 35%	0% 30%	48 68
Sitting without support to month 18	OR=3, event rate = 40%	0% 30%	189 270

The calculations show that a statistical power of 0.9 for sitting at month 18 might require about 4 times more patients than for EFS. Changing the association between confounders and treatment from 0 to 30% results in a change of about 50% in the number of patients required.

Population NGT-B

For the study population of patients with 3 copies of the SMN2 gene, the sample sizes shown in

Table 28 result. For patients with 3 copies of the SMN2 gene, it is more likely to achieve power = 0.9 for motor milestones than for EFS.

Table 28: Required total sample size for patients with 3 copies of the SNM2 gene

Endpoint	Input	Association between confounders and treatment R^2	Ratio 1:1
EFS until month 18	HR=0.4, event rate = 20%	0% 30%	256 365
Standing without support to month 24	OR=3.5, event rate = 45%	0% 30%	155 221

8.2.1.4 Discussion

The sample sizes depicted in Table 27 and Table 28 would have to be targeted for enrollment to ensure adequate power. Based on current estimates of patient enrollment (section 8.3.1), the study will be powered for EFS and independent sitting in study population NGT-A (2 copy SMN2). The study will also likely be powered for independent standing in study population NGT-B (3 copy SMN2) based on current assumptions.

Due to the high degree of uncertainty regarding both effect measures and event rates used for sample size calculation as well as patient enrollment, NGT had proposed to link sample size calculations along with their updates at 18 and 36 months

to actual enrollment of patients by performing final outcome analysis only after sample size is reached in protocol version 1.01. However, G-BA requested that all planned outcome analyses are to be performed at fixed dates defined in the G-BA resolution and thus irrespective of the actual enrollment of patients compared to the number of patients needed to ensure adequate power for at least one key endpointd derived from sample size calculations (change request No. 22, Table 6).

8.2.2 G-BA approach

8.2.2.1 Assumptions of effect measures and event rates

The assumptions depicted in Table 29, which were derived from the ITC in type I SMA patients (68) and the assumptions presented in section 8.2.1.1, were used for sample size calculations.

Table 29: Assumptions for sample size calculations: G-BA approach

Population	EFS		Independent sitting/ standing	
	HR/RR	Event rate nusinersen	RR	Event rate nusinersen
Pop C: Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 2 copies of the SMN2 gene Pop D: Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA	0.2	50%	1.86	29%
Pop E: Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and 3 copies of the SMN2 gene Pop F: Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type	0.4	20%	1.86	29%

Population	EFS		Independent sitting/ standing	
	HR/RR	Event rate nusinersen	RR	Event rate nusinersen
2 SMA and up to 3 copies of the SMN2 gene				

8.2.2.2 Further assumptions and methods of case number calculation

In its review of the study protocol and the SAP (39), IQWiG criticized that no shifted null hypothesis was used in sample size considerations. It was argued, that a statement on the benefit or harm of an intervention could only be derived from effects observed above or below a certain effect size because of potentially unknown confounders in this non-randomized study. According to IQWiG's review of the study protocol and SAP, statement on benefit or harm can be made if the 95% confidence interval for the observed effect is above or below a threshold to be defined and refers to its rapid report (39) for a potential threshold.

IQWiG's rapid report (33) names the range $RR_0 = 2 \; to \; 5$ (or $RR_0 = 0.5 \; to \; 0.2$ for risk-reduction) as the spectrum of such thresholds for non-randomized trials. It remains unclear how IQWiG derived that the threshold is to be applied to the boundaries of the 95% confidence interval.

Since IQWiG derives this range from the effect measures defining a "dramatic effect" (RR = 5-10) in its general methods (46) by extending the range of values to 2-5, it is natural to apply the same rationale to this range as to the dramatic effect. IQWiG's general methods define the criteria for a dramatic effect to be (a) statistically significant on a .01 level and (b) a relative risk in the range 5-10. This is also depicted in G-BA's resolution practice, e.g. its resolution granting an additional benefit for cerliponase alfa due to a dramatic effect based on a HR of 0.1 with a 95% confidence interval of 0,03-0,38 and p=0,0005 (69).

However, IQWiG applies its relative risk threshold of 2-5 for the Routine Data Collection and Evaluations to the bounderies of the 95% confidence interval instead of the effect estimate. Such a threshold would require effect estimates to be well above the threshold of 2-5 and thus in or very close to the range of a "dramatic effect" (relative risk of 5-10). By applying the threshold to the bounderies of the 95% confidence interval, the criteria for the Routine Data Collection and Evaluations of onasemnogene abeparvovec would thus not be "well below the value for the 'dramatic effect'" but rather very much in the same range.

Against this background, two approaches for sample size calculations are presented.

Following the request of using a shifted null hypothesis (change request #16), $RR_0 = 0.5$ is used for EFS and $RR_0 = 2$ for sitting/standing without support. Additional asumptions are

- alpha = 0.05 two-sided
- beta = 0.1 (power = 0.9)

Following the methodological approach within the framework of the dramatic effect, no shifted null hypothesis is used $(RR_0 = 1)$ and the significance level is set to 1%, i.e.

- alpha = 0.01 two-sided
- beta = 0.1 (power = 0.9)

As the sample size calculation presented by IQWiG in its concept development (30) could not be reproduced due to insufficient information (neither algorithms nor the software used were mentioned) and contradictory parameters (same number of events in scenarios 1 and 2 despite considerably longer observation time seems implausible), the methodology in appendix A of the IQWiG's methods paper was referred to (46).

Sample sizes for RR are estimated using the formula of Farrington and Manning (70) in its implementation function *nBinomial* in the R-library *gsDesign* (71).

Since IQWiG only accepts non-randomized trials with balanced known confounders between treatment arms, no association between confounders and treatment in terms of R^2 is reflected in the following sample size calculations.

8.2.2.3 Results of the sample size calculations

EFS

In line with the sample size calculation conducted by IQWiG in the rapid report for the routine data collection and evaluation of onasemnogene abeparvovec (14), it is assumed that censoring occurs at the end of study. HRs for EFS depicted in section 8.2.1.1 are taken as relative risks due to the censoring assumption. Table 30 depicts results of sample size calculations for EFS.

Table 30: Results of sample size calculations for EFS: G-BA approach

Population	HR/RR	Event rate nusinersen	Sample size	
			Shifted null hypotheses	"Dramatic effect" derived
			$\boldsymbol{RR_0 = 0.5}$ $alpha = 0.05$, $\boldsymbol{beta = 0.1}$	$\boldsymbol{RR_0 = 1.0}$ $alpha = 0.01$, $\boldsymbol{beta = 0.1}$
Pop C: Presymptomatic	0.2	50%	2 x 92 =	2 x 37 =

Population	HR/RR	Event rate nusinersen	Sample size	
			Shifted null hypotheses $\boldsymbol{RR_0 = 0.5}$ $alpha = 0.05,$ $\boldsymbol{beta = 0.1}$	"Dramatic effect" derived $\boldsymbol{RR_0 = 1.0}$ $alpha = 0.01,$ $\boldsymbol{beta = 0.1}$
patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 2 copies of the SMN2 gene			184	74
Pop D: Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA			2 x 92 = 184	2 x 37 = 74
Pop E: Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and 3 copies of the SMN2 gene	0.4	20%	2 x 3,135 = 6,270	2 x 247 = 494
Pop F: Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene			2 x 3,135 = 6,270	2 x 247 = 494

Sitting/Standing without support to month 18

The estimated sample sizes are depicted in Table 31 and Table 32 for the two approaches.

Table 31: Results of sample size calculations for sitting without support: G-BA approach

Population	RR	Event rate nusinersen	Sample size	
			Shifted null hypotheses	"Dramatic effect" derived
			$\boldsymbol{RR_0 = 2}$ $alpha = 0.05$, $\boldsymbol{beta = 0.1}$	$\boldsymbol{RR_0 = 1.0}$ $alpha = 0.01$, $\boldsymbol{beta = 0.1}$
Pop C: Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 2 copies of the SMN2 gene	1.86	29%	2 x 6,931 = 13,862	2 x 114 = 228
Pop D: Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA			2 x 6,931 = 13,862	2 x 114 = 228

Table 32: Results of sample size calculations for standing without support: G-BA approach

Population	RR	Event rate nusinersen	Sample size	
			Shifted null hypotheses	"Dramatic effect" derived
			$\boldsymbol{RR_0 = 2}$ $alpha = 0.05$, $\boldsymbol{beta = 0.1}$	$\boldsymbol{RR_0 = 1.0}$ $alpha = 0.01$, $\boldsymbol{beta = 0.1}$
Pop E: Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and 3 copies of the SMN2 gene	1.86	29%	2 x 6,931 = 13,862	2 x 114 = 228
Pop F: Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene			2 x 6,931 = 13,862	2 x 114 = 228

Alpha = 0.5 two-sided, beta = 0.1, $RR_0 = 2$

8.2.2.4 Discussion

The sample sizes depicted in Table 30, Table 31, and Table 32 would have to be targeted for enrollment to ensure adequate power. Based on current estimates of patient enrollment (section 8.3.1), the study will only be powered for EFS in population GBA-B (symptomatic patients with a clinically diagnosed type 1 SMA). For all other endpoints and G-BA mandated study populations that were included in sample size calculations, patient numbers are expected to be insufficient to ensure adequate power based on the current assumptions.

Due to the high degree of uncertainty regarding both effect measures and event rates used for sample size calculation as well as patient enrollment, NGT had proposed to link sample size calculations along with their updates at 18 and 36 months to actual enrollment of patients by performing final outcome analysis only after sample size is reached in protocol version 1.01 (55). However, G-BA requested that all planned outcome analyses are to be performed at fixed dates defined in the G-BA resolution and thus irrespective of the actual enrollment of patients compared to the number of patients needed to ensure adequate power for at least one key endpoint derived from sample size calculations (change request No. 22, Table 6).

8.2.3 Update of sample size calculations after 18 and 36 months

Due to substantial uncertainties regarding patient proportions, drop-out rates, event rates, effect sizes, and the association of confounders and treatment outcomes, sample size will be re-calculated with first and second interim analyses 18 and 36 months after the G-BA resolution date of 4 February 2021.

Sample sizes are re-estimated using the procedures as described in section 5.4 of the SAP and use effect estimates and event rates generated with the corresponding interim analysis. If adjusted effect measures cannot be derived, re-calculation of sample sizes is done with unadjusted effect measures. Due to the short observation times and low patient numbers at the time of first interim analysis, only the endpoints EFS, sitting, and standing will be included in sample size re-calculation.

With the second interim analysis, using the methodological approaches for sample size estimation as described in section 5.4 of the SAP and taking into account the effect measures generated in the interim analysis, the remaining observation period until the final data cut, and the expected numbers of therapy-naïve patients and switches to onasemnogene abeparvovec, an assessment of the endpoints is made as to what extent they can support the assessment of an additional benefit.

For the most appropriate and feasible endpoint per analysis population (which need not necessarily be EFS or a motor function endpoint), a hypothesis is formulated and sample size calculation is conducted according to section 5.4 of the SAP while considering additional interim analyses and adjustments of the alpha error.

The results of sample size re-calculation with second interim analysis will be depicted in detail in an amendment. Results will also be included in the submission of module 4 of the dossier template to G-BA.

8.3 Expected patient numbers

Due to the non-interventional design of this study, Novartis Gene Therapies has no control over enrollment in the study. All patients fulfilling in inclusion and exclusion criteria (section 7) will be included in the study.

Nationwide newborn screening for SMA is performed in Germany starting from October 2021 (56) and pilot nationwide newborn screening was also introduced in Austria in 2021 (72). All prospective patients of this study are thus expected to be identified from newbown screening. However, per G-BA change request No. 4 (Table 6), historic patients including patients treated with nusinersen before the introduction of onasemnogene abeparvovec (non-parallel patients) will be included in the study. As a consequence, patients diagnosed predominantly symptomatically before the introduction of newborn screening will also be included in the study.

The estimates of expected patient numbers are based on the incidence of SMA based on the results of pilot newborn screening for SMA in Germany (63). Based on 297,163 screened newborns, the SMA incidence was determined to be 1 per 6,910 births. Based on aprox. 780,000 live births in Germany (73) and aprox. 85,000 live births in Austria per year (74), this results in a total of 125 patients with SMA being born in Germany and Austria together each year. Pilot newborn screening reports 40% of SMA incidence to show up to 2 copies of the SMN2 gene and 23% to show 3 copies of the SMN2 gene (63).

All estimates of the required case numbers as well as the included patient numbers are subject to considerable uncertainty, as Novartis Gene Therapies has no influence on the course of this non-interventional study. It is currently unknown how many historical patients treated with nusinersen or onasemnogene abeparvovec per study population are recorded in the SMArtCARE registry, who meet both the inclusion and exclusion criteria of the study and the eligibility criteria depicted in section 7. It is thus assumed that all patients diagnosed with SMA from 2022 onward are documented in SMArtCARE while an average of 75% of patients diagnosed with SMA between the start of enrollment in SMArtCARE in July 2018 to December 2021 are documented in SMArtCARE.

8.3.1 NGT approach

8.3.1.1 Population NGT-A

Table 33 summarizes the calculation of potential patient numbers for population NGT-A (up to 2 copies of the SMN2 gene).

Table 33: Expected patient numbers for Germany and Austria: Population NGT-A

Step	Description	No.
1	Patients diagnosed per year in Germany and Austria (2 copy SMN2)	49
2	Patients diagnosed between July 2018 (enrollment start of SMArtCARE) and December 2021 *Calculation: 3.5*(1)*	173
3	Patients diagnosed from January 2022 to December 2026 (data cut for final analysis) *Calculation: 5*(1)*	247
4	Total number of potentially eligible patients enrolled in SMArtCARE *Calculation: (2)*0.75+(3)*	377
5	Patients with less that 18 months of observation time at time of data cut for final analysis *Calculation:* 1.5*(1)	74
6	Patients potentially available for outcome analysis at time of data cut for final analysis Calculation: (4)-(5)	303
Note: Illustration of rounded numbers. Calculation based on exact numbers.		

Based on the stated assumptions, up to 377 patients for population NGT-A may be enrolled in SMArtCARE. However, it is unclear what percentage of these patients fulfills the inclusion and exclusion criteria of the study (section 7). Due to limitations in analyzing motor function endpoints before an age of 18 months, 74 patients with treatment initiation within 18 months of the final data cut will not be fully available for outcome analysis. Up to 303 patients may thus be fully eligable for final outcome analysis.

8.3.1.2 Population NGT-B

Table 34 summarizes the calculation of potential patient numbers for population NGT-A (3 copies of the SMN2 gene).

Table 34: Expected patient numbers for Germany and Austria: Population NGT-B

Step	Description	No.
1	Patients diagnosed per year in Germany and Austria (3 copy SMN2)	29
2	Patients diagnosed between July 2018 (enrollment start of SMArtCARE) and December 2021 *Calculation: 3.5*(1)*	102
3	Patients diagnosed from January 2022 to December 2026 (data cut	146

Step	Description	No.
	for final analysis) *Calculation: 5*(1)*	
4	Total number of potentially eligible patients enrolled in SMArtCARE *Calculation: (2)*0.75+(3)*	222
5	Patients with less that 18 months of observation time at time of data cut for final analysis *Calculation:* 1.5*(1)	44
6	Patients potentially available for outcome analysis at time of data cut for final analysis Calculation: (4)-(5)	178
Note: Illustration of rounded numbers. Calculation based on exact numbers.		

Based on the stated assumptions, up to 222 patients for population NGT-B may be enrolled in SMArtCARE. However, it is unclear what percentage of these patients fulfills the inclusion and exclusion criteria of the study (section 7). Due to limitations in analyzing motor function endpoints before an age of 18 months, 44 patients with treatment initiation within 18 months of the final data cut will not be fully available for outcome analysis. Up to 178 patients may thus be fully eligable for final outcome analysis.

8.3.2 G-BA approach

An estimate of the distribution of patients based on a stratification by symptom status is subject to high uncertainty. It is assumed that 80% of patients were diagnosed symptomatically prior to the introduction of newborn screening, which is dated to January 2022 for both Germany and Austria for reasons of simplifying calculations. After the introduction of nationwide newborn screening, significant challenges remain in classifying patients by symptom status in routine clinical practice (section 8.1). For pilot newborn screening, children with normal muscle tone, a CHOP INTEND score of > 35 points, an ulnar CMAP amplitude > 1 mV, and no deterioration in their first 4 weeks of life were considered pre-symptomatic (63). 53% of 2 copy SMN2 children were pre-symptomatic while 47% of 2 copy SMN2 children were classified as symptomatic. 100% of 3 copy SMN2 children were diagnosed pre-symptomatically (63).

While these shares are used for estimating patient numbers for G-BA-mandated study populations, it is expected that the application of CHOP-INTEND and ulnar CMAP amplitude for determining symptom status, which is not performed in routine clinical practice in Germany, may have lead to significantly higher shares of symptomatic patients compared to a purely clinical assessment on the presence of symptoms in newborns.

8.3.2.1 Population GBA-A

Table 35 summarizes the calculation of potential patient numbers for population GBA-A (presymptomatic patients with up to 2 copies of the SMN2 gene).

Table 35: Expected patient numbers for Germany and Austria: Population GBA-A

Step	Description	No.
1	Patients diagnosed per year in Germany and Austria (2 copy SMN2)	49
2	Patients diagnosed between July 2018 (enrollment start of SMArt-CARE) and December 2021 *Calculation: 3.5*(1)*	173
3	Patients diagnosed from January 2022 to December 2026 (data cut for final analysis) *Calculation: 5*(1)*	247
4	Presymptomatic patients diagnosed between July 2018 (enrollment start of SMArtCARE) and December 2021 *Calculation: 0.2*(2)*	35
5	Presymptomatic patients diagnosed from January 2022 to December 2026 (data cut for final analysis) *Calculation: 0.53*(3)*	131
6	Total number of potentially eligible patients enrolled in SMArtCARE *Calculation: (4)*0.75+(5)*	157
Note: Illustration of rounded numbers. Calculation based on exact numbers.		

Based on the stated assumptions, up to 157 patients for population GBA-A may be enrolled in SMArtCARE. However, it is unclear what percentage of these patients fulfills the inclusion and exclusion criteria of the study (section 7).

8.3.2.2 Population GBA-B

Table 36 summarizes the calculation of potential patient numbers for population GBA-B (symptomatic patients with a clinically diagnosed type 1 SMA).

Table 36: Expected patient numbers for Germany and Austria: Population GBA-B

Step	Description	No.
1	Patients diagnosed per year in Germany and Austria (2 copy SMN2)	49
2	Patients diagnosed between July 2018 (enrollment start of SMArt-CARE) and December 2021 *Calculation: 3.5*(1)*	173

Step	Description	No.
3	Patients diagnosed from January 2022 to December 2026 (data cut for final analysis) *Calculation: 5*(1)*	247
4	Symptomatic patients diagnosed between July 2018 (enrollment start of SMArtCARE) and December 2021 *Calculation: 0.8*(2)*	139
5	Symptomatic patients diagnosed from January 2022 to December 2026 (data cut for final analysis) *Calculation: 0.47*(3)*	116
6	Total number of potentially eligible patients enrolled in SMArtCARE *Calculation: (4)*0.75+(5)*	220
Note: Illustration of rounded numbers. Calculation based on exact numbers.		

Based on the stated assumptions, up to 220 patients for population GBA-B may be enrolled in SMArtCARE. However, it is unclear what percentage of these patients fulfills the inclusion and exclusion criteria of the study (section 7).

8.3.2.3 Population GBA-C

Table 37 summarizes the calculation of potential patient numbers for population GBA-C (presymptomatic patients with 3 copies of the SMN2 gene).

Table 37: Expected patient numbers for Germany and Austria: Population GBA-C

Step	Description	No.
1	Patients diagnosed per year in Germany and Austria (3 copy SMN2)	29
2	Patients diagnosed between July 2018 (enrollment start of SMArtCARE) and December 2021 *Calculation: 3.5*(1)*	102
3	Patients diagnosed from January 2022 to December 2026 (data cut for final analysis) *Calculation: 5*(1)*	146
4	Presymptomatic patients diagnosed between July 2018 (enrollment start of SMArtCARE) and December 2021 *Calculation: 0.2*(2)*	20
5	Presymptomatic patients diagnosed from January 2022 to December 2026 (data cut for final analysis) *Calculation: 1*(3)*	146
6	Total number of potentially eligible patients enrolled in SMArtCARE *Calculation: (4)*0.75+(5)*	161

Step	Description	No.
Note: Illustration of rounded numbers. Calculation based on exact numbers.		

Based on the stated assumptions, up to 161 patients for population GBA-C may be enrolled in SMArtCARE. However, it is unclear what percentage of these patients fulfills the inclusion and exclusion criteria of the study (section 7).

8.3.2.4 Population GBA-D

Table 38 summarizes the calculation of potential patient numbers for population GBA-D (symptomatic patients with a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene).

Table 38: Expected patient numbers for Germany and Austria: Population GBA-D

Step	Description	No.
1	Patients diagnosed per year in Germany and Austria (3 copy SMN2)	29
2	Patients diagnosed between July 2018 (enrollment start of SMArtCARE) and December 2021 *Calculation: 3.5*(1)*	102
3	Patients diagnosed from January 2022 to December 2026 (data cut for final analysis) *Calculation: 5*(1)*	146
4	Symptomatic patients diagnosed between July 2018 (enrollment start of SMArtCARE) and December 2021 *Calculation: 0.8*(2)*	82
5	Symptomatic patients diagnosed from January 2022 to December 2026 (data cut for final analysis) *Calculation: 0*(3)*	0
6	Total number of potentially eligible patients enrolled in SMArtCARE *Calculation: (4)*0.75+(5)*	61
Note: Illustration of rounded numbers. Calculation based on exact numbers.		

Based on the stated assumptions, up to 61 patients for population GBA-D may be enrolled in SMArtCARE. However, it is unclear what percentage of these patients fulfills the inclusion and exclusion criteria of the study (section 7).

8.4 Feasibility assessment

Due to considerable uncertainties regarding the required number of cases (section 8.2) and the actual number of patients included, an a priori assessment of the

study feasibility for each study population is impossible. G-BA has requested that a feasibility assessment is performed with each interim analysis, i.e. 18, 36, and 60 months after its 4 February 2021 resolution (change request No. 22, Table 6).

The assessment will be made per study population based on the following information:

- Updated sample size calculations (section 8.2)
- Number of eligible patients fulfilling inclusion and exclusion criteria per study population and extrapolation of patient numbers for nusinersen and onasemnogene abeparvovec based on study enrollment until time of interim analysis

If results indicate that the sample size required for at least one key endpoint (e.g. EFS, motor milestones, motor function scores, nutrition) will not be reached until final analysis, the population is terminated for infeasibility. No outcome analysis will be performed. If infeasibility is only determined for one study population, other study populations will continue. If all study populations are deemed unfeasible, the study will be terminated for infeasibility.

For G-BA populations (GBA-A, GBA-B, GBA-C, GBA-D), sample sizes will be calculated using both the approach of a shifted null hypothesis as well as the approach derived from a “dramatic effect”. The approach derived from a “dramatic effect” will be used to assess study feasibility for reasons described in section 8.2.2.2.

At the time of first interim analysis, updated sample sizes will still be subject to high uncertainty due to low patient numbers. Feasibility per patient population thus cannot be conclusively evaluated. No termination for infeasibility will take place at the time of first interim analysis but study feasibility will be discussed based on actual patient numbers fulfilling inclusion and exclusion criteria.

8.5 Planned Analyses

8.5.1 First status report and interim analysis (submission 18 months after G-BA resolution)

Per the G-BA resolution of 4 February 2021, a first interim analysis will be submitted to G-BA 18 months after the resolution date, i.e. by 4 August 2022. This interim analysis will be submitted using module 4 of the dossier template and cover the following aspects:

- Methodological description, study populations, and bias potential on study level in section 4.3.2.2.2 (Characteristics of non-randomized comparative studies)
- Baseline characteristics for all study populations including number of eligible patients and observation times in section 4.3.2.2.2.1 (Characteristics of non-randomized comparative studies)

- Operationalization and bias potential on endpoint level in section 4.3.2.2.3.1 (Results from non-randomized comparative studies)
- Extend of treatment switching on a study level (patients with treatment switch) per study population in section 4.3.2.2.2.1 (Characteristics of non-randomized comparative studies)
- Results of main and sensitivity analyses for all endpoints in section 4.3.2.2.3.1 (Results from non-randomized comparative studies)
- Extend of treatment switching on an endpoint level (patients with treatment switch before a respective endpoint) per study population in section 4.3.2.2.3.1 (Results from non-randomized comparative studies)
- Results of subgroup analyses in section 4.3.2.2.3.2

In addition, sample size recalculation as described in section 8.2.2 and potential deviations from expected patient numbers described in section 8.3 will be provided via an annex to module 4 of the dossier template.

It is expected that data cleaning, data harmonization, statistical analysis and drafting of the submission documents for G-BA will require 6 months due to the number of populations, endpoints, and subgroup analyses requested by G-BA. As such, data for the first interim analysis will be cut in January 2022.

Due to the mandated time of first interim analysis, the subsequent time of data cut, and the time from documentation of an event on SMArtCARE's paper-based CRF to the depiction in the SMArtCARE database, it is expected that analyzable patient numbers for onasemnogene abeparvovec will be very low. Sample size recalculation thus cannot be conclusive as effect estimates will be characterized by very high uncertainty if they can be calculated at all. A feasibility assessment – although requested by G-BA – thus cannot be performed with the first interim analysis and will be performed with the second and third interim analyses.

8.5.2 Second status report and interim analysis (submission 36 months after G-BA resolution)

Per the G-BA resolution of 4 February 2021, a second interim analysis will be submitted to G-BA 36 months after the resolution date, i.e. by 4 February 2024. This interim analysis will be submitted using module 4 of the dossier template and cover the following aspects:

- Methodological description, study populations, and bias potential on study level in section 4.3.2.2.2 (Characteristics of non-randomized comparative studies)
- Baseline characteristics for all study populations including number of eligible patients and observation times in section 4.3.2.2.2.1 (Characteristics of non-randomized comparative studies)

- Operationalization and bias potential on endpoint level in section 4.3.2.2.3.1 (Results from non-randomized comparative studies)
- Extend of treatment switching on a study level (patients with treatment switch) per study population in section 4.3.2.2.2.1 (Characteristics of non-randomized comparative studies)
- Results of main and sensitivity analyses for all endpoints in section 4.3.2.2.3.1 (Results from non-randomized comparative studies)
- Extend of treatment switching on an endpoint level (patients with treatment switch before a respective endpoint) per study population in section 4.3.2.2.3.1 (Results from non-randomized comparative studies)
- Results of subgroup analyses in section 4.3.2.2.3.2

In addition, sample size recalculation as described in section 8.2.2, potential deviations from expected patient numbers described in section 8.3, and results of the feasibility assessment described in section 8.4 will be provided via an annex to module 4 of the dossier template.

It is expected that data cleaning, data harmonization, statistical analysis and drafting of the submission documents for G-BA will require 6 months due to the number of populations, endpoints, and subgroup analyses requested by G-BA. As such, data for the first interim analysis will be cut in August 2023.

8.5.3 Third status report (submission 54 months after G-BA resolution)

Per the G-BA resolution of 4 February 2021, a third status report will be submitted to G-BA 54 months after the resolution date, i.e. by 4 August 2025.

Analysis for the status report will include the number and the respective medicinal treatment of the patients included so far, patient-related observation times, and possible deviations regarding the expected number of included patients. It will also include the extend of treatment switching on a study level per population. In addition, the extent of (dis)balance of confounders in the respective treatment groups will be analyzed descriptively. PS densities overlap between the treatment groups is analyzed (before and after weighting) and reported.

8.5.4 Forth status report and interim analysis (submission 60 months after G-BA resolution)

Per the G-BA resolution of 4 February 2021, a second interim analysis will be submitted to G-BA 60 months after the resolution date, i.e. by 4 February 2026. This interim analysis will be submitted using module 4 of the dossier template and cover the following aspects:

- Methodological description, study populations, and bias potential on study level in section 4.3.2.2.2 (Characteristics of non-randomized comparative studies)

- Baseline characteristics for all study populations including number of eligible patients and observation times in section 4.3.2.2.2.1 (Characteristics of non-randomized comparative studies)
- Operationalization and bias potential on endpoint level in section 4.3.2.2.3.1 (Results from non-randomized comparative studies)
- Extend of treatment switching on a study level (patients with treatment switch) per study population in section 4.3.2.2.2.1 (Characteristics of non-randomized comparative studies)
- Results of main and sensitivity analyses for all endpoints in section 4.3.2.2.3.1 (Results from non-randomized comparative studies)
- Extend of treatment switching on an endpoint level (patients with treatment switch before a respective endpoint) per study population in section 4.3.2.2.3.1 (Results from non-randomized comparative studies)
- Results of subgroup analyses in section 4.3.2.2.3.2

In addition, potential deviations from expected patient numbers described in section 8.3, and results of the feasibility assessment described in section 8.4 will be provided via an annex to module 4 of the dossier template.

It is expected that data cleaning, data harmonization, statistical analysis and drafting of the submission documents for G-BA will require 6 months due to the number of populations, endpoints, and subgroup analyses requested by G-BA. As such, data for the first interim analysis will be cut in August 2025.

8.5.5 Final analysis for value dossier (submission on July 1, 2027)

Per the G-BA resolution of 4 February 2021, a value dossier for the benefit assessment is to be submitted to G-BA by 1 July 2027. The value dossier will be based on an interim analysis and include the following aspects:

- Methodological description, study populations, and bias potential on study level
- Baseline characteristics for all study populations including number of eligible patients and observation times
- Operationalization and bias potential on endpoint level
- Extend of treatment switching on a study level (patients with treatment switch) per study population
- Results of main and sensitivity analyses
- Extend of treatment switching on an endpoint level (patients with treatment switch before a respective endpoint) per study population
- Results of subgroup analyses

It is expected that data cleaning, data harmonization, statistical analysis and drafting of the value dossier for G-BA will require 6 months due to the number of populations, endpoints, and subgroup analyses requested by G-BA. As such, data for the first interim analysis will be cut in December 2026.

8.6 Prognostic factors and potential confounders

8.6.1 Confounder identification and validation

Based on a systematic identification of potential confounders in national and international guidelines and publications as well as their validation by clinical experts, the convergence to structural comparability in the study arms is achieved by appropriate adjustment methods for pre-specified confounders. Validation of the identified confounders was performed by six German clinical SMA experts. Validation was performed by categorizing each confounder identified via systematic literature review (SLR) into one of the following three categories:

- **Very important:** These parameters have a significant effect on patient's outcomes and are essential for adjustment of statistical analyses in a non-randomized trial.
- **Less important:** These parameters have a moderate effect on patient's outcomes and should be controlled in statistical analysis. However, if selected confounders of this category cannot be controlled, results would still be considered valid.
- **Not important:** These parameters are not considered relevant for the specific study, e.g. due to coverage as endpoints or because of the specific study setting (quality controlled centers in Germany).

The confounders listed in Table 39 have been identified as clinically (very or less) important and are thus potentially relevant for the population included in this study. All confounders identified in the literature and categorized as clinically very important and less important for the population of this study are depictable in SMArtCARE and included in the study. All confounders identified via SLR and considered not important in the context of this study are depicted in annex A1.

Table 39: Overview of identified confounders, their clinically relevance and corresponding availability in SMArtCARE

Con-founder	Clinical rele-vance[2]	In-cluded in Study	Definition	Definition in SMArtCARE CRF (47)	Applicable to analysis popu-lations
Age at symp-tom on-set	Less im-portant	Yes	Age of symp-tom onset in months for symptomatic patients	▪ Baseline: Age at symp-tom onset	G-BA ap-proach: GBA-B, GBA-D
Symp-tom status at treat-ment initia-tion	Very im-portant	Yes	<u>Symptomatic:</u> Diagnosis not made pre-symptomati-cally OR docu-mentation of symptoms re-lated to SMA at any medi-cal assess-ment prior to treatment ini-tiation <u>Pre-sympto-matic:</u> Diagnosis made pre-symptomati-cally AND no symptoms re-lated to SMA at any medi-cal assess-ment prior to treatment ini-tiation	Symptomatic: ▪ Baseline: Was diagno-sis made pre-sympto-matically? = No OR ▪ Medical Assessment: Neurology: Symptoms related to SMA = Yes AT ▪ Medical Assessment: Visit date ≤ Nusinersen/Zolgensma: MIN(Date of treat-ment) Pre-symptomatic: ▪ Baseline: Was diagno-sis made pre-sympto-matically? = Yes AND ▪ Medical Assessment: Neurology: Symptoms related to SMA = No AT ▪ Medical Assessment: Visit date ≤ Nusinersen/Zolgensma: MIN(Date of treat-ment)	NGT approach: NGT-A, NGT-B G-BA ap-proach: none (stratification parameter)
Age at treat-ment	Very im-portant	Yes	Age in weeks at treatment initiation	▪ Medical Assessment: Age at visit AT ▪ Medical Assessment:	NGT approach: NGT-A, NGT-B

[2] According to the assessment of the six clinical experts consulted during the confounder valida-tion process

Con-founder	Clinical rele-vance[2]	In-cluded in Study	Definition	Definition in SMArtCARE CRF (47)	Applicable to analysis popu-lations
initia-tion				Visit date = Nusinersen/Zolgensma: MIN(Date of treat-ment)	G-BA ap-proach: ▪ Directly: GBA-A, GBA-C ▪ Derived (treatment delay de-fined as time from symptom onset to treatment initiation: GBA-B, GBA-D
Nutri-tion support	Very im-portant	Yes	Gastric tube or nasal feed-ing tube (ex-clusive/sup-plemental/no ne) at treat-ment initia-tion	▪ Medical assessment: Does the patient use a gastric or nasal feeding tube? AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treat-ment)	NGT approach: NGT-A, NGT-B G-BA ap-proach: GBA-B, GBA-D
Ventila-tion support	Very im-portant	Yes	Duration of ventilator use (nighttime/in-termit-tent/perma-nent (≥16h/day) at treatment ini-tiation	▪ Medical assessment: Does the patient re-ceive ventilator sup-port? = Yes AND ▪ Medical assessment: Time of ventilator use ○ Night (during sleep) ○ Intermittent day time and continuous at night ○ Continuous (>16h/day) AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treat-ment)	NGT approach: NGT-A, NGT-B G-BA ap-proach: GBA-B, GBA-D

Con-founder	Clinical rele-vance[2]	In-cluded in Study	Definition	Definition in SMArtCARE CRF (47)	Applicable to analysis popu-lations
Con-trac-tures	Less im-portant	Yes	Contractures limiting func-tion (yes/no) at treatment initiation	▪ Medical Assessment: Are any contractures present? = Yes AND ▪ Medical assessment: Type of limitation = Se-vere (imposing limits to function) AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treat-ment)	NGT approach: NGT-A, NGT-B G-BA ap-proach: GBA-B, GBA-D
Motoric func-tion: Highest motor mile-stone	Very im-portant	Yes	Highest motor milestone at treatment ini-tiation: ▪ None/n.a. ▪ Sitting without support ▪ Crawl on hands and knees ▪ Standing without support ▪ Walking without support ▪ Climb stairs	▪ Medical assessment: Best current motor function AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treat-ment)	All
Motoric func-tion: CHOP-INTEND	Very im-portant	Yes	CHOP-INTEND score at treat-ment initia-tion	▪ CHOP-INTEND: Score AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treat-ment)	All
Ulnar CMAP (com-pound muscle	n.a.	Sensi-tivity analy-sis only	Ulnar CMAP at treatment initiation ▪ Re-sponse,	▪ Medical Assessment: CMAP amplitude (mV): Ulnar AT ▪ Medical Assessment:	All

Con-founder	Clinical rele-vance[2]	In-cluded in Study	Definition	Definition in SMArtCARE CRF (47)	Applicable to analysis popu-lations
action poten-tial) (only for sen-sitivity analy-sis)			ampli-tude > 1mV ▪ No re-sponse or response ≤ 1mV ▪ Unknown	Visit date = Nusinersen/Zolgensma: MIN(Date of treat-ment)	

A detailed description of the process of confounder identification and validation is given in Annex A1 to this protocol. The clinically very important confounder of SMN2 copy number is depicted in this study via stratification of study populations (section 8.1) in both NGT and G-BA approaches.

Potential effects from different standards of care between HSPs will be addressed in via sensitivity analysis (section 8.5 of SAP).

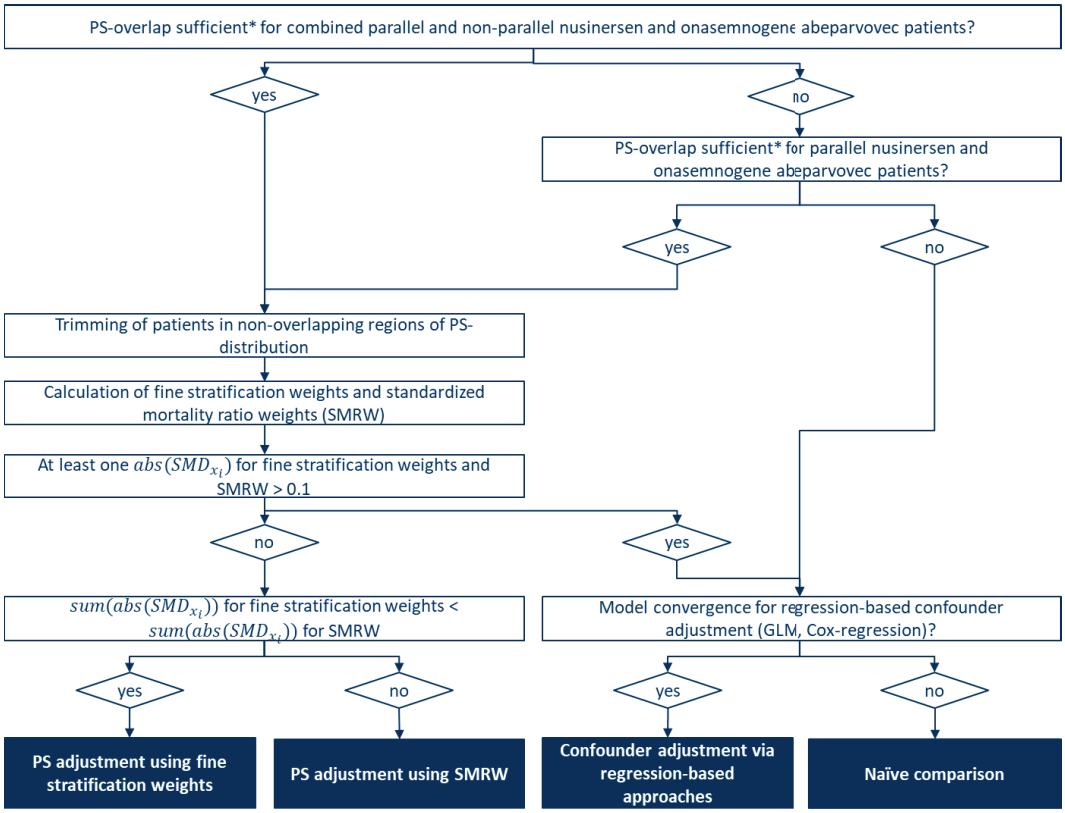
For sensitivity analysis, ulnar compound muscle action potential (CMAP) amplitude will be included in baseline confounders (see section 8.5 of SAP).

8.6.2 Adjustment for confounders

Registry data are associated with several disadvantages: lack of randomization and thus unbalanced covariates and potentially different treatment time periods between study interventions. Bias due to time-shifts needs to be discussed in the study report, missing randomization will be countered with adjustment methods.

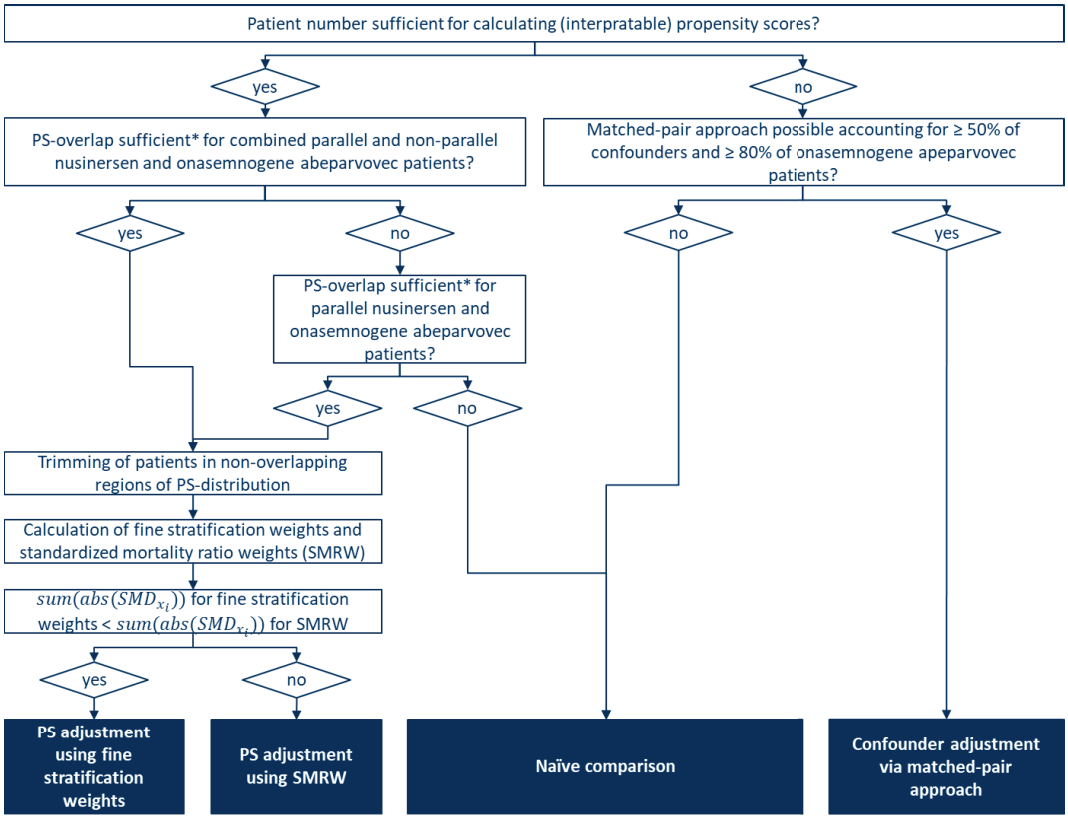
For both NGT and G-BA approaches, adjustment of confounders will take place using appropriate methods following a pre-specified decision tree. Figure 4 illustrates the decision tree for NGT approach, Figure 5 illustrates the decision tree for G-BA approach. See SAP section 8.1 for details.

Figure 4: Adjustment for confounders: NGT approach



*Sufficient overlap if 50% of patients in one treatment arm do not have a PS < 0.3 and 50% of patients in the other treatment arm have a PS > 0.7.

Figure 5: Adjustment of confounders: G-BA approach



*Sufficient overlap if 50% of patients in one treatment arm do not have a PS < 0.3 and 50% of patients in the other treatment arm have a PS > 0.7.

8.7 Subgroup analyses

8.7.1 Subgroups for baseline characteristics

As far as possible, subgroup analyses for all endpoints are planned based on the following patients' baseline characteristics. Table 40 contains all planned subgroup analyses in this study.

Table 40: Overview of planned subgroup analyses in this comparative analysis

Planned subgroups	Patients' baseline status	Fields of SMArtCARE CRF	Applicable for study populations
Age at treatment initiation	▪ ≤ 4 weeks ▪ > 4 weeks	▪ Enrolment: Date of birth ▪ Nusinersen/Zolgensma: Date of treatment	All

Planned sub-groups	Patients' baseline status	Fields of SMArtCARE CRF	Applicable for study populations
		MIN(Date of treatment)	
Gender	▪ Male ▪ Female ▪ Undifferentiated ▪ Unknown	▪ Enrolment: Gender	All
Region	▪ Germany ▪ Austria	▪ N.a. (Treatment center information not part of SMArtCARE CRF but available in SMArtCARE database)	All
Symptom status at treatment initiation	▪ Symptomatic ▪ Pre-symptomatic	▪ Baseline: Was diagnosis made pre-symptomatically? ▪ Medical Assessment: Neurology: Symptoms related to SMA AT ▪ Medical Assessment: Visit date ≤ Nusinersen/Zolgensma: MIN(Date of treatment)	NGT approach: NGT-A, NGT-B
Nutrition support (Does the patient use a gastric or nasal feeding tube?)	▪ No ▪ Yes - exclusively fed by tube ▪ Yes – supplementary e.g. for fluids	▪ Medical assessment: Does the patient use a gastric or nasal feeding tube? AT ▪ Medical Assessment: Visit Date = Nusinersen/Zolgensma: MIN(Date of treatment)	NGT approach: NGT-A, NGT-B G-BA approach: GBA-B, GBA-D
Ventilation support (Does the patient receive ventilator support?)	▪ No ▪ Yes	▪ Medical assessment: Does the patient receive ventilator support? AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treatment)	NGT approach: NGT-A, NGT-B G-BA approach: GBA-B, GBA-D
Contractures (Contractures limiting function)	▪ No ▪ Yes	▪ Medical Assessment: Are any contractures present? = Yes AND ▪ Medical assessment:	NGT approach: NGT-A, NGT-B G-BA approach: GBA-B, GBA-D

Planned sub-groups	Patients' baseline status	Fields of SMArtCARE CRF	Applicable for study populations
		Type of limitation = Severe (imposing limits to function) AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treatment)	
Motor function: Highest motor milestone	▪ None/n.a. ▪ Sitting without support ▪ Crawl on hands and knees ▪ Standing with-out support ▪ Walking with-out support ▪ Climb stairs	▪ Medical assessment: Best current motor function AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treatment)	All
Motor function: CHOP-INTEND score	▪ ≤ Median CHOP-INTEND ▪ > Median CHOP-INTEND	▪ CHOP-INTEND: Score AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treatment)	All
Ulnar CMAP	▪ Response, amplitude > 1mV ▪ No response or response ≤ 1mV ▪ Unknown	▪ Medical Assessment: CMAP amplitude (mV): Ulnar AT ▪ Medical Assessment: Visit date = Nusinersen/Zolgensma: MIN(Date of treatment)	All

8.7.2 Analysis methods

Subgroups analyses are planned for all endpoints in all analysis populations.

Effect measures are calculated for each subgroup category as well as overall. A p-value for the interaction treatment * subgroup is derived within the analytical framework as described in section 8.4 of the SAP.

Subgroup analyses are conducted only for variables resulting in subgroups of at least 10 patients.

Subgroup analyses for binary events per variable are conducted only if at least 10 events occurred in one of the subgroups.

Since confounding variables serve for subgroup analysis, there is a demand to adjust the subgroup analysis for the influence of the remaining confounding variables. Therefore, if PS-weights are used for adjustment of covariates, for each subgroup analysis based on a confounder, a new PS-weight is determined, where the confounder itself is not part of the logistic regression.

9. Safety

As this is a study based on secondary use of data, safety monitoring and safety reporting, where there is a safety relevant result, will be provided on an aggregate level only; no reporting on an individual case level to NGT is required.

In studies based on secondary use of data with a safety relevant result, reports of adverse events/adverse reactions will be summarized in the study report, i.e. the overall association between an exposure and an outcome will be presented. Relevant findings from the study report will be included in the periodic aggregated regulatory reports submitted to Health Authorities.

10. Data Handling and Monitoring

10.1 Data Management

All clinical data for this project are collected and stored exclusively in the SMArtCARE registry. Study site personnel is responsible for patient data collection and data entry into SMArtCARE. Data will be entered into electronic case report forms (eCRFs) of the SMArtCARE registry.

SMArtCARE uses a clinical database provided by OpenApp. According to SMArtCARE, the clinical database offers a query workflow for a documented and efficient data review process. Validation of patient data in the clinical database is carried out via automated edit checks as well as manual checks raised by clinical research associates during on-site routine monitoring visits (RMVs).

10.2 Source Data verification

To minimize the potential for bias in the use of registry data as part of the Routine Data Collection and Evaluations, 100% on-site source data verification will be performed for all data fields in the SMArtCARE registry that are applied to determine inclusion and exclusion criteria, confounders, and endpoints for the study (Annex A2).

Source data verification will be performed by CSG Clinische Studiengesellschaft mbH. A site initiation visit (SIV) will be performed at each study site. Approx. 18 routine monitoring visits (RMVs) at each study site will be conducted. It is expected that two visits per site will be carried out with a focus on the historical data for nusinersen and 16 RMVs (4 p.a. per site) for the prospective data. The first RMV at each study site will be performed within 2 weeks after inclusion of the first patient. The frequency of further RMVs will be dependent on the enrollment rate and the site's data documentation. A close-out visit (COV) at each study site will be performed at the end of the study.

Source data verification will be performed by clinical monitors on the basis of all available patient records. Novartis Gene Therapies will bear the financial expenses for the implementation of the source data verification.

At current, there are uncertainties regarding the possibilities and limitations of performing source data verification as part of the study. The extent of archived documentation, especially for historical nusinersen patients, cannot be estimated at present and could differ between the participating centers. Based on the assessments of clinical experts as well as those responsible for the SMArtCARE registry, the use of the paper-based CRF of the SMArtCARE registry has also become established in the care setting as part of the documentation for patient records. The extent to which independent documentation is carried out in paper-based or electronic patient records is also currently unclear and probably varies between individual centers. If necessary, changes to the possible extend of SDV will be depicted in an amendment to the study protocol.

10.3 Minimization of missing data

Due to the non-interventional nature of a Routine Data Collection and Evaluation, complete avoidance of missing or implausible data is impossible. Source data verification as described in section 10.2 will significantly reduce the frequency of missing or implausible data. Remaining missing data will be addressed in statistical analysis (see section 8.2 of the SAP).

In addition, all participating centers will be supported with "flying study nurses" at their request to further reduce the incidence of missing data. This support is aimed at processing any backlog of paper-based CRFs completed but not entered into the SMArtCARE registry's clinical database. This support is to be applied to patients who meet the inclusion and exclusion criteria of the study. It is planned to be implemented during the first months of the study for historical nusinersen patients and in preparation of each planned analysis (section 8.5).

10.4 Data analysis

Data for analysis is transferred to IGES Institute GmbH via a secure data transfer for statistical analysis. Data transfer is strictly limited to the purpose of the study and as far as required for intended statistical analysis.

11. Ethical and regulatory aspects

11.1 Regulatory and ethical compliance

This non-interventional, non-randomized, registry-based data collection will be performed in accordance with the ethical principles laid down in the Declaration of Helsinki and in consistence with applicable regulatory requirements.

According to the Professional Code for Physicians in Germany (Berufsordnung Ärzte, BO-Ä) Art 15, the final study protocol will be reviewed and approved by an Independent Ethics Committee before study start depending on the local requirements.

11.2 Informed Consent

The legal guardian of prospective patients will be asked for informed consent at the time of the patients' initial enrollment in SMArtCARE. The legal guardian of historical patients for nusinersen will be contacted to give informed consent for this study, unless the patients are documented as deceased. Eligible patients may only be included in the study after written consent of their legal guardian.

It is currently explored by SMArtCARE if the existing informed consent for participation in SMArtCARE will be amended to also include all aspects of this study or if a separate informed consent for data collection for this study will be used. In any case, informed consent will be obtained by SMArtCARE and cover the secondary use of the data for the purposes of this study.

12. Outcome

Only aggregated data will be presented to Novartis Gene Therapies, no patient-level data will be disclosed.

Results of the three interim analyses will be submitted using module 4 of the dossier template and contain the information described in sections 8.5.1, 8.5.2, and 8.5.4. Based on the results and an alignment with G-BA, an amendment to the study protocol may be required.

The third status report (section 8.5.3) will include the number and the respective medicinal treatment of the patients included so far, study sites, patient-related observation times, and possible deviations regarding the expected number of recruits. In addition, it will include information on the balance of confounders before and after adjustment to inform about potential limitations in adjusting for observed inhomogeneity.

Results of final analysis (section 8.5.5) will be submitted to G-BA in form of a value dossier for benefit assessment on 1 July, 2027. Upon completion of the study, a study report with all results of the comparison is prepared and serves as the basis for the description of the results that will be submitted to G-BA.

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14. Annex

A1 Methodology for Confounder Identification

A2 Relevant variables in SMArtCare Registry

A1 Methodology for Confounder Identification

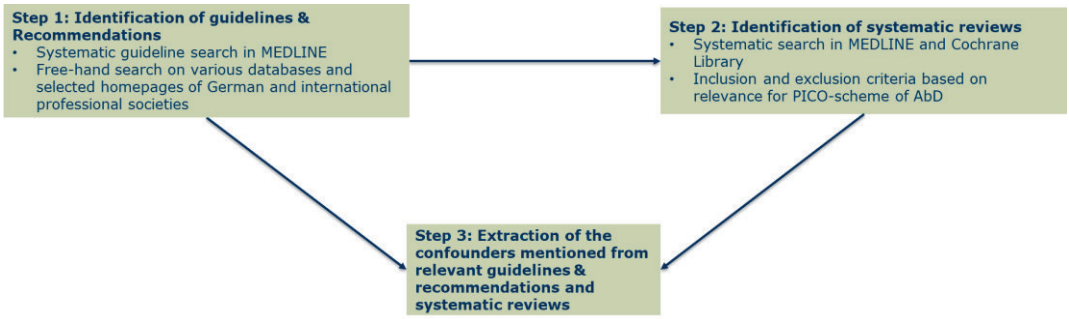
1. Methodical approaches for identifying confounders in SMA

The Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) rapid report „Konzepte zur Generierung versorgungsnaher Daten und deren Auswertung zum Zwecke der Nutzenbewertung von Arzneimitteln nach § 35a SGB V“ (Concepts for the generation of data in health care settings and their evaluation for the purpose of assessing the benefit of drugs according to § 35a SGB V), version 1.1 as of May 13, 2020, provides some guidance for the analysis of patient-specific data within the framework of the benefit assessment according to § 35a SGB V. Therein, IQWiG not only discusses various aspects of study and statistical analysis planning, but also the relevance of confounders in studies without randomization (1). It is stated, that confounders putatively relevant for the research question must be defined *a priori* on the basis of scientific literature and, if necessary, by clinical expert validation.

In order to meet these requirements for confounder identification in non-randomized studies, a methodological 2-step-approach was applied (steps 1 and 2) as shown in Figure A6. First, evidence-based guidelines and recommendations were identified via a systematic search of the MEDLINE bibliographic database. Further, a supplementary structured free-hand search on various databases and on selected websites of German and international professional societies was conducted, as this type of publication provides a broad and expert-validated data basis. Secondly, a systematic search was conducted in the bibliographic databases MEDLINE and the Cochrane Database of Systematic Reviews to identify systematic reviews and meta-analyses, since these documents would fundamentally supplement the data basis provided by the evidence-based guidelines.

The applied search strings have been designed analogously to the evidence search performed by the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) to identify the appropriate comparator therapy (2). Literature search was followed by a literature selection process performed by two independent reviewers. This process comprised an initial title-abstract screening step as per pre-specified inclusion and exclusion criteria followed by an according full-text screening procedure.

Figure A6: Overview of the methodical procedure



1.1 Indication/question

Confounders were identified specifically for the present indication according to the PICO scheme given in G-BA resolution of February 4, 2021 (3):

- Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.
- Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and clinically diagnosed type 1 SMA.
- Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene

1.2 Systematic research and data sources

A systematic evidence collection was carried out to identify relevant confounders in the above mentioned question. For this purpose, based on the systematic literature search carried out by G-BA to determine the appropriate comparator therapy according to § 35a SGB V for onasemnogene abeparvovec (2), systematic literature searches were carried out for evidence-based guidelines and recommendations (step 1) and systematic reviews and meta-analyses (step 2) in the indication of spinal muscular atrophy (SMA). The results were selected according to the previously defined inclusion and exclusion criteria (see section 2.3 and section 3.2). Two independent reviewers performed the screening of the retrieved results.

The bibliographic databases MEDLINE (PubMed) and the Cochrane Library (Cochrane Database of Systematic Reviews) were used for systematic information retrieval. Structured free-hand search was carried out in the databases and websites of the following organizations: AWMF, CMA Infobase, TRIP Database, google scholar. In addition, a free internet search was conducted for current German (Gesellschaft für Neuropädiatrie, Deutsche Gesellschaft für Muskelkranke e.V.) and international guidelines (Treat-NMD Neuromuscular Network, SMA Europe, Cure

SMA) as well as in PubMed. A detailed description of the search strategies is given in section 5.1 and section 5.2.

The research was completed on March 23th 2021.

Table A41: Overview

Population	▪ Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene ▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA ▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene
Intervention	-
Comparators	-
Endpoints	Confounders, risk factors, prognostic factors
Language	German and English
Publication types	(I) Guidelines, recommendations (II) Systematic reviews, meta-analyses

Sections 2 (Identification of relevant guidelines and recommendations (step 1)) and 3 (Identification of systematic reviews and meta-analyses (step 2)) describe the procedure for identifying the confounders, the inclusion and exclusion criteria and the results of the two search areas in detail.

2. Identification of relevant guidelines and recommendations (step 1)

2.1 Bibliographic literature research – Guidelines and recommendations

In accordance with the above-mentioned specifications, the search was carried out on March 23th, 2021 in the MEDLINE bibliographic database. The search strategy was individually adapted and structured to the database. The detailed search strategy is described in section 5.1 Search strategy – Bibliographic literature search (Guidelines and recommendations in the indication SMA). The PRISMA flow-chart representing the selection process as per pre-specified inclusion- and exclusion criteria (section 2.3) is shown in Figure A7 and the final results of the search and selection process are listed in section 2.4.

2.2 Free-hand search – Guidelines and recommendations

In accordance with the above-mentioned specifications, the structured free-hand search was carried out on March 23th 2021 in the various databases and websites shown in Table A42. The search strategies were individually adapted and structured to the respective databases and websites. The search results are presented in section 5.3.

Table A42: Various Guidelines databases and selected websites

Guidelines databases
AWMF Guidelines
CMA Infobase: (CPGs) – Clinical Practice Guidelines Database
TRIP Database
Selected websites of German and international professional societies
Gesellschaft für Neuropädiatrie
Deutsche Gesellschaft für Muskelkranke e.V.
Treat NMD Neuromuscular Network
SMA Europe
Cure SMA
Additional Free-hand search & PubMed
PubMed
Google
Google-Scholar

2.3 Inclusion / exclusion criteria – Guidelines and recommendations

The identification of relevant guidelines and recommendations comprised the entire indication area of SMA. The applied inclusion- and exclusion criteria are listed in Table A43.

Table A43: Inclusion / exclusion criteria – Guidelines and recommendations

	Inclusion criteria		Exclusion criteria	
Patient population	I1	Guideline for SMA Recommendation for SMA	E1	I1 not fulfilled.
Intervention	I2/E2	No limitation		
Appropriate comparator therapy	I3/E3	No limitation		
Endpoints	I4	Information on prognostic factors contained in guideline	E4	I4 not fulfilled.
(Study) guideline type	I5	Current valid version	E5	I5 not fulfilled.
Language	I6	English or German	E6	I6 not fulfilled.

I: inclusion criteria; SMA: spinal muscular atrophy; E: exclusion criteria

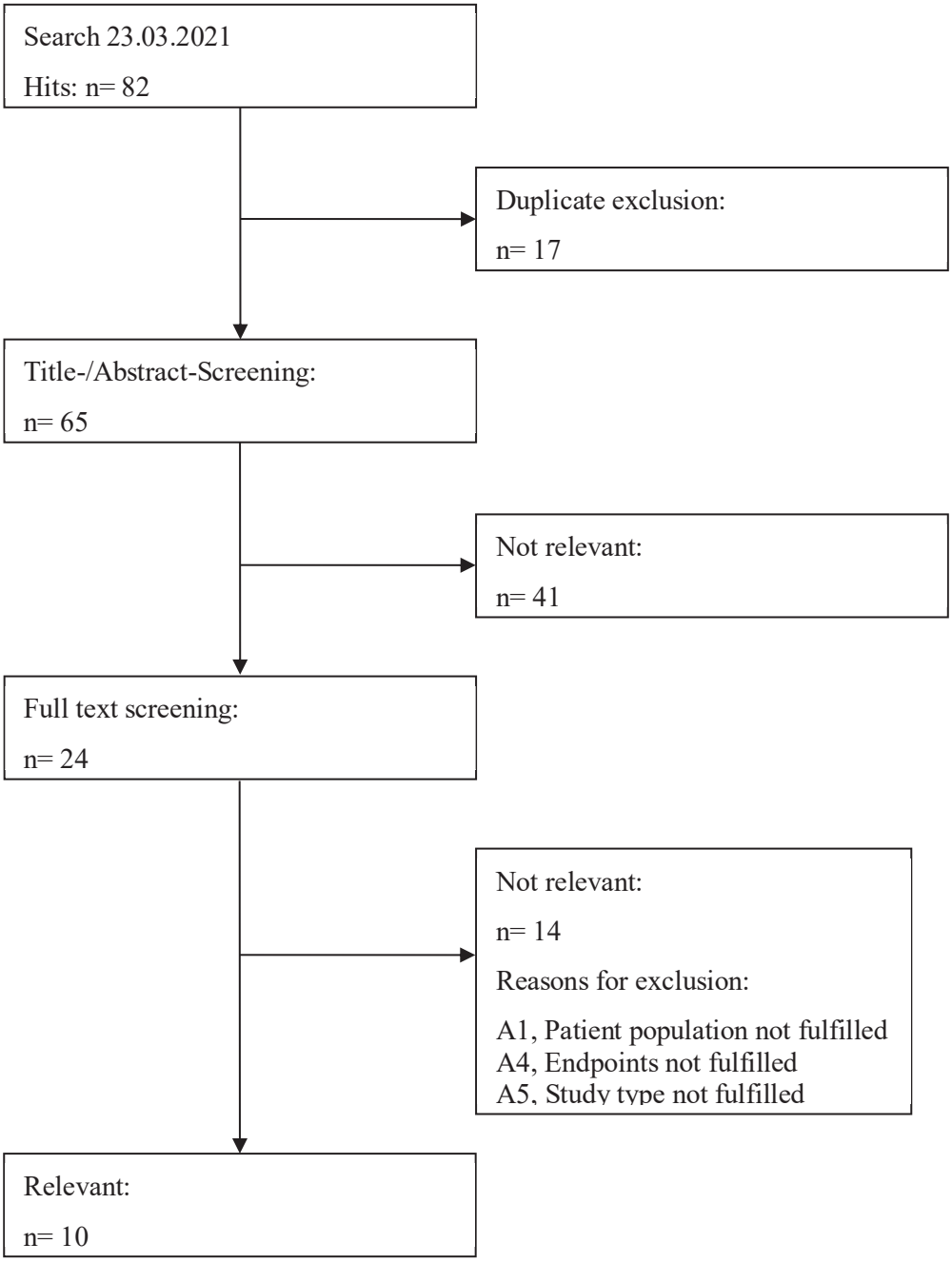
2.4 Results – Guidelines and recommendations

The PRISMA diagram shown in Figure A7 illustrates the screening and selection process for relevant guidelines and recommendations, which form the basis for the identification of confounders.

The search yielded 34 hits in the MEDLINE bibliographic database. In the structured free-hand search, 48 potentially relevant publications were identified. After excluding duplicates, 65 hits remained to be evaluated via the 2-step selection/screening procedure.

During the first screening, non-relevant publications were excluded based on title and abstract by checking for population, study type and language. In total, 41 publications were excluded. In the second screening, full texts of publications remaining from the first screening (24 hits) were reviewed and checked for relevance. In addition to the criteria from the first screening, the full texts were also be checked for information on prognostic endpoints. As a result, a total of 10 guidelines and recommendations for the indication spinal muscle atrophy were included.

Figure A7: PRISMA diagram – Guidelines and recommendations



3. Identification of relevant systematic reviews and Meta-analyses (step 2)

3.1 Bibliographic literature research – Systematic reviews and Meta-analyses

The bibliographic search was conducted in accordance with the above-mentioned specifications, the search was carried out on March 23th 2021 in the MEDLINE bibliographic database and in the Cochrane Database of Systematic Reviews. The search strategies were individually adapted and structured to each database. The detailed search strategy is described in section 5.2 Search strategy – Bibliographic literature search (systematic reviews and Meta-analyses in the indication SMA).

3.2 Inclusion / exclusion criteria – Systematic reviews and Meta-analyses

Inclusion / exclusion criteria for the literature selection have been designed analogously to the evidence search performed by the G-BA to identify the appropriate comparator therapy (2). The criteria listed in Table A44 were taken into account for the inclusion of systematic reviews and meta-analyses as a basis for the identification of confounders.

Table A44: Inclusion / exclusion criteria – Systematic reviews and Meta-analyses

	Inclusion criteria		Exclusion criteria	
Patient population	I1	▪ Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene ▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 1 SMA ▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and a clinically diagnosed type 2 SMA and up to 3 copies of the SMN2 gene	E1	I1 not fulfilled.
Intervention	I2/E2	No limitation		
Appropriate comparator therapy	I3/E3	No limitation		
Endpoints	I4	Collection of at least one patient-relevant outcome in the dimensions	E4	I4 not fulfilled, or no separate evaluation for the

Inclusion criteria			Exclusion criteria	
		of: ▪ Mortality ▪ Deaths ▪ Morbidity ▪ motor function (assessed with age-appropriate instruments, depending on disease severity, especially achievement of WHO milestones of motor development) ▪ respiratory function (need for [permanent] ventilation) ▪ bulbar function (ability to swallow and speak, need for non-oral nutritional support) ▪ other complications of the disease (e.g., pain, orthopedic complications) ▪ Side effects ▪ Adverse events ▪ Health-related quality of life ▪ health-related quality of life (assessed with an age-appropriate instrument)		relevant population.
Study type	I5	▪ Systematic reviews ▪ Meta-Analyses	E5	I5 not fulfilled ▪ HTA report ▪ Dose-finding ▪ studies ▪ Non-interventional studies ▪ narrative reviews ▪ Case reports ▪ Retrospective studies and cohort study ▪ Opinions ▪ Animal studies / in vitro studies
Duration of study	I6	No limitation		
Type of documentation	I7	Full text publication	E7	Document types other than full text publication

Inclusion criteria			Exclusion criteria	
				(e.g. conference abstracts, editorials, notes, letters to the editor)
Language	I8	English or German	E8	I8 not fulfilled

I: inclusion criteria; SMA: spinal muscular atrophy; E: exclusion criteria

3.3 Results – Systematic reviews and Meta-analyses

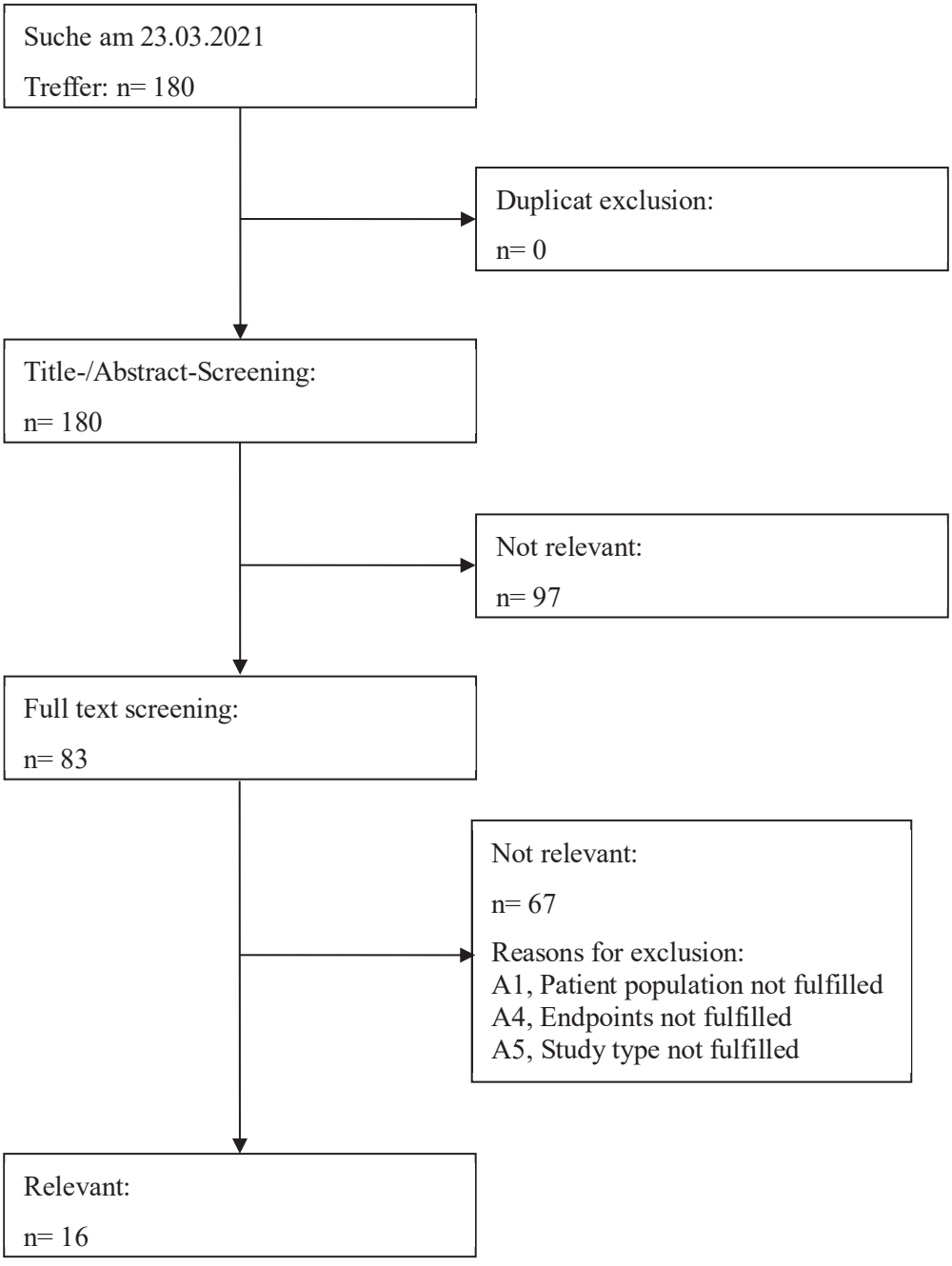
The PRISMA diagram shown in Figure A8 illustrates the screening and selection process for relevant systematic reviews and meta-analyses, which form the second basis for the identification of confounders.

The search yielded 165 hits in the MEDLINE bibliographic database and 15 hits were identified in the Cochrane Library. After excluding duplicates, 180 hits remained to be evaluated via the 2-step selection / screening procedure.

During the first screening, non-relevant publications were excluded based on title and abstract by checking for population, endpoints, study type, documentation type and language. In total, of 97 publications were excluded.

In the second screening, full texts of publications remaining from the first screening (83 hits) were reviewed and checked for relevance. The same criteria were used as in the first screening. As a result, 16 systematic review was included for the indication.

Figure A8: PRISMA diagram – Systematic reviews and Meta-analyses



4. Result presentation of the confounder identification and clinical perspective

After identification of the relevant national and international guidelines and recommendations as well as systematic reviews and meta-analyses, all confounders that were considered potentially relevant for SMA were identified and extracted.

The results were then validated by clinical experts in a joint workshop on May 12, 2021. For this purpose, all identified and potentially relevant confounders were discussed regarding their importance for the target population with the following six clinical experts:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

The systematic literature searches revealed two potential categories of confounders. The majority of potential confounders manifest at baseline (Table A45 – A31). The clinical experts agreed that baseline should be equated with the time of treatment initiation. Some confounders, called progression confounders, that occur after baseline during treatment were also identified in the systematic literature research (Table A51 – A35). According to the clinical experts, the relevance of these confounders is not proven. For this reason, only baseline confounders are considered relevant and included in the study.

The assessment from a clinical perspective resulted in a categorization of the identified confounders into one of three groups:

- Very important: these confounders have a significant impact on the results and are essential for adjusting the statistical analyses in a non-randomized study
- Less important: These confounders have a minor influence on the results and should be controlled in the statistical analysis if possible. However, if selected confounders in this category cannot be controlled, the results are still considered valid
- Not important: These confounders are not considered relevant to this study, e.g., due to being captured as endpoints or due to the specific study setting

Operationalization of confounders for the study was directly proposed and whether they could currently be mapped in the SMArtCARE registry was queried.

Table A45: Confounders at baseline - Category Patient characteristics

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies 3	SMA Type I	SMA Type II				
Age onset	▪ Age at symptom onset	n.a.	n.a.	X	X	▪ Age at symptom onset	Less important	Yes	(4, 5)
Age Treatment initiation	▪ Age at treatment ▪ Age at study start (first dose)	X	X	X X	X X	▪ Age at study start (first dose)	Very important	Yes	(6–8)
Comorbidities	▪ Comorbidities	X	X	X	X	▪ Include as general flag (yes/no) specific ones?	Not relevant in routine care due to rarity	Yes	(9, 8)
Lean body mass	▪ Lean body mass	n.a.	n.a.	X	X	▪ BMI?	Not important	Yes ▪ Weight ▪ Height	(10)
Race	▪ Race				X	Do not include	Not important	No	(11)

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies	SMA Type I 3	SMA Type II				
Region	▪ Regional and cultural standards	X	X	X	X	Do not include ▪ Study limited to Germany If Austria were included: Potentially include Austria vs. Germany	Not important	Yes ▪ Place of birth ▪ Location of treatment center?	(10)

Table A46: Confounders at baseline - Category Origin of SMA disease

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic SMN2 copies 3	SMA Type I	SMA Type II				
SMA Type	▪ SMA Type	n.a.	n.a.	X	X	Individual study populations: ▪ Pre-symptomatic 1-2 copy SMN2 ▪ Pre-symptomatic 3 copy SMN2 ▪ Symptomatic Type I ▪ Symptomatic Type II	Not important: Age at onset & highest motor milestone at baseline captured individually	SMA type not explicitly available? Derivation from age at symptom onset: ▪ <6M: Type I ▪ 6M-18M: Type II	(10, 6, 12–14),
SMN2 copy number	▪ SMN2 copy number	X	X	X	X	SNM2 copy number	Very Important[3]	Yes	(15, 10, 16–19, 4, 20–22, 12, 23, 6, 14)
SMN2 genotype/ variants	▪ Genotype of SMN2	X	X	X	X		Not important	No ▪ SNM1 mutation type only	(15, 10, 16, 22, 11)

[3] Due to the stratification according to SMN2 copy number, this confounder is not taken into account

Table A47: Confounders at baseline - Category Impact on the Treatment response

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic SMN2 copies 3	SMA Type I	SMA Type II				
Pre-symptomatic/ symptomatic at treatment initiation	▪ Pre-symptomatic vs. symptomatic at the time of disease-modifying therapy (DMT)	X	X	(X)	(X)	Individual study populations: ▪ Pre-symptomatic 1-2 copy SMN2 ▪ Pre-symptomatic 3 copy SMN2 ▪ Symptomatic Type I ▪ Symptomatic Type II at treatment initiation	Very important	Yes	(11, 15, 5)

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic SMN2 copies 3	SMA Type I	SMA Type II				
Treatment delay	▪ Time between diagnosis and start of treatment	X	X	X	X	Do not include ▪ Age at symptom onset and age at treatment initiation included	Not important: ▪ Age at symptom onset and age at treatment initiation relevant	No ▪ Time of diagnosis not specified?	(10, 17, 9)
	▪ Time between symptom onset and 1st DMT	X	X	X	X				(9)

Table A48: Confounders at Baseline - Category Nutrition manifestations

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies 3	SMA Type I	SMA Type II				
Gastroesopha-geal reflux	▪ Gastroesophageal reflux	X	X	X	X	?	Not important	No	(10)
Gastrostomy	▪ Gastrostomy tube feeding ▪ Gastrostomy placement	(X)	(X)	X X	X X	Nutritional support: ▪ Proportion with nutritional support part-time ▪ Proportion with Nutritional support full time Use gastric/ nasal feeding tube information?	Nutritional Support general: Very important Gastrostomy vs. nasal feeding: not important	Does the patient use a gastric or nasal feeding tube? ▪ Exclusively ▪ Supplemen-tary	(22) (24, 10, 25)

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies 3	SMA Type I	SMA Type II				
Nutrition	▪ Growth and Undernutrition ▪ Overnutrition problems	X	X	X	X	Weight at or above the 3rd percentile of age group → If included likely other percentile relevant for SMA, (above 1st?) Nutrition support via gastric/nasal feeding tube (see above)	Not important because captured via nutritional support Suggestion: Eliminate weight at or above the 3rd percentile of age group because not influenced by DMD but by standard of care	Yes ▪ Weight ▪ Height ▪ Age	(10) (10, 26) (27)
	▪ Nutrition	X	X	X	X				
	▪ Nutrition support			X	X				
Bone mineral density	▪ Bone mineral density	X	X	X	X	Do not include	Not important	No	(10)

Table A49: Confounders at Baseline - Category Orthopedic and motoric manifestations

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies	SMA Type I 3	SMA Type II				
Contractures	▪ Contractures	(X)	(X)	X	X	Yes/No ▪ Limit to selected lo-calizations / types?	Less important	Yes ▪ Are any contractures present? (including limitations by contrature and localisation/ type)	(8, 22) (10)
	▪ Flexion Contractures	X	X	X	X				
Motoric function	▪ CHOP-INTEND score at baseline	X	X	X	X	▪ Mean CHOP-INTEND score at baseline (as applicable) → Include for all (also pre-symptomatic) ▪ Mean Hammersmith score at baseline	Very important	Yes? ▪ Physiotherapy assessment on day 1, 30, 60, 180, followed by 4-monthly	(4) (28)
	▪ HFMSE score from baseline			X	X				

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies	SMA Type I 3	SMA Type II				
	▪ Highest motor milestone at base-line					(as applicable) → Do not include (only measured at age 2+) ▪ Highest motor milestone at baseline → include		examinations → **CHOP-IN-TEND, HMFSE?** ▪ Motor Func-tion: Best current mo-tor function: Sitting without support; Crawl on hands an knees; Standing without support; Walking without support; Climb stairs; Other	(6)

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies	SMA Type I 3	SMA Type II				
Physical activity	▪ Physical activity	X	X	X	X	▪ Do not include	Not important	No	(5)
Orthotics	▪ Scoliosis	(X)	(X)	X	X	▪ Yes/no	Not important	Yes. Does the Patient have scoliosis?	(10, 25)

Table A50: Confounders at Baseline - Category Access to and quality of treatment

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symptom-matic 3 SMN2 copies	SMA Type I	SMA Type II				
Access/ Quality	▪ COVID-19 Pandemic	X	X	X	X	Not relevant for study? ▪ Inclusion in case of treatment requires access ▪ Application of G-BA quality criteria for participating centers	Not important if study only includes HSPs qualifying for Zolgensma If other HSPs are included for Nusinersen: potentially important and should be included	No	(29)
	▪ Medical practitioners' knowledge	X	X	X	X				(10)
	▪ Multidisciplinary or interdisciplinary team	X	X	X	X				(10, 16)
	▪ Treatment Center			X	X				(10)

Table A51: Confounders after Baseline – Category Access to and quality of treatment

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies	SMA Type I 3	SMA Type II				
Access/ Quality	▪ Engagement with health care	X	X	X	X	No./Proportion of missed routine visits And	Not important	Yes ▪ Date of each visit	(10)
	▪ Providing families with information	X	X	X	X	No. of missed doses for nusinersen			(10)
	▪ Access to therapeutic interventions	X	X	X	X	Discussion: ▪ All routine visits performed at participating treatment center?			(18)
Adaptation	▪ Mechanical ventilation			X		Do not include ▪ Changes in ventilator and ▪ nutritional support represent endpoints	Not important (endpoint, not confounder)	Yes	(18)
	▪ Tracheostomy			X					(18)
	▪ Gastrostomy			X					(18)
	▪ Motor and respiratory physiotherapy			X					(18)
	▪ Nursing care			X					(18)
				X					(18)

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic 3 SMN2 copies	SMA Type I	SMA Type II				
	▪ Occupational therapy ▪ Speech therapy for alternative communication and dysphagia			X					(18)

Table A52: Confounders after Baseline – Category Assistive equipment

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symptomatic 1/2 SMN2 copies	Pre-symptomatic SMN2 copies 3	SMA Type I	SMA Type II				
Assistive equipment	▪ Assistive equipment			X	X	Do not include	Not important	Yes ▪ Assistance in airway clearance and secretion mobilization (type, frequency) ▪ Wheelchair use (including type and frequency of use)	(4) (10)
	▪ Wheelchair	X	X	X	X				

Table A53: Confounders after Baseline – Category Orthopedic and motoric manifestations

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies 3	SMA Type I	SMA Type II				
Orthotics	▪ Kneeankle- foot orthoses				X	Do not include ▪ Contractures at baseline included ▪ Baseline motor function included Discussion: ▪ Confounder on pain?	Not important	Yes ▪ Orthoses/ Devices (incl. Type, type of use, and frequency)	(26)
	▪ Limb orthotics								(26)
	▪ Orthosis			X	X				(10)
	▪ Positioning and seating alterations and orthotic devices	X	X	X	X				(10)
	▪ Posture management	X	X	X	X				(10)
	▪ Surgical correction of scoliosis			X	X				(10)
Physiotherapy	▪ Occupational therapy			X	X	Yes/no (per time between visits) Reliable operationalization not possible,	Less important: No evidence on effect of physio-therapy	Yes ▪ Therapy interventions (physio, feeding/	(5)
	▪ Physical therapy			X	X				(10)
	▪ Physiotherapy	X	X	X	X				(10)

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies	SMA Type I 3	SMA Type II				
	▪ Regular exercise	X	X	X	X	because it would require quantity and quality → Do not include in study		speech, occupational, other)	(10)
Motoric function	▪ Position (supine/ seated)	X	X	X	X	Do not include ▪ Baseline confounder and end-point	Not important (endpoint, not confounder)		(25)

Table A54: Confounders after Baseline – Category Others

Confounder/ prognostic factor	Characteristics	Relevant for (according to literature)				Proposed operationalization in study	Importance for study (very important, less important, not important)	Currently depictable in SMArtCARE	Sources
		Pre-symp-tom-matic 1/2 SMN2 copies	Pre-symp-tom-matic SMN2 copies 3	SMA Type I	SMA Type II				
Nutrition	▪ Education about nutrition	X	X	X	X	Do not include?	Not important	Unclear ▪ Therapy interventions: feed/speech includes Education?	(10)
Pain management	▪ Pain management			X	X	Do not include?	Not important	Unclear ▪ May be partly covered by "Other medication taken on a regular basis?"	(20, 5)
Support	▪ Support ▪ support from family	X X	X X	X X	X X	Do not include	Not important	No	(19) (4, 5)

5. Detailed presentation of the search strategy

5.1 Search strategy – Bibliographic literature search (Guidelines and recommendations in the indication SMA)

Table A55: Search string for guidelines and recommendations

Database	MEDLINE	
Search interface	PubMed	
Search date	24.03.2021	
#	Search terms	Results
1	"Muscular Atrophy, Spinal"[mh] OR "Motor Neuron Disease"[mh:noexp]	9.563
2	motor[Title/Abstract] AND neuron*[Title/Abstract] AND disease*[Title/Abstract]	22.950
3	spinal[tiab] OR bulbo-spinal[tiab] OR bulbospinal[tiab] OR myelopath*[tiab] OR progressiv*[tiab] OR spinobulbar[tiab] AND (muscular[tiab] OR muscle[tiab]) AND atroph*[tiab]	10.585
4	(spinal[tiab] OR (neurogenic scapuloperonea*[tiab])) AND amyotroph*[tiab]	5.453
5	(Spinal[tiab] OR bulbo-spinal[tiab] OR bulbospinal[tiab] OR spinobulbar[tiab] OR spinopontin*[tiab] OR (hereditary motor[tiab])) AND neuronopath*[tiab]	289
6	#1 OR #2 OR #3 OR #4 OR #5	36.514
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title])	95
8	(#7) AND ("2015/06/01"[PDAT] : "3000"[PDAT])	34
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])	34

5.2 Search strategy – Bibliographic literature search (systematic reviews and Meta-analyses in the indication SMA)

Table A56: Search string for systematic reviews in MEDLINE

Database	MEDLINE	
Search interface	PubMed	
Search date	24.03.2021	
#	Search terms	Results
1	"muscular atrophy, spinal"[MeSH Terms]	5.299
2	("spinal"[Title/Abstract] OR "bulbo-spinal"[Title/Abstract] OR "bulbospinal"[Title/Abstract] OR "myelopath*"[Title/Abstract] OR "progressiv*"[Title/Abstract] OR "spinobulbar"[Title/Abstract]) AND ("muscular"[Title/Abstract] OR "muscle"[Title/Abstract]) AND "atroph*"[Title/Abstract]	10.585
3	("spinal"[Title/Abstract] OR "neurogenic scapuloperonea*"[Title/Abstract]) AND "amyotroph*"[Title/Abstract]	5.453

4	("spinal"[Title/Abstract] OR "bulbo-spinal"[Title/Abstract] OR "bulbospinal"[Title/Abstract] OR "spinobulbar"[Title/Abstract] OR "spinopontin*"[Title/Abstract] OR "hereditary motor"[Title/Abstract]) AND "neuronopath*"[Title/Abstract]	289
5	#1 OR #2 OR #3 OR #4	16.385
6	(#5) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review[ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri*[tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication[tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab])) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))	278
7	(#6) AND ("2015/06/01"[PDAT] : "3000"[PDAT])	169
8	(#7) NOT "The Cochrane database of systematic reviews"[Journal]	165
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])	165

Table A57: Search string for systematic reviews in Cochrane.

Database	Cochrane Database of Systematic Reviews	
Search interface	Cochrane Library	
Search date	24.03.2021	
#	Search terms	Results
1	[mh "spinal muscular atrophy"]	91
2	[mh "motor neuron disease"]	718
3	(motor NEXT neuron* NEXT disease*):ti,ab,kw	459
4	(spinal OR "bulbo spinal" OR bulbospinal OR myelopath* OR progressiv* OR spinobulbar):ti,ab,kw AND (Muscular OR muscle):ti,ab,kw AND (Atroph*):ti,ab,kw	520
5	(Spinal OR (neurogenic NEXT scapuloperonea*)):ti,ab,kw AND (Amyo-troph*):ti,ab,kw	127
6	(Spinal OR "bulbo spinal" OR bulbospinal OR spinobulbar OR spinopontin* OR "hereditary motor"):ti,ab,kw AND (Neuronopath*):ti,ab,kw	2
7	{OR #1-#6}	1310
8	#7 with Cochrane Library publication date from Jun 2015 to Jun 2020, in Cochrane Reviews and Cochrane Protocols	15

5.3 Search Results – Free-hand search (Guidelines and recommendations for the indication SMA)

Table A58: List of guidelines found by the freehand search and their reasons for inclusion and exclusion

Plattform	Hits	Inclusion/exclusion
Systematic search - various databases		
AWMF Leitlinien Suche	Guideline application: **S1: Spinale Muskelatrophie (SMA), Diagnostik und Therapie** Registration number: 022-030 Planned completion: 15.01.2021	Exclusion No current version available
CMA Infobase: Clinical Practice Guidelines Database (CPGs)	**1. Pediatric home mechanical ventilation: a Canadian Thoracic Society clinical practiceguideline executive summary** Amin et al. Canadian Thoracic Society Published on: 2017	Inclusion
Trip Database	**Evidence in focus: Nusinersen use in spinal muscular atrophy** Michelson et al. Neurology Published on: 2018	Exclusion Duplicate

	Pediatric home mechanical ventilation: A Canadian Thoracic Society clinical practiceguideline executive summary Amin et al. Respiratory, critical care and Sleep Medicine Published on: 2017	Exclusion Duplicate
	Genetic Testing for Reproductive Carrier Screening and Prenatal Diagnosis Anonym Published on: 2020	Exclusion A4, Endpoints not fulfilled
	Carrier Screening for Genetic Conditions Committee on Genetics Published on: 2011	Exclusion A4, Endpoints not fulfilled
Google-Suche	**Handlungsempfehlungen zur Gentherapie der spinalen Muskelatrophie mit Onasemnogene Abeparvovec – AVXS-101 : Konsensuspapier der deutschen Vertretung der Gesellschaft für Neuropädiatrie (GNP) und der deutschen Behandlungszentren unter Mitwirkung des Medizinisch-Wissenschaftlichen Beirates der Deutschen Gesellschaft für Muskelkranke (DGM) e. V.** Hagenacker et al. Published on: 2017 Fortschritte Neurologie Psychiatrie	Exclusion Duplicate
	Spinale Muskelatrophie – Expertenempfehlungen zur Behandlung von erwachsenen Patienten mit Nusinerse Hagenacker et al. Published on: 2019 Fortschritte Neurologie Psychiatrie	Exclusion Duplicate
	Handlungsempfehlungen zur Gentherapie der spinalen Muskelatrophie mit Onasemnogene Abeparvovec – AVXS-101: Konsensuspapier der deutschen Vertretung der Gesellschaft für Neuropädiatrie (GNP) und der deutschen Behandlungszentren unter Mitwirkung des Medizinisch-Wissenschaftlichen Beirates der Deutschen Gesellschaft für Muskelkranke (DGM) e. V. Ziegler et al. Published on: 2017 Der Nervenarzt	Exclusion Duplicate
Google-Scholar	**Best practice guidelines for molecular analysis in spinal muscular atrophy** Scheffer et al. Published on: 2001 European Journal of Human Genetics	Inclusion

Spinal Muscular Atrophy Prior et al. Published on: 2020 GeneReviews®	Inclusion
Handlungsempfehlungen zur Gentherapie der spinalen Muskelatrophie mit Onasemnogene Abeparvovec – AVXS-101: Konsensuspapier der deutschen Vertretung der Gesellschaft für Neuropädiatrie (GNP) und der deutschen Behandlungszentren unter Mitwirkung des Medizinisch-Wissenschaftlichen Beirates der Deutschen Gesellschaft für Muskelkranke (DGM) e. V. Ziegler et al. Published on: 2017 Der Nervenarzt	Exclusion Duplicate
Recommendations for the diagnosis and management of typical childhood spinal muscular Atrophy Recommandations pour le diagnostic et la prise en charge de l'amyotrophie spinale typique de l'enfant Cuisset et al. Published on: 2012 Revue Neurologique	Inclusion
Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics Finkel et al. Published on: 2018 Neuromuscular Disorder	Exclusion Duplicate
1st Italian SMA Family Association Consensus Meeting: Management and recommendations for respiratory involvement in spinal muscular atrophy (SMA) types I–III Sansone et al. Published on: 2015 Neuromuscular Disorder	Exclusion Duplicate
Revised Recommendations for the Treatment of Infants Diagnosed with Spinal Muscular Atrophy Via Newborn Screening Who Have 4 Copies of SMN2 Glascock et al. Published on: 2020 Journal of Neuromuscular Diseases	Exclusion Duplicate
Management of children with spinal muscular atrophy type 1 in Australia Tassie et al. Published on: 2013 Journal of Pediatrics and Child Health	Exclusion A5, Study type not fulfilled

	Special Considerations in the Respiratory Management of Spinal Muscular Atrophy Schroth et al. Published on: 2009 Pediatrics	Inclusion
	Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening Glascock et al. Published on: 2018 Journal of Neuromuscular Diseases	Inclusion
	Practical guidelines to manage discordant situations of SMN2 copy number in patients with spinal muscular atrophy Cuscó et al. Published on: 2020 Neurology Genetics	Exclusion Duplicate
	Carrier screening for spinal muscular atrophy Prior et al. Published on: 2008 genetics in medicine	Inclusion
	Evidence in focus: Nusinersen use in spinal muscular atrophy Michelson et al. Published on: 2018 Neurology	Exclusion Duplicate
	Consensus Statement for Standard of Care in Spinal Muscular Atrophy Wang et al. Published on: 2007 Sage Open	Exclusion Duplicate
Cochrane Deutschland		No guideline found for the indication SMA.
Pubmed	**Treatment Advances in Spinal Muscular Atrophy** Bharucha-Goebel et al. Published on: 2017 Current neurology and neuroscience reports	Exclusion A5, Study type not fulfilled
	Spinal muscular atrophy care in the COVID-19 pandemic era Veerapandiyan et al. Published on: 2020 Muscle & Nerve	Exclusion A5, Study type not fulfilled

	Spinal muscular atrophy D´Amico et al. Published on: 2011 Orphanet Journal of Rare Diseases	Exclusion A5, Study type not fulfilled
	Recommendations for gene therapy of spinal muscular atrophy with onasemnogene abeparvovec-AVXS-101 : Consensus paper of the German representatives of the Society for Pediatric Neurology (GNP) and the German treatment centers with collaboration of the medical scientific advisory board of the German Society for Muscular Diseases (DGM)] Ziegler et al. Published on: 2020 Der Nervenarzt	Exclusion Duplicate
Selected homepages of German and international professional societies		
NHS - Protocol and Guidelines		No guideline found for the indication SMA.
NICE Guidelines		No guideline found for the indication SMA.
Gesellschaft für Neuropädiatrie	**Diagnosestellung und Behandlung bei SMA Patienten**	Exclusion A5, Study type not fulfilled
Treat-NMD Neuromuscular Network	**Behandlungsstandards für Spinale Muskelatrophie** Wang et al. Journal of Child Neurology Published on: 2007	Inclusion
	Diagnosestellung und Behandlung bei SMA Patienten Translation of Wang et al. by Schwersenz et al.	Exclusion A5, Study type not fulfilled
Deutsche Gesellschaft für Muskelkranke e.V.	**Leitfaden zu den Internationalen Therapiestandards für Spinale Muskelatrophie** Published on: 2017	Exclusion A5, Study type not fulfilled
	Diagnosis and management of spinal muscular atrophy: Part 1:Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care Mercuri et al. Published on: 2018 Neuromuscular Disorders	Exclusion Duplicate
	Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonaryand acute care; medications, supplements and immunizations; other organsystems; and ethics Mercuri et al. Published on: 2018 Neuromuscular Disorders	Exclusion Duplicate

	Management of Neuromuscular Diseases Spinale Muskelathrophie Deutsche Gesellschaft für Muskelkranke e.V. Published on: 2005	Exclusion A5, Study type not fulfilled
Initiative SMA		No guideline found for the indication SMA.
Schweizerischen Muskelgesellschaft		No guideline found for the indication SMA.
Neurologienetz		No guideline found for the indication SMA.
Deutsche Gesellschaft für Humangenetik e.V.		No guideline found for the indication SMA.
Deutsche Gesellschaft für Kinder- und Jugendmedizin e.V.		No guideline found for the indication SMA.
Deutsche Muskelstiftung		No guideline found for the indication SMA.
Deutsche Muskelschwund-Hilfe e.V.		No guideline found for the indication SMA.
Muskeln für Muskeln		No guideline found for the indication SMA.
Patientenstimme SMA		No guideline found for the indication SMA.
SMA Europe	**SPINAL MUSCULAR ATROPHY:PATHOLOGY, DIAGNOSIS,CLINICAL PRESENTATION,THERAPEUTIC STRATEGIES & TREATMENTS** Published on: 11/2020	Exclusion A5, Study type not fulfilled
	Consensus Statement for Standard of Care in Spinal Muscular Atrophy Wang et al. Published on: 2007 Journal of Child Neurology	Exclusion Duplicate
Marathon		No guideline found for the indication SMA.
CTM-austria		No guideline found for the indication SMA.
AFM Telethon		No guideline found for the indication SMA.

Spierziekten Nederland		This website is not available in English or German.
European Neuro Muscular Centre		No guideline found for the indication SMA.
Asami – Associazione per lo Studio delle Atrofie Muscolari Spinali Infantili		This website is not available in English or German.
Muscular Dystrophy UK		No guideline found for the indication SMA.
Cure SMA	**Respiratory muscle function in infants with spinal muscular atrophy type I** Finkel et al. Published on: 2014 Pediatric Pulmonology	Exclusion A5, Study type not fulfilled
	Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care Mecuri et al. Published on: 2018 Neuromuscular Disorders	Exclusion Duplicate
	Assessing the Needs of the SMA Population: Survey Results of Health Care Providers and Families Halanski et al. Published on: 2014 SAGE Open	Exclusion A5, Study type not fulfilled
	The Experience of Families With Children With Spinal Muscular Atrophy Type I Across Health Care Systems Murrell et al. Published on: 2016 Journal of Child Neurology	Exlusion A5, Study type not fulfilled
	Opening the window: The case for carrier and perinatal screening for spinal muscular atrophy Burns et al. Published on: 2016 Neuromuscular Disorders	Exclusion A5, Study type not fulfilled
	What Matters Most: A Perspective From Adult Spinal Muscular Atrophy Patients Hunter et al. Published on: 2016 Journal of Neuromuscular Diseases	Exclusion A5, Study type not fulfilled

	Nutritional Status and Nutrient Intake Challenges in Children With Spinal Muscular Atrophy Metha et al. Published on: 2015 Pediatric Neurology	Exclusion A5, Study type not fulfilled
	Baseline results of the NeuroNEXT spinal muscular atrophy infant biomarker study Kolb et al. Published on: 2016 Annals of Clinical an Translational Neurology	Exclusion A5, Study type not fulfilled
	Understanding the experiences and needs of individuals with Spinal Muscular Atrophy and their parents: a qualitative study Qian et al. Published on: 2015 BMC Neurology	Exclusion A5, Study type not fulfilled
	Responses to Fasting and Glucose Loading in a Cohort of Well Children with Spinal Muscular **Atrophy Type II** Davis et al. Published on: 2015 Journal of pediatrics	Exclusion A5, Study type not fulfilled
	209th ENMC International Workshop: Outcome Measures and Clinical Trial Readiness in Spinal Muscular Atrophy 7-9 November 2014, Heemskerk, The Netherlands Finkel et al. Published on: 2015 Neuromuscular Disorders	Exclusion A5, Study type not fulfilled
	Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics Mecuri et al. Published on: 2018 Neuromuscular Disorders	Exclusion Duplicate
Spinal Muscular Atrophy Foundation **My Care Plus**		No guideline found for the indication SMA. No guideline found for the indication SMA.
World Muscle Society		No guideline found for the indication SMA.

5.4 List of documents viewed in full text and excluded with reason for exclusion (Bibliographic literature research – Guidelines and recommendations)

Table A59: List of guidelines and recommendations viewed in full text and excluded

Ongoing number	Excluded reference	Reason for exclusion
1	Anonym, ADDENDUM: Technical standards and guidelines for spinal muscular atrophy testing. Genet Med 2016:18(7):752.	A5, Study type not fulfilled
2	Anonym, CADTH Canadian Drug Expert Committee Recommendation: Nusinersen (Spinraza — Biogen Canada Inc.): Indication: Treatment of 5q Spinal Muscular Atrophy. CADTH Common Drug Reviews 2017.	A5, Study type not fulfilled
3	Anonym, CADTH Canadian Drug Expert Committee Recommendation: Nusinersen (Spinraza — Biogen Canada Inc.): Indication: Treatment of 5q Spinal Muscular Atrophy. CADTH Com-mon Drug Reviews 2017.	A4, Endpoints not fulfilled
4	Bergin et al. Recommendations to support informal carers of people living with motor neurone disease. Br J Community Nurs 2016:21(10):518-524.	A1, Patient population not fulfilled
5	Deignan et al. Addendum: Technical standards and guidelines for spinal muscular atrophy testing. Genet Med 2020.	A5, Study type not fulfilled
6	Glascock et al. Revised Recommendations for the Treatment of Infants Diagnosed with Spinal Muscular Atrophy Via Newborn Screening Who Have 4 Copies of SMN2.J Neuromuscul Dis 2020:7(2):97-100.	A5, Study type not fulfilled
7	Hagenacker et al. [Spinal Muscular Atrophy - expert recommendations for the use of nusinersen in adult patients]. Fortschr Neurol Psychiatr 2019:87(12):703-710.	A4, Endpoints not fulfilled
8	Harvey et al. ACR Appropriateness Criteria® Movement Disorders and Neurodegenerative Diseases. J Am Coll Radiol 2020:17(5):175-187.	A1, Patient population not fulfilled
9	Mercuri et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord 2018:28(2):103-115.	A5, Study type not fulfilled
10	Anonym, Motor Neurone Disease: Assessment and Management. NICE Guideline 2016:42:1-7.	A1, Patient population not fulfilled
11	Oliver et al. The development of the UK National Institute of Health and Care Excellence evidence-based clinical guidelines on motor neurone disease. Amyotroph Lateral Scler Frontotemporal Degener 2017:18:5-6:313-323.	A1, Patient population not fulfilled
12	Silvinato et al. Spinal muscular atrophy 5Q - Treatment with nusinersen. Rev Assoc Med Bras (1992) 2018:64(6):484-491.	A4, Endpoints not fulfilled
13	Writing Group For Practice Guidelines For et al. [Clinical practice guidelines for spinal muscular atrophy]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi Actions 2020:37(3):263-268	A6, Language

5.5 List of documents viewed in full text and excluded with reason for exclusion (Bibliographic literature research – systematic reviews and Meta-analyses)

Table A60: List of systematic reviews and Meta-analyses viewed in full text and excluded

Ongoing number	Excluded reference	Reason for exclusion
1	Anonym. Global, regional, and national burden of motor neuron diseases 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018:17(12):1083-1097.	A1, Patient population not fulfilled
2	Abati et al. Pregnancy outcomes in women with spinal muscular atrophy: A review. J Neurol Sci 2018:388():50-60.	A1, Patient population not fulfilled
3	Ahmadian-Moghadam et al. Therapeutic potential of stem cells for treatment of neurodegenerative diseases. Biotechnol Lett 2020:42(7):1073-1101.	A5, Study type not fulfilled
4	Alhammoud et al. The impact of scoliosis surgery on pulmonary function in spinal muscular atrophy: a systematic review. Spine Deform 2021.	A4, Endpoints not fulfilled
5	Ali et al. Healthcare utilisation in children with SMA type 1 treated with nusinersen: a single centre retrospective review. BMJ Paediatr Open 2019:3(1):e000572.	A5, Study type not fulfilled
6	Azadinia et al. Can lumbosacral orthoses cause trunk muscle weakness? A systematic review of literature. Spine J 2017:17(4):589-602.	A1, Patient population not fulfilled
7	Bartels et al. Physical exercise training for type 3 spinal muscular atrophy. Cochrane Database of Systematic Reviews 2019: (3).	A1, Patient population not fulfilled
8	Bernardes Neto et al. Weaning from mechanical ventilation in people with neuromuscular disease: protocol for a systematic review. BMJ Open 2019:9(11):e029890.	A1, Patient population not fulfilled
9	Bharucha-Goebel et al. Treatment Advances in Spinal Muscular Atrophy. Curr Neurol Neurosci Rep 2017:17(11):91	A5, Study type not fulfilled
10	Boardman et al. Impairment Experiences, Identity and Attitudes Towards Genetic Screening: the Views of People with Spinal Muscular Atrophy. J Genet Couns 2018:27(1):69-84.	A4, Endpoints not fulfilled
11	Boentert et al. Respiratory involvement in neuromuscular disorders. Curr Opin Neurol 2017:30(5):529-537.	A5, Study type not fulfilled
12	Bowerman et al. Therapeutic strategies for spinal muscular atrophy: SMN and beyond. Dis Model Mech 2017:10(8):943-954.	A5, Study type not fulfilled
13	Bray et al. Preference-based measures of health-related quality of life in congenital mobility impairment: a systematic review of validity and responsiveness. Health Econ Rev. 2020:10(1):9.	A4, Endpoints not fulfilled
14	Butchbach et al. Copy Number Variations in the Survival Motor Neuron Genes: Implications for Spinal Muscular Atrophy and Other Neurodegenerative Diseases. Front Mol Biosci 2016:3():7.	A4, Endpoints not fulfilled
15	Calder et al. Small Molecules in Development for the Treatment of Spinal Muscular Atrophy. J Med Chem 2016:59(22):10067-10083.	A4, Endpoints not fulfilled

16	Castro-Codesal et al. Long-term non-invasive ventilation therapies in children: A scoping review. Sleep Med Rev 2018:37():148-158.	A1, Patient population not fulfilled
17	Chiriboga et al. Nusinersen for the treatment of spinal muscular atrophy. Expert Rev Neurother 2017:17(10):955-962.	A5, Study type not fulfilled
18	Cohen et al. Diffusion MRI of the spinal cord: from structural studies to pathology. NMR Biomed 2017:30(3).	A1, Patient population not fulfilled
19	Dangouloff et al. Systematic literature review of the economic burden of spinal muscular atrophy and economic evaluations of treatments. Orphanet J Rare Dis 2021:16(1):47.	A4, Endpoints not fulfilled
20	Dial et al. The Role of AMPK in Neuromuscular Biology and Disease. Trends Endocrinol Metab 2018:29(5):300-312.	A5, Study type not fulfilled
21	Dubowitz et al. Critical Review Ahead of Publication. Neuromuscul Disord 2019:29(6):412.	A5, Study type not fulfilled
22	Dunaway Young et al. Six-minute walk test is reliable and valid in spinal muscular atrophy. Muscle Nerve 2016:54(5): 836-842.	A1, Patient population not fulfilled
23	Elshafay et al. Efficacy and Safety of Valproic Acid for Spinal Muscular Atrophy: A Systematic Review and Meta-Analysis. CNS Drugs. 2019:33(3):239-250.	A4, Endpoints not fulfilled
24	Finsterer et al. Fasciculations in human hereditary disease. Acta Neurol Belg 2015:115(2):91-95.	A4, Endpoints not fulfilled
25	Göhl et al. [Respiratory Muscle Training: State of the Art]. Pneumologie 2016:70(1):37-48.	A1, Patient population not fulfilled
26	Grayev et al. A Systematic Review of Procedural Complications from Transforaminal Lumbar Puncture for Intrathecal Nusinersen Administration in Patients with Spinal Muscular Atrophy. AJNR Am J Neuroradiol 2021.	A1, Patient population not fulfilled
27	Grotto et al. Type 0 Spinal Muscular Atrophy: Further Delineation of Prenatal and Postnatal Features in 16 Patients. J Neuromuscul Dis 2016:3(4):487-495.	A1, Patient population not fulfilled
28	Grychtol et al. The role of sleep diagnostics and non-invasive ventilation in children with spinal muscular atrophy. Paediatr Respir Rev 2018:28():18-25.	A5, Study type not fulfilled
29	Hensel et al. The Actin Cytoskeleton in SMA and ALS: How Does It Contribute to Motoneuron Degeneration? Neuroscientist 2018:24(1):54-72.	A5, Study type not fulfilled
30	Hu et al. Gene therapeutic strategies and relevant clinical trials in neuromuscular disorder in China. Gene Ther 2020:27(7-8):321-328.	A5, Study type not fulfilled
31	Iftikhar et al. Current and emerging therapies for Duchenne muscular dystrophy and spinal muscular atrophy. Pharmacol Ther 2021:220: 107719.	A5, Study type not fulfilled
32	Jablonka et al. Developmental regulation of SMN expression: pathophysiological implications and perspectives for therapy development in spinal muscular atrophy. Gene Ther 2017:24(9):506-513.	A5, Study type not fulfilled
33	Janoudi et al. Nusinersen for Adolescents and Adults with Spinal Muscular Atrophy: A Review of Clinical Effectiveness. CADTH Rapid Response Reports 2020.	A1, Patient population not fulfilled
34	Kennedy et al. Walking and weakness in children: a narrative review of gait and functional ambulation in paediatric neuromuscular disease. J Foot Ankle Res 2020:13(1):10.	A1, Patient population not fulfilled

36	Kilcher et al. Medical use of cannabis in Switzerland: analysis of approved exceptional licences. Swiss Med Wkly 2017:147():w14463.	A4, Endpoints not fulfilled
36	Kreider et al. Creatine in Health and Disease. Nutrients 2021:13(2).	A4, Endpoints not fulfilled
37	Kremer et al. Transcriptomics: molecular diagnosis of inborn errors of metabolism via RNA-sequencing. J Inherit Metab Dis 2018:41(3):525-532.	A4, Endpoints not fulfilled
38	Lager et al. Pain in adolescents with spinal muscular atrophy and Duchenne and Becker muscular dystrophy. Eur J Paediatr Neurol 2015:19(5):537-546.	A1, Patient population not fulfilled
39	Landfeldt et al. Costs of Illness of Spinal Muscular Atrophy: A Systematic Review. Appl Health Econ Health Policy 2021.	A4, Endpoints not fulfilled
40	Lanigan et al. Comparative Pathology of the Peripheral Nervous System. Vet Pathol 2021:58(1):10-33.	A5, Study type not fulfilled
41	Li et al. The prevalence of spinal muscular atrophy carrier in China: Evidences from epidemiological surveys. Medicine (Baltimore) 2020:99(5):e18975.	A4, Endpoints not fulfilled
42	Lin et al. Molecular Therapies for Muscular Dystrophies. Curr Treat Options Neurol 2018:20(7):27.	A5, Study type not fulfilled
43	Long et al. Genome Editing of Monogenic Neuromuscular Diseases: A Systematic Review. JAMA Neurol 2016:73(11):1349-1355.	A1, Patient population not fulfilled
44	MacDonald et al. The Use of Medical Cannabis with Other Medications: A Review of Safety and Guidelines - An Update. CADTH Rapid Response Reports 2019.	A1, Patient population not fulfilled
45	Magalhães et al. Is transcutaneous electrical muscle stimulation an alternative for preventing acquired muscle weakness in the pediatric intensive care unit? A scoping review. Pediatr Pulmonol 2019:54(8):1108-116.	A1, Patient population not fulfilled
46	Mandarakas et al. Functional outcome measures for infantile Charcot-Marie-Tooth disease: a systematic review. J Peripher Nerv Syst 2018:23(2):99-107.	A4, Endpoints not fulfilled
47	Martin et al. Translating state-of-the-art spinal cord MRI techniques to clinical use: A systematic review of clinical studies utilizing DTI, MT, MWF, MRS, and fMRI. Neuroimage Clin 2016:10():192-238.	A1, Patient population not fulfilled
48	Mensch et al. Instruments for the evaluation of motor abilities for children with severe multiple disabilities: A systematic review of the literature. Res Dev Disabil 2015:47():185-198.	A4, Endpoints not fulfilled
49	Messina et al. A critical review of patient and parent caregiver oriented tools to assess health-related quality of life, activity of daily living and caregiver burden in spinal muscular atrophy. Neuromuscul Disord 2019:29(12):940-950.	A4, Endpoints not fulfilled
50	Miladi et al. Minimally Invasive Surgery for Neuromuscular Scoliosis: Results and Complications in a Series of One Hundred Patients. Spine (Phila Pa 1976) 2018:43(16):E968-E975.	A1, Patient population not fulfilled
51	Nidetz et al. Adeno-associated viral vector-mediated immune responses: Understanding barriers to gene delivery. Pharmacol Ther 2020:207():107453.	A5, Study type not fulfilled
52	O'Sullivan et al. Effect of Lung Volume Recruitment on Pulmonary Function in Progressive Childhood-Onset Neuromuscular Disease: A Systematic Review. Arch Phys Med Rehabil 2020.	A1, Patient population not fulfilled

53	Paganoni et al. Evidence-Based Physiatry: Pediatric Neuromuscular Rehabilitation in the Era of Precision Medicine. Cochrane Database of Systematic Reviews 2018:97(12):920.	A5, Study type not fulfilled
54	Payne et al. Interventions for fatigue and weight loss in adults with advanced progressive illness. Cochrane Database of Systematic Reviews 2017:(4).	A1, Patient population not fulfilled
55	Perez et al. Management of Neuroinflammatory Responses to AAV-Mediated Gene Therapies for Neurodegenerative Diseases. Brain Sci 2020:10(2).	A5, Study type not fulfilled
56	Sansone et al. 1st Italian SMA Family Association Consensus Meeting: Management and recommendations for respiratory involvement in spinal muscular atrophy (SMA) types I-III, Rome, Italy, 30-31 January 2015. Neuromuscul Disord 2015:25(12)979-989.	A5, Study type not fulfilled
57	Silvinato et al. Spinal muscular atrophy 5Q - Treatment with nusinersen.Rev Assoc Med Bras (1992) 2018:64(6):484-491.	A5, Study type not fulfilled
58	Simon et al. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. Cochrane Database of Systematic Reviews 2016:(10).	A1, Patient population not fulfilled
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A2 Relevant variables in SMArtCare Registry

Table A61: Relevant variables in SMArtCARE Registry

CRF	CRF Section	CRF Item	at or before Baseline	after Baseline
Enrolment		Date of consent	x	
		Genetically proven 5q SMA	x	
		Date of Birth	x	
		Gender	x	
Baseline		Date recorded	x	
	Genetic Test Result	SMN2 copy number performed?	x	
		SMN2 copy number	x	
		Was diagnosis made pre-symptomatically?	x	
	Clinical diagnosis	Age at symptom onset	x	
	Motor function	Sitting without support	x	
		Sitting without support: Age gained	x	
		Crawl on hands and knees	x	
		Crawl on hands and knees:	x	

CRF	CRF Section	CRF Item	at or before Baseline	after Baseline
		Age gained		
		Standing without support	x	
		Standing without support: Age gained	x	
		Walking without support	x	
		Walking without support: Age gained	x	
		Climb stairs	x	
		Climb stairs: Age gained	x	
	Registries, clinical trials	Is the patient currently or was previously included in a clinical trial?	x	
		Name of drug	x	
Medical Assessment		Visit date	x	x
		Age at visit	x	x
	Pulmonary	Does the patient receive ventilator support?	x	x
		Type of ventilation		x
		Time of ventilator use	x	x
		Start of ventilator use	x	x

CRF	CRF Section	CRF Item	at or before Baseline	after Baseline
	Nutrition	Does the patient use a gastric or nasal feeding tube?	x	x
		Start of tube feeding	x	x
		Swallowing?		x
		Chewing?		x
	Orthopedics	Does the patient have scoliosis?		x
		Orthopedic surgery since last visit		x
	Hospitalisation	Planned hospitalisation since last visit (except for treatment administration)?		x
		Admission date		x
		Reason for hospitalisation		x
	Medication	Is the patient on any approved medication for SMA?	X	x
		Name of drug	X	x
		Start date	X	x
		Other medication taken on a regular basis?	x	x

CRF	CRF Section	CRF Item	at or before Baseline	after Baseline
		Name of medication	x	x
		Start date	x	x
	Clinical Trial	Is the patient currently in a clinical trial?	x	x
		Name of drug	x	x
		Start Date	x	x
	Motor function	Any changes in motor milestones?	x	x
		Age gained of best motor function	x	x
		Age loss of previous best motor function	x	x
		Best current motor function	x	x
	HINE	Score	x	x
		Head control	x	x
	Clinical examination	Body weight	x	
		Neurology: Symptoms related to SMA	x	
		Are any contractures present?	x	

CRF	CRF Section	CRF Item	at or before Baseline	after Baseline
		Contractures: Type of limitation	x	
	Neurophysiology (optional)	Ulnar CMAP amplitude	x	
Physiotherapeutic Assessment	HFMSE	Date of Evaluation		x
		Score		x
	RULM	Date of Evaluation		x
		Score		x
	CHOP-INTEND	Date of Evaluation	x	x
		Score	x	x
Zolgensma	Admission day	Date of treatment	x	
Nusinersen		Date of treatment	x	x
		Care setting	x	x
Adverse Events		Date recorded		x
		Type of unexpected event: Hydrocephalus		x
		Type of unexpected event: Hepatotoxicity		x (to be added)
		Type of unexpected event: Thrombocytopenia		x (to be added)

CRF	CRF Section	CRF Item	at or before Baseline	after Baseline
		Type of unexpected event: Cardiac events		x (to be added)
		Type of unexpected event: Dorsal root ganglia cell inflammation		x (to be added)
		Type of unexpected event: Renal toxicity		x (to be added)
		Type of unexpected event: Respiratory tract infection		x
		Type of unexpected event: Epileptic seizure		x
		Type of unexpected event: Post lumbar puncture syndrome		x
		Has there been any adverse event since the last visit?		x
		Has there been unplanned or prolonged hospitalisation?		x
		Type of unexpected event		x
		MedDRA code of acute event		x
		Admission date		x
		Is the adverse event related		x

CRF	CRF Section	CRF Item	at or before Baseline	after Baseline
		to drug treatment?		
		Name of drug		x
		Any unexpected events without hospitalisation?		x
		Type of unexpected event		x
		MedDRA code of acute event		x
		Start date		x
		Is the adverse event related to drug treatment?		x
		Name of drug		x
End of data collection		Date recorded		x
		Is the patient deceased?		x
		Date of death		x

Source: SMArtCARE Case Report Form 2021

IQWiG-Berichte – Nr. 1265

Anwendungsbegleitende Datenerhebung zu Onasemnogen-Abeparvovec: Prüfung des Studienprotokolls und des statistischen Analyseplans

2. Addendum zum Auftrag A20-61

Addendum

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Keywords

Onasemnogene Abeparvovec, Muscular Atrophy – Spinal, Registries, Benefit Assessment, Research Design, Peer Review – Research

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Abkürzungsverzeichnis

Abkürzung	Bedeutung
AbD	Anwendungsbegleitende Datenerhebung
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
EFS	Event-free-survival
G-BA	Gemeinsamer Bundesausschuss
HINE	Hammersmith Infant Neurological Examination
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
MedDRA	Medical Dictionary for Regulatory Affairs
PICO	Patient, Intervention, Comparator, Outcome
PS	Propensity Score
pU	pharmazeutischer Unternehmer
QS-RL	Qualitätssicherungs-Richtlinie
SAP	Statistischer Analyseplan
SMD	Standardisierte Mittelwertdifferenz
SGB	Sozialgesetzbuch
SMA	spinale Muskelatrophie
SMN	Survival of Motor Neuron
SUE	schwerwiegendes unerwünschtes Ereignis
UE	unerwünschtes Ereignis

1 Hintergrund

Der Gemeinsame Bundesausschuss (G-BA) hat das Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) am 24.11.2021 mit der Prüfung des überarbeiteten Studienprotokolls und des statistischen Analyseplans (SAP) zur anwendungsbegleitenden Datenerhebung (AbD) zu Onasemnogen-Abeparvovec beauftragt.

In seiner Sitzung am 04.02.2021 hat der G-BA beschlossen, eine AbD und Auswertungen nach § 35a Absatz 3b Satz 1 SGB V für den Wirkstoff Onasemnogen-Abeparvovec in der Behandlung der spinalen Muskelatrophie zu fordern [1,2]. Dem Beschluss liegt unter anderem das vom IQWiG erstellte Konzept für eine AbD zu Onasemnogen-Abeparvovec zugrunde (Rapid Report A20-61 vom 01.10.2020 [3]).

Zur Prüfung, ob die Anforderungen des G-BA an die AbD und an Auswertungen durch die vom pharmazeutischen Unternehmer (pU) erstellten Unterlagen zum Studienprotokoll und SAP umgesetzt worden sind, hat der G-BA dem IQWiG die erste Version dieser Unterlagen übermittelt [4,5] und es mit der Prüfung dieser Unterlagen beauftragt. Neben dem G-BA-Beschluss zur Onasemnogen-Abeparvovec sollen die Inhalte der diesbezüglichen Beratungen des pU zur Studienplanung der AbD (2021-B-190 [6], 2021-B-122 [7]) berücksichtigt werden.

Auf Basis der Ergebnisse dieser Prüfung (Addendum A21-107 zum Rapid Report A20-61) hat der G-BA mit Schreiben vom 28.09.2021 den pU schriftlich darüber informiert, bei welchen Angaben im vorgelegten Studienprotokoll und SAP Anpassungsbedarf besteht. Der pU hat am 23.11.2021 überarbeitete Unterlagen beim G-BA eingereicht. Der G-BA hat dem IQWiG diese Unterlagen am 24.11.2021 übermittelt.

2 Prüfung der Unterlagen zur Planung der AbD von Onasemnogen-Abeparvovec

2.1 Allgemeine Anmerkungen zu den vom pU vorgelegten Unterlagen

Der pU hat das Studienprotokoll und den SAP (jeweils in der Version vom 18.11.2021) auf Basis der Anforderungen des G-BA, die ihm mit Schreiben vom 28.09.2021 übermittelt wurden, überarbeitet. Die Prüfung des Protokolls und SAP bezieht sich ausschließlich auf die Punkte aus der Liste des G-BA und die vom pU in seiner Übersicht der Anpassungen in Studienprotokoll und SAP beschriebenen Änderungen. Darüber hinaus wird ausschließlich die vom pU als G-BA Ansatz benannte Studienplanung kommentiert (siehe Abschnitt 2.2.1).

Die Prüfung der Änderungen des Studienprotokolls und des SAP hat zu einigen Punkten weiteren Anpassungsbedarf ergeben. Diese verbleibenden Mängel können in einer weiteren Revision der Studienunterlagen behoben werden. Die Bewertung der Umsetzung und der abschließenden Methodik der Studie können nach Einschätzung des IQWiG im Rahmen der Nutzenbewertung unter Berücksichtigung der Ergebnisse der AbD erfolgen.

2.2 Anmerkungen zur Umsetzung des vom G-BA formulierten Anpassungsbedarfs

2.2.1 Fragestellung gemäß PICO: Patientenpopulation

Position des G-BA

Die Definition der Patientenpopulation und die Auswertung der Daten sollten entsprechend der Vorgaben des G-BA getrennt für präsymptomatische und symptomatische Patientinnen und Patienten erfolgen.

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

Definition von zwei Analyse-Ansätzen innerhalb der Studie, wobei im „G-BA-Ansatz“ eine Stratifizierung in vier Studienpopulationen erfolgt. Einer Stratifizierung prä-symptomatischer Patienten anhand der Kopienzahl des *SMN2*-Gens wurde im Rahmen des Beratungsgesprächs am 29. Juni 2021 zugestimmt (Frage 10). Konkordante Folgeanpassungen ergeben sich bei der Fallzahlplanung sowie den erwarteten Patientenzahlen.

Aufgrund der bereits im Beratungsgespräch vom 11. August 2021 vorgetragenen Herausforderungen einer Stratifizierung von Patienten anhand des Symptomstatus in der Routineversorgung sowie maßgeblichen Auswirkungen auf die notwendige Anzahl von Patienten erfolgt im NGT-Ansatz weiterhin eine Stratifizierung allein anhand der Kopienzahl des *SMN2*-Gens.

Für eine detaillierte Darstellung des Sachverhalts wird auf Abschnitt 8.1 des Studienprotokolls verwiesen.

Bewertung der vom pU vorgenommenen Änderungen durch das IQWiG

Der pU setzt die Anforderung des G-BA zur Definition der Patientenpopulationen in der Fragestellung der AbD um. In einer Populationsdefinition, die er als G-BA Ansatz bezeichnet,

berücksichtigt er präsymptomatische und symptomatische Patientinnen und Patienten getrennt. Symptomatische Patientinnen und Patienten werden gemäß Anforderung des G-BA noch einmal in solche mit Typ-1-SMA und Typ-2-SMA unterteilt. Die prä-symptomatischen Patientinnen und Patienten stratifiziert der pU anhand der Kopienzahl des *SMN2*-Gens (≤ 2 Kopien / 3 Kopien). Diese Populationsdefinition entspricht den Anforderungen des G-BA und erscheint sachgerecht.

Ausgehend von dieser Populationsdefinition plant der pU die weitere Methodik der AbD. Dabei benennt er das an diese Population gebundene Vorgehen im Studienprotokoll und im SAP jeweils als G-BA Ansatz.

Parallel zum G-BA Ansatz beschreibt der pU im Studienprotokoll und im SAP ein Vorgehen, das er als Novartis Gene Therapies (NGT) Ansatz bezeichnet. Dieser Ansatz beruht auf einer im Vergleich zur ersten Protokollversion unveränderten Definition der Patientenpopulation, die lediglich zwischen Patientinnen und Patienten mit bis zu 2 bzw. mit 3 Kopien des *SMN2*-Gens unterscheidet, den Symptomstatus aber unberücksichtigt lässt. Diese Populationsdefinition und damit auch die darauf aufbauende Studienplanung entsprechen nicht den Anforderungen des G-BA und sind damit für eine der Datenerhebung folgende Nutzenbewertung nicht geeignet. Das als NGT Ansatz bezeichnete Vorgehen wird deshalb im Folgenden nicht weiter bewertet. Alle Ausführungen in den folgenden Kapiteln beziehen sich auf die als G-BA Ansatz bezeichnete Studienplanung.

2.2.2 Fragestellung gemäß PICO: Outcome (Morbidität)

Position des G-BA

Die durch die Vielzahl der Endpunkte zur Beschreibung der motorischen Funktion entstehende Multiplizität sollte verringert werden, indem die relevanten Endpunkte selektiert und die Endpunkte insgesamt hierarchisiert werden. Diese Entscheidungen müssen im Studienprotokoll präspezifiziert werden. Primär sollten Endpunkte, die den gesamten relevanten Beobachtungszeitraum abdecken, herangezogen werden.

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

G-BA-Ansatz: Reduktion der Endpunkte zur Abbildung der motorischen Funktion bei gleichzeitiger Fokussierung auf TTE-Analysen.

Bewertung der vom pU vorgenommenen Änderungen durch das IQWiG

Der pU reduziert die Anzahl der Endpunkte zur motorischen Funktion. Er plant jeweils die Erhebung der Zeit bis zum Erreichen der Meilensteine Sitzen, Stehen und Gehen ohne Unterstützung sowie die Zeit von der maximalen Ausprägung eines dieser Meilensteine bis zum vollständigen Verlust eines Meilensteins. Damit bildet er das Erreichen der Meilensteine und den Erhalt der Funktion ab. Darüber hinaus beschränkt er die Erhebung der motorischen Funktion durch Instrumente von 4 auf 2 (CHOP-INTEND und den HINE). Diese Planung stellt eine Verbesserung im Vergleich zum ursprünglich geplanten Protokoll dar. Die Interpretation

der Effekte bezüglich motorischen Funktion sollte unter Berücksichtigung der Gesamtheit der Endpunkte erfolgen.

Der pU weist im Studienprotokoll darauf hin, dass Unsicherheiten bezüglich der Dokumentation des Alters bei Erreichen eines Meilensteins der motorischen Funktion (Bericht der Eltern oder Beurteilung durch Neuropädiaterinnen oder Neuropädiater) bestehen und darüber hinaus eine weitere Verzerrung durch die unterschiedliche Häufigkeit von Visiten unter den verschiedenen Therapieoptionen entstehen könnte. Solche Verzerrungen sollten im Studienverlauf wo möglich vermieden werden. Um die Beurteilung der Relevanz dieser potenziellen Verzerrungen zu ermöglichen, müssen die angesprochenen Faktoren dokumentiert werden und Teil der Berichterstattung über die Studie sein.

2.2.3 Fragestellung gemäß PICO: Outcome (Nebenwirkungen)

Position des G-BA

Die Grenzwerte für die Erhebung der im Beschluss genannten spezifischen UE sollten vor Studienbeginn definiert und präspezifiziert sein.

Als Annäherung an die Erhebung von SUE sollte ein kombinierter Endpunkt aus UE, die zum Tod führen und UE, die zu einer Hospitalisierung führen, ausgewertet werden.

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

Ergänzung eines kombinierten Endpunkts aus UE mit Hospitalisierung und Tod jeglicher Ursache, da in SMArtCARE keine spezifische Erfassung von UE, die zum Tod führen, erfolgt.

Ergänzung spezifischer UE auf Grundlage der mit SMArtCARE abgestimmten und durch SMArtCARE angestoßenen, notwendigen Anpassungen des CRFs.

Für eine detaillierte Darstellung des Sachverhalts wird auf Abschnitte 5.2.2 und 5.2.3 des Studienprotokolls verwiesen.

Bewertung der vom pU vorgenommenen Änderungen durch das IQWiG

Spezifische UE

In der ersten Version des Protokolls hatte der pU den Verzicht auf die Erhebung spezifischer UE, die auf Anforderungen der EMA aus Risk-Management Plänen zu Onasemnogen-Abeparvovec und Nusinersen zurückgehen, damit begründet, dass für die Erhebung dieser UE keine klinisch relevanten Grenzwerte definiert seien. Die Forderung nach solchen Grenzwerten lässt der pU in der überarbeiteten Version des Protokolls fallen. Stattdessen sollen diese UE durch konkrete Abfrage im CRF des SMArtCARE-Registers erhoben werden. Dieses Vorgehen erscheint in der vorliegenden Situation sachgerecht.

Eines der aus Risk-Management Plänen identifizierten spezifischen UE wurde auch vor der Protokollanpassung bereits erhoben (Hydrocephalus). Für die weitere spezifischen UE (Hepatotoxizität, Thombozytopenie, kardiale Ereignisse, Entzündung der

Spinalganglionzellen, renale Toxizität) erfolgt die aktive Abfrage erst durch die Protokollanpassung. Der pU weist jedoch darauf hin, dass diese UE für den Zeitraum der Datenerhebung vor der Protokollanpassung aus der unspezifischen Erhebung der UE auf Basis der MedDRA-kodierten Auswertung abgeleitet werden können. Die potenziell unterschiedlichen Häufigkeiten von UE, die auf einer generellen Abfrage basieren, und solchen, die aktiv abgefragt werden, sollten bei dieser Auswertung berücksichtigt werden.

Annäherung an die Erhebung von SUE

Die Auswertung von SUE dient der Charakterisierung schwerwiegender Nebenwirkungen der Therapie. Innerhalb des SMArtCARE-Registers wird dokumentiert, ob ein UE zur Hospitalisierung oder zur Verlängerung einer Hospitalisierung führt, die weiteren Kriterien für SUEs (UEs, die zum Tod führen, lebensbedrohliche UEs, UEs, die zu einer dauerhaften oder schwerwiegenden Behinderung führen sowie Entwicklungen von kongenitalen Anomalien oder Geburtsfehlern) werden nicht erhoben. Als Annäherung an die Erhebung von SUE hat der G-BA deshalb einen kombinierten Endpunkt aus UEs, die zur Hospitalisierung führen, und UEs, die zum Tod führen, angefordert.

Der pU beschreibt, dass er den Vorschlag des G-BA nicht umsetzen kann. Der Grund sei, dass im SMArtCARE-Register keine Daten zu UEs, die zum Tod führen, erhoben werden. Der pU plant stattdessen, als Annährung an SUEs die Auswertung eines kombinierten Endpunkts aus UEs, die zu einer Hospitalisierung führen, und Todesfällen jeglicher Ursache. Dieses Vorgehen erscheint nicht sachgerecht.

Die vom pU vorgeschlagene Kombination von UEs, die zur Hospitalisierung führen mit Todesfällen jeglicher Art ist in der vorliegenden Indikation nicht geeignet, Nebenwirkungen der Therapie abzubilden. Da die SMA bei einem relevanten Anteil der Patientinnen und Patienten zum Tod führt, würde ein solcher kombinierter Endpunkt nicht zwischen Nebenwirkungen und Fortschreiten der Erkrankung differenzieren. Potenziell bestehende Unterschiede der Nebenwirkungen der Therapiealternativen könnten überdeckt werden.

Um die Annäherung an SUEs gemäß Vorschlag des G-BA umzusetzen, wäre es nicht notwendig, für alle UEs die potenzielle Folge Tod zu erheben. Es müsste aber für alle Todesfälle dokumentiert werden, ob diese auf UEs zurückgehen. Sollte dies nicht möglich sein, ist die Beschränkung der Auswertung auf UEs, die zur Hospitalisierung führen, sinnvoller als die Gesamtheit der Todesfälle mit einzubeziehen.

2.2.4 Studiendesign: prospektive / retrospektive Datenerhebung

Position des G-BA

Die Nutzung bereits erhobener Daten zu Nusinersen und Onasemnogen- Abeparvovec (aus dem Register SMArtCARE und ggf. weiteren Registern) sollte, sofern diese den genannten Anforderungen an die Datenqualität im Beschluss zur AbD zu Onasemnogen-Abeparvovec entsprechen, für die Registerstudie eingeplant werden

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

Heranziehen nicht-paralleler Daten zu Nusinersen bei Erfüllung des präspezifizierten Kriteriums zur Überlappung der Propensity Score Verteilungen.

Bewertung der vom pU vorgenommenen Änderungen durch das IQWiG

Der pU beschreibt im Studienprotokoll die Datenerhebung im SMArtCARE-Register vor Beginn der AbD (aktuell geplant im Januar 2022). Aus dieser Beschreibung geht hervor, dass Daten zu Nusinersen seit Juli 2018 erhoben werden, Daten zu Onasemnogen-Abeparvovec seit Juli 2020 bzw. in geringem Umfang auch vorher. Damit liegen 2 Arten von retrospektiven Daten für die AbD vor. Es handelt sich zum einen um Daten zu Nusinersen und Onasemnogen-Abeparvovec, die parallel erhoben wurden (mindestens seit Juli 2020), zum anderen um Daten zu Nusinersen, die nicht parallel zur Verfügbarkeit von Onasemnogen-Abeparvovec vor dessen Zulassung im Juli 2020 erhoben wurden.

Der pU folgt der Anforderung des G-BA nur teilweise. Er plant grundsätzlich die Berücksichtigung von retrospektiven Daten (die vor dem Start der Studie im SMArtCARE-Register erhoben wurden) zu Nusinersen in der AbD ein. Der pU weist darauf hin, dass eine Berücksichtigung der retrospektiven Daten unter dem Vorbehalt der Eignung und Qualität dieser Daten steht. Das erscheint sachgerecht.

Eine Berücksichtigung von retrospektiven Daten zu Onasemnogen-Abeparvovec ist dagegen gemäß Protokoll nicht vorgesehen. Die Einschlusskriterien für Patientinnen und Patienten verlangen weiterhin, dass der Behandlungsbeginn nach Studienstart für die AbD liegen muss, und geben an, dass dieses Kriterium ausschließlich für Nusinersen aufgehoben werden kann, wenn auf historische Daten zurückgegriffen werden soll. Damit ist der Einschluss von Patientinnen und Patientinnen, die vor Beginn der AbD (geplant Januar 2022) mit Onasemnogen-Abeparvovec behandelt wurden, nach wie vor ausgeschlossen. Der pU begründet nicht, warum er die retrospektiven Daten zu Onasemnogen-Abeparvovec (parallel erhoben zu Nusinersen) nicht in der AbD berücksichtigen möchte. Die Beschränkung der Berücksichtigung retrospektiver Daten auf Nusinersen entspricht nicht den Anforderungen des G-BA und erscheint nicht sachgerecht.

Die Mängel sollten in einer weiteren Revision des Studienprotokolls und des SAP behoben werden.

2.2.5 Studiendesign: Auswahl von Confoundern

Position des G-BA

Die Liste der Confounder sollte an die im Beschluss genannten Patientenpopulationen und an die für die Registerstudie genutzten Datenquellen (siehe nachfolgende Punkte) angepasst werden.

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

Zuordnung der Confounder zu den jeweils relevanten Studienpopulationen. Für eine Anpassung an weitere Datenquellen wird auf Punkt 6 verwiesen.

Bewertung der vom pU vorgenommenen Änderungen durch das IQWiG

Der pU passt die Liste der jeweils relevanten Confounder an die verschiedenen Subpopulationen der Gesamtstudienpopulation an. Dieses Vorgehen und die jeweils zugewiesenen Confounder erscheinen sachgerecht.

2.2.6 Datenquelle 1: Einbindung des RESTORE-Registers

Position des G-BA

Der pharmazeutische Unternehmer sollte an dem selbst geführten RESTORE-Register die notwendigen Anpassungen gemäß finalem Studienprotokoll und SAP für die AbD vornehmen, um Auswertungen auf Basis des RESTORE-Registers gemeinsam mit der vorliegenden Registerstudie z. B. in Form einer Metaanalyse für die AbD nutzen zu können.

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

Eine Präspezifikation sämtlicher Analysen für das RESTORE- Register sowie etwaiger struktureller Anpassungen war in der vom G-BA gewährten Frist von acht Wochen nicht umsetzbar. Darüber hinaus stehen nach Auffassung von Novartis Gene Therapies die Bestimmungen des G-BA- Beschlusses vom 4. Februar 2021 hinsichtlich der Eignung internationaler Datenquellen vor dem Hintergrund der Übertragbarkeit auf den deutschen Versorgungskontext bisher einem Heranziehen von Ergebnissen des RESTORE-Registers bisher entgegen.

Novartis Gene Therapies wird während der Prüfung der angepassten Studiendokumente durch G-BA und IQWiG die Arbeit zur Präspezifikation sämtlicher Analysen für das RESTORE-Register fortsetzen. Sollte der G-BA im Rahmen eines Änderungsbeschlusses mit Blick auf Übertragbarkeitsanforderungen ein Heranziehen von Ergebnissen aus dem RESTORE-Register für eine erneute Nutzenbewertung im Jahr 2027 ermöglichen, kann Novartis Gene Therapies die entsprechend präspezifizierten Analysen im Rahmen eines Amendments im ersten Quartal 2022 dem G-BA bereitstellen. In diesem Falle würde ebenfalls eine Berücksichtigung des RESTORE-Registers im ersten Zwischenbericht an den G-BA (Einreichung am 4. August 2022) erfolgen.

Bewertung der vom pU vorgenommenen Änderungen

Der pU postuliert, dass für eine mögliche Einbindung der Ergebnisse des RESTORE-Registers vom G-BA nur eine Frist von acht Wochen gewährt worden sei. Dies ist sachlich falsch.

Bereits im Konzept des IQWiG für die AbD zu Onasemnogen-Abeparvovec wurden Voraussetzungen für die Einbindung von Ergebnissen internationaler Register beschrieben und diese Option zur Erweiterung der Fallzahl eröffnet [3]. Im Fachaustausch zur Diskussion des

Konzepts am 23.11.2020, an dem der pU teilgenommen hat, wurden in diesem Zusammenhang einige notwendige strukturelle Anpassungen für das RESTORE-Register, für das der pU Sponsor ist, erörtert [8]. Diese betrafen unter anderem Vorgaben zur Datenerhebung für die Zentren analog dem Vorgehen im SMArtCARE-Register, Maßnahmen zur Vermeidung großer Mengen fehlender Werte, insbesondere auch für mit Nusinersen behandelte Patientinnen und Patienten, sowie eine Source Data Verification. Der pU hatte in diesem Zusammenhang im Fachgespräch angegeben, „flexibel für Diskussionen bezüglich technischer Änderungen" des RESTORE-Registers zu sein. Die Möglichkeit und die Voraussetzungen für die Einbindung von Ergebnissen des RESTORE-Registers sind dem pU daher seit mehr als 1 Jahr bekannt.

Die mögliche Einbindung internationaler Register wurden im Beschluss des G-BA vom 04.02.2021 sowie in beiden Beratungsgesprächen zur AbD am 29.06.2021 sowie am 11.08.2021 erneut vom G-BA adressiert [1,6,7]. Entsprechend wurde auch in der Prüfung der ersten Version des Studienprotokolls zur AbD die mögliche Einbindung des RESTORE-Registers beschrieben (Addendum A21-107).

Im vorliegenden Studienprotokoll beschreibt der pU primär jedoch lediglich bereits bekannte Eigenschaften des RESTORE-Registers. Daraus geht nicht hervor, dass der pU die notwendigen strukturellen und organisatorischen Änderungen des RESTORE-Registers herbeigeführt hat. Im Gegenteil findet sich z. B. zum Kriterium „Source Data Verification" weiterhin die Angabe „No", obwohl dieser Punkt explizit im Fachaustausch am 23.11.2020 adressiert wurde und der pU selbst dieses Kriterium, u. a. auf Basis des Beratungsgesprächs am 11.8.2021, im Zusammenhang mit dem SMArtCARE-Register als zwingend erforderlich anerkannt hat.

Der pU beschreibt schließlich, dass aus seiner Sicht ein Amendment zum Studienprotokoll und SAP zur Einbindung des RESTORE-Registers erforderlich sei. Es erscheint jedoch ausreichend, die im Beschluss des G-BA beschriebenen Anforderungen zur Einbindung weiterer Register (siehe Abschnitt 1.2.3 des G-BA-Beschlusses vom 04.02.2021) im Studienprotokoll aufzuführen und die notwendigen Bezüge zu den jeweiligen Ausführungen im Studienprotokoll zur AbD, z. B. zur Source Data Verification, herzustellen. Studienprotokoll und SAP zur Datenerhebung im SMArtCARE-Register können dann, wie bereits im Konzept A20-61 des IQWiG zur AbD von Onasemnogen-Abeparvovec vom 01.10.2020 beschrieben, Ausgangspunkt für die Einbindung weiterer internationaler Register einschließlich des RESTORE-Registers sein [3].

Ob und inwieweit der pU dann das RESTORE-Register entsprechend adaptiert und dadurch ermöglicht, dass Ergebnisse aus dem RESTORE-Register eingebunden und gemeinsam mit der finalen Analyse der AbD aus dem SMArtCARE-Register im Dossier zur Nutzenbewertung vorgelegt und sinnvoll interpretiert werden können, liegt im Verantwortungsbereich des pU.

2.2.7 Datenquelle 2: SMArtCARE-Zentren außerhalb Deutschlands

Position des G-BA

SMArtCARE-Zentren außerhalb Deutschlands sollten nicht grundsätzlich als Datenquelle ausgeschlossen werden, da diese u. a. auch prospektiv Daten für symptomatische Patienten liefern können.

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

Erweiterung auf österreichische Studienzentren innerhalb von SMArtCARE und Ergänzung entsprechender Subgruppenanalyse nach Region (Deutschland, Österreich).

Bewertung der vom pU vorgenommenen Änderungen durch das IQWiG

Die vom pU vorgenommene Erweiterung auf Studienzentren in Österreich erscheint in Verbindung mit den Zentrums-bezogenen Einschlusskriterien (siehe Abschnitt 2.2.8) sachgerecht.

2.2.8 Datenquelle 3: Einschluss von Studienzentren, die die Qualitätssicherungsrichtlinie des G-BA nicht erfüllen

Position des G-BA

Es sollte keine ausschließliche Beschränkung auf Zentren, die die Qualitätssicherungs-Richtlinie (QS-RL) des G-BA für die Anwendung von Onasemnogen-Abeparvovec erfüllen, vorgenommen werden. Vielmehr sollte die Entscheidung, ob ein Zentrum eingeschlossen wird oder nicht, von der tatsächlich in diesem Zentrum umgesetzten Qualität bzw. Versorgung abhängen.

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

Heranziehen von Daten aus Studienzentren unabhängig von der Verfügbarkeit beider Studieninterventionen oder der Erfüllung der QS-RL des G-BA.

Ableitung von notwendigen Patientenzahlen pro Zentrum zur Gewährleistung eines Mindestmaßes an Erfahrung und Vergleichbarkeit in der Behandlung und Dokumentation von Confoundern und Endpunkten als Approximation der vom G-BA nicht näher definierten tatsächlichen Qualität auf Grundlage von SMArtCARE-Daten.

Für eine detaillierte Darstellung des Sachverhalts wird auf Abschnitt 6.3 des Studienprotokolls verwiesen.

Bewertung der vom pU vorgenommenen Änderungen durch das IQWiG

Der pU beschreibt in Anlehnung an die QS-RL des G-BA zu Onasemnogen-Abeparvovec, dass für die AbD im Wesentlichen 2 Kriterien angewendet werden sollten, um eine ausreichende Versorgungsqualität der an der AbD beteiligten Studienzentren sicherzustellen:

1) Ausreichende Erfahrung in der Behandlung von Menschen mit SMA:
   Zur Operationalisierung einer ausreichenden Erfahrung in der Behandlung von Menschen mit SMA sieht der pU vor, dass in dem jeweiligen Zentrum mindestens 10 Kinder und Jugendliche im Alter unter 18 Jahren, darunter mindestens 5 Kinder im Alter unter 10 Jahren, in den letzten 3 Jahren vor Beginn der AbD medikamentös behandelt wurden. Diese Fallzahl liegt zwar unter der in der QS-RL für Onasemnogen-Abeparvovec angegebenen Fallzahl (mindestens 15 Behandlungsfälle insgesamt, darunter mindestens 5 bei Kindern unter 1 Lebensjahr). Die vom pU eingesetzten Fallzahlen erscheinen jedoch als Kompromiss zwischen einer Annäherung an die Anforderungen der QS-RLAnforderungen einerseits und einer Erweiterung der Fallzahl für die AbD andererseits sachgerecht.
2) Ausreichende Erfahrung insbesondere der Physiotherapeutinnen und Physiotherapeuten in der Erhebung der motorischen Meilensteine anhand der im SMArtCARE-Register verwendeten Skalen:

   Eine ausreichende Erfahrung in der Erhebung der motorischen Meilensteine sieht der pU durch eine Teilnahme der Zentren am SMArtCARE-Register als ausreichend gewährleistet an, da entsprechende Vorgaben und Schulungen Bestandteil des SMArtCARE-Registers sind. Dies erscheint ebenfalls sachgerecht.

Die Definition der beiden Kriterien Behandlungserfahrung und Erfahrung in der Erhebung motorischer Meilensteine als Zentrums-bezogene Einschlusskriterien für die AbD erscheint zusammenfassend sachgerecht, ebenso wie die konkrete Operationalisierung im Studienprotokoll.

2.2.9 Auswertung der Datenerhebung; Fallzahlplanung

Position des G-BA

Die Beschreibung der Rekalkulation der Fallzahlplanung (36-Monats-Analyse) im SAP sollte deutlich detaillierter erfolgen, darüber hinaus sollte die genaue Verwendung des Maß R^2und dessen genaue Definition ergänzt werden. Die Beschreibung der Rekalkulation sollte auf Basis einer verschobenen Hypothesengrenze für die Beurteilung der Effekte erfolgen.

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

Konkretisierung der verwendeten Annahmen und Methoden für die Fallzahlplanung sowie konkordante Anpassungen resultierend aus Stratifikationsanforderungen des G-BA. Klarstellung der Anwendung des beschriebenen methodischen Vorgehens auch im Rahmen der Rekalkulation von Fallzahlen zu 18 und 36 Monaten.

Ergänzung einer Fallzahlplanung mit verschobener Hypothesengrenze.

Bewertung der vom pU vorgenommenen Änderungen durch das IQWiG

In den überarbeiteten Versionen des Protokolls und des SAP werden Konkretisierungen der verwendeten Annahmen und Methoden für die Fallzahlplanung sowie Anpassungen resultierend aus Stratifikationsanforderungen des G-BA vorgenommen. Es wird zusätzlich auch eine Fallzahlplanung für eine verschobene Nullhypothese ergänzt. Zudem wird eine weitere Fallzahlplanung ohne verschobene Nullhypothese vorgenommen mit dem Ziel, die Situation eines dramatischen Effekts abzubilden.

Die Fallzahlplanung ohne verschobene Nullhypothese für die Situation eines dramatischen Effekts erscheint nicht sachgerecht, da diese Berechnung nur 1 Kriterium für einen dramatischen Effekt beinhaltet, nämlich das reduzierte Signifikanzniveau von α=0,01. Ein dramatischer Effekt ist aber weiterhin dadurch charakterisiert, dass orientierend ein beobachteter Effekt von RR=10 vorliegen muss. Dieses Kriterium bleibt in der Fahlzahlplanung unberücksichtigt.

Die vorgelegte Fallzahlplanung für eine verschobene Nullhypothese wird vereinfachend mit der Farrington-Manning-Formel für die Datensituation einer Vierfeldertafel durchgeführt, obwohl ein Endpunkt mit zensierten Daten betrachtet wird. Da im vorliegenden Fall die Fallzahlplanung nur orientierenden Charakter hat, erscheint die Anwendung dieser Methode durchaus sachgerecht. Allerdings wird die Berechnung nur zu einem Zeitpunkt durchgeführt. Es ist unklar, ob diese Fallzahlplanung sich auf die Studiendauer von 36 Monaten bezieht.

Zudem erscheint die Fallzahlkalkulation für den Endpunkt „Sitting without support to month 18“ fehlerhaft (siehe Tabellen 11 und 12 im SAP bzw. 31 und 32 im Studienprotokoll). Für die verschobene Hypothese wird eine Hypothesengrenze von 2, für den tatsächlichen Effekt jedoch mit 1,86 ein Wert kleiner als 2 angelegt. Statt eine relevante Überlegenheit zur Grenze 2 statistisch zu testen, wird hier fälschlicherweise die Fallzahl für einen Test auf Nichtunterlegenheit mit Grenze 2 berechnet. Da hier Hypothesengrenze und tatsächlicher Effekt mit 2 bzw. 1,86 sehr dicht beieinanderliegen, resultiert entsprechend die sehr große Fallzahl von fast 14.000.

Unverständlich ist zudem die Kritik an der Fallzahlplanung des IQWiG, dass im Addendum A21-107 die angewendete Methode nicht angegeben werde und widersprüchliche Angaben beinhalte, da in den beiden Szenarien trotz deutlich unterschiedlicher Beobachtungsdauer die gleiche Anzahl von Ereignissen verwendet worden sei. Im Addendum A21-107 wurde aber gar keine Fallzahlplanung vorgenommen. Vermutlich ist die Fallzahlplanung im Rapid Report A20-61 [3] gemeint. Hier wird aber sehr wohl die Methode genannt (Cox-Modell bei verschobener Nullhypothese) und es wird angegeben, dass in den beiden Szenarien mit deutlich unterschiedlichen Beobachtungsdauern auch deutlich unterschiedliche Anzahlen von Ereignissen auftreten [3].

Von den vorgelegten Fallzahlplanungen erscheint lediglich diejenige für eine verschobene Nullhypothese methodisch sachgerecht, und das auch nur für den Endpunkt EFS. Für den Endpunkt „Sitting without support to month 18“ ist die Testrichtung falsch. Beim Endpunkt EFS ist jedoch unklar, auf welche Studiendauer sich die Fallzahlplanung bezieht und woher die Annahmen über die Ereigniswahrscheinlichkeiten in der Nusinersengruppe kommen. Zudem ist es nicht nachvollziehbar, warum in einer Situation mit eingeschränkter Fallzahl eine Power von 90 % gefordert wird, was den benötigten Stichprobenumfang unnötig in die Höhe treibt. Es sollte eine grobe Fallzahlabschätzung für den Zeitraum 36 Monate mit einer Power von 80 % unter Berücksichtigung einer verschobenen Nullhypothese durchgeführt werden. Diese hat in diesem Projekt aber nur orientierenden Charakter.

2.2.10 Auswertung der Datenerhebung: Confounderadjustierung 1

Position des G-BA

Die Aufteilung der Patienten in die vorgeschlagenen „Behandlungsgruppen“ für die Confounderadjustierung sollte geändert werden. Eine Aufteilung der Patienten muss durch Informationen erfolgen, die zu Studienbeginn vorliegen.

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

Ergänzung des G-BA-Ansatzes unter Zuordnung sämtlicher Patienten innerhalb der betreffenden Studienpopulationen zur Erstbehandlung.

Bewertung der vom pU vorgenommenen Änderungen durch das IQWiG

Die geforderte Zuordnung aller therapie-naiven Patienten zur Erstbehandlung wird in den überarbeiteten Versionen des Protokolls und des SAP vorgenommen. Dieses Vorgehen erscheint sachgerecht.

2.2.11 Auswertung der Datenerhebung: Confounderadjustierung 2

Position des G-BA

Fehlende Details für die Propensity-Score-Analyse sollten ergänzt werden (Überprüfung der Güte, konkrete Kriterien für eine ausreichende Überlappung und Balanciertheit).

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

Explizite Erwähnung der Überprüfung der Güte, Ergänzung prä-spezifizierter Kriterien für die Überlappung und Balance sowie die Entscheidungsstruktur zur Modellauswahl.

Bewertung der vom pU vorgenommenen Änderungen durch das IQWiG

In der überarbeiteten Version des SAP werden fehlende Details für die Propensity-Score-Analyse (Überprüfung der Güte, konkrete Kriterien für eine ausreichende Überlappung und Balanciertheit) ergänzt. Diese Ergänzungen sind aber unvollständig, nur zum Teil sachgerecht und insgesamt widersprüchlich. Im Einzelnen liegen folgende Mängel vor:

- Das Kriterium für eine ausreichende Überlappung ist so wie formuliert unlogisch und nicht sinnvoll. Es wird angegeben, dass eine ausreichende Überlappung vorliegt, wenn in einer Behandlungsgruppe für 50% der Patientinnen und Patienten nicht gilt PS < 0,3 und in der anderen Behandlungsgruppe für 50% der Patientinnen und Patienten gilt PS > 0,7. Die Anwendung dieses Kriteriums würde bedeuten, dass zum einen Situationen mit 0 % Überlappung als ausreichend überlappend gelten (z. B. eine PS-Verteilung im 1. Arm zwischen 0,2 und 0,4, sodass die 1. Bedingung gilt und eine PS-Verteilung im 2. Arm zwischen 0,6 und 0,8, sodass die 2. Bedingung gilt), aber andererseits Situationen mit 100 % Überlappung als nicht ausreichend überlappend angesehen werden (z. B. eine PS-Verteilung in beiden Armen zwischen 0,4 und 0,6, sodass beide Bedingungen nicht gelten). Es bleibt offen, ob es sich hierbei um ein Versehen des pU handelt, zumal sich der Fehler an mehreren Stellen im SAP findet.
- Zur Beurteilung der Balanciertheit wird zunächst folgendes Kriterium für die standardisierten Mittelwertdifferenzen (SMDs) aller Confounder zwischen den Behandlungsgruppen nach Gewichtung angegeben:
  - *abs*(SMD) < 0,1: adäquate Balanciertheit
  - *abs*(SMD) zwischen 0,1 und 0,2: keine schwerwiegende Unbalanciertheit
  - *abs*(SMD) > 0,2: schwerwiegende Unbalanciertheit

  Dieses Kriterium wäre sachgerecht. Allerdings wird das Kriterium dadurch abgeschwächt, dass Ergebnisse mit *abs*(SMD) > 0,1 (ohne weitere Einschränkungen) in Abhängigkeit vom Stichprobenumfang und möglichen Konvergenzproblemen bei der PS-Analyse doch als ausreichend balanciert angesehen werden. Die oben beschriebenen Kriterien werden damit nicht angewendet. Was das konkret bedeutet bleibt unklar. Zudem sieht der Entscheidungsalgorithmus zur Modellwahl (Abb. 3 im SAP) vor, dass die Gewichtungsart gewählt wird, für die die Summe der Werte für *abs*(SMD) aller Confounder am geringsten ausfällt. Es wird nicht angegeben, dass keine PS-Analyse durchgeführt wird, wenn für einen der Confounder eine schwerwiegende Unbalanciertheit festgestellt wird.
- Es fehlt die Angabe, dass die Zielpopulation, für die der in der PS-Analyse (nach Trimming und Gewichtung) letztlich geschätzte Behandlungseffekt gilt, genau zu beschreiben ist und dass zu begründen ist, dass diese Zielpopulation für die Ausgangsfragestellung angemessen ist.

Zusammenfassend sind somit die Details für die Propensity-Score-Analyse (Überprüfung der Güte, konkrete Kriterien für eine ausreichende Überlappung und Balanciertheit) unvollständig, nur zum Teil sachgerecht, und widersprüchlich.

Die Mängel sollten in einer weiteren Revision des Protokolls und des SAP behoben werden.

2.2.12 Auswertung der Datenerhebung: Confounderadjustierung 3

Position des G-BA

Eine Beschreibung eines Entscheidungsalgorithmus zur Anpassung der Propensity-Score-Analyse bei fehlender Überlappung und Balanciertheit nach Anwendung des ersten Verfahrens sollte ergänzt werden. Gleichfalls sollte die korrekte Konsequenz benannt werden, wenn kein Propensity-Score-Verfahren gefunden werden kann, mit dem eine ausreichende Überlappung und eine ausreichende Balanciertheit der zu vergleichenden Gruppen erreicht werden kann.

In einem solchen Fall ist der Versuch einer Effektschätzung weder mithilfe von Propensity Scores noch mithilfe von Regressionsmodellen sinnvoll.

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

Ergänzung und Visualisierung der Entscheidungsstruktur sowie entsprechenden Kriterien zur Modellauswahl (u.a. Überlappung und Balanciertheit).

Bewertung der vom pU vorgenommenen Änderungen durch das IQWiG

In der überarbeiteten Version des SAP wird ein Entscheidungsalgorithmus zur Anpassung der Propensity-Score-Analyse bei fehlender Überlappung und Balanciertheit nach Anwendung des ersten Verfahrens ergänzt (Abb. 3 im SAP). Dieser Entscheidungsalgorithmus erscheint allerdings nicht sachgerecht. Im Einzelnen liegen folgende Mängel vor:

- Die Kriterien zur Modellauswahl (Überlappung und Balanciertheit) erscheinen wie oben dargestellt nicht sachgerecht.
- Es fehlt eine konkrete Angabe, wie das im Entscheidungsalgorithmus angegebene Trimming durchgeführt werden soll.
- Der Entscheidungsalgorithmus enthält auch einen Ansatz über Matching, bei dem es ausreichend ist, wenn nur mindestens 50 % der Confounder berücksichtigt werden. Dieser Ansatz erscheint per se nicht sachgerecht.

Der ergänzte Entscheidungsalgorithmus erscheint damit insgesamt nicht sachgerecht.

Die Mängel sollten in einer weiteren Revision des Protokolls und des SAP behoben werden.

2.2.13 Auswertung der Datenerhebung: Analyse der Endpunkte 1

Position des G-BA

Die Modelle für die Effektschätzung sollten im Detail dargestellt werden. In die Analyse sollte das Zentrum weder als zufälliger noch als fester Effekt eingehen. Ein möglicher Zentrumseffekt sollte in einer Sensitivitätsanalyse untersucht werden.

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

Detaillierte Beschreibung der Modelle zur Effektschätzung pro Endpunktart und Analyse-Ansatz unter Streichung eines Zentrumeffekts. Hinzufügen einer Sensitivitätsanalyse für möglichen Zentrumseffekt.

Bewertung der vom pU vorgenommenen Änderungen durch das IQWiG

In der überarbeiteten Version des SAP werden die geplanten Modelle ausreichend detailliert dargestellt unter Streichung des Zentrumseffekts. Es werden Sensitivitätsanalysen für mögliche Zentrumseffekte geplant. Dieses Vorgehen erscheint sachgerecht.

2.2.14 Auswertung der Datenerhebung: Analyse der Endpunkte 2

Position des G-BA

Im SAP sollte im Detail beschrieben werden, in welcher Form die Confounder als feste Effekte in das jeweilige Endpunkt-Modell eingehen sollen.

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

Konkretisierung des Eingangs von Counfoundern in die Adjustierungsmodelle.

Bewertung der vom pU vorgenommenen Änderungen durch das IQWiG

In der überarbeiteten Version des SAP wird beschrieben in welcher Form die Confounder in die PS-Analyse eingehen. Dieses Vorgehen erscheint sachgerecht. Es bleibt jedoch die Option ungenutzt, im Fall unzureichender Überlappung und Balanciertheit durch die Betrachtung von Wechselwirkungen möglicherweise eine ausreichende Überlappung und Balanciertheit zu erreichen.

2.2.15 Auswertung der Datenerhebung: Analyse der Endpunkte 3

Position des G-BA

Angaben, wie überprüft werden soll, ob zeitlich parallele und nicht parallele Daten bzw. Daten aus unterschiedlichen Datenquellen für gepoolte Analysen herangezogen werden können, fehlen und sollten ergänzt werden.

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

Präspezifikation der Überprüfung der Eignung von nicht- parallelen Daten zu Nusinersen.

Bewertung der vom pU vorgenommenen Änderungen durch das IQWiG

Es wird in der überarbeiteten Version des SAP ergänzt, in welcher Form die Eignung von nicht-parallelen Daten zu Nusinersen überprüft wird. Im Entscheidungsalgorithmus (Abb. 3 im SAP) wird angegeben, dass bei unzureichender Überlappung für die kombinierte Stichprobe überprüft wird, ob die Verwendung nur der parallelen Daten zu Nusinersen zu einer ausreichenden Überlappung führt. Neben dem Problem des unlogischen und nicht sinnvollen Kriteriums zur Überprüfung der Überlappung (siehe Abschnitt 2.2.11) erscheint der Wechsel

von der kombinierten Stichprobe zu der Stichprobe mit ausschließlich parallelen Daten im Entscheidungsalgorithmus zu früh. Es sollten zunächst die anderen Verfahren, die zu einer verbesserten Überlappung und Balanciertheit führen können (Trimming, Gewichtungsmethode), angewendet werden. Der Wechsel von der kombinierten Stichprobe zu der Stichprobe mit ausschließlich parallelen Daten sollte erst vollzogen werden, wenn alle anderen Optionen gescheitert sind. Zudem sollten die Methoden, die bei einem gänzlichen Scheitern der PS-Analyse geplant sind (Matching, naiver Vergleich), auch zunächst mit der kombinierten Stichprobe durchgeführt werden. Es erscheint nicht sachgerecht, sofort nach Feststellung einer nicht ausreichenden Überlappung im 1. Schritt der PS-Analyse in allen weiteren Schritten nur noch die Stichprobe mit ausschließlich parallelen Daten zu verwenden.

Zudem sollten die beiden Stichproben der zeitlich parallel und nicht parallel erhobenen Daten deskriptiv verglichen werden und bei zentralen Auswertungen der kombinierten bzw. der Teilstichprobe die jeweils andere Stichprobe für Sensitivitätsanalysen verwendet werden.

Die Mängel sollten in einer weiteren Revision des Protokolls und des SAP behoben werden.

2.2.16 Auswertung der Datenerhebung: Berücksichtigung verschobener Hypothesengrenzen

Position des G-BA

Die Berücksichtigung einer verschobenen Hypothesengrenze bei der Auswertung der Daten fehlt und sollte ergänzt werden. Diese Ergänzungen könnten beispielsweise bei der (bisher fehlenden) Formulierung einer Hypothese erfolgen.

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

Die Bewertung der Ergebnisse dieser nicht- interventionellen Beobachtungsstudie obliegt dem G-BA im Rahmen einer erneuten Nutzenbewertung im Jahr 2027. Es erfolgt eine umfassende Berichterstattung über sämtliche in Studienprotokoll und SAP vorgesehenen Analysen zu dem im G-BA-Beschluss vom 4. Februar 2021 vorgesehenen Zeitpunkten.

Die Anwendung der vom IQWiG vorgeschlagenen Hypothesengrenzen wird von Novartis Gene Therapies dabei insb. mit Blick auf die Konsistenz zur methodischen Herleitung aus den Kriterien des „dramatischen Effekt“ sowie der praktischen Umsetzbarkeit in seltenen Erkrankungen – dem maßgeblichen Regelungsbereich des § 35a Abs. 3b SGB V – als nicht sachgerecht eingeschätzt. Insbesondere in der spezifischen Verfahrenskonstellation zu Onasemnogen-Abeparvovec, in welcher durch den G-BA bereits vor Beginn der Anwendungsbegleitenden Datenerhebung kein demonstrierter Zusatznutzen beschieden wurde, erscheint es sinnvoll, im Rahmen einer erneuten Nutzenbewertung auf Grundlage der besten verfügbaren Evidenz ausgeprägte Vorteile, die mit einer 99-prozentigen statistischen Sicherheit festgestellt werden können (vgl. Kriterien zum „dramatischen Effekt“), zu berücksichtigen.

Gemäß den Bestimmungen des G-BA-Beschlusses vom 4. Februar 2021, welcher die Anwendung einer „verschobenen Nullhypothese“ explizit auf die Fallzahlplanung der Studie

bezieht, erfolgte ergänzend eine Fallzahlplanung unter Anwendung der vom IQWiG vorgeschlagenen Hypothesengrenzen.

Für eine detaillierte Darstellung des Sachverhalts wird auf Abschnitt 8.2.2.2 des Studienprotokolls verwiesen.

Bewertung der vom pU vorgenommenen Änderungen durch das IQWiG

Die Berücksichtigung einer verschobenen Hypothesengrenze bei der Auswertung der Daten wird in den überarbeiteten Versionen des Protokolls und des SAP nicht ergänzt. Das erscheint nicht sachgerecht, und Studienprotokoll und SAP sollten entsprechend ergänzend werden. Unabhängig davon wird auf Basis der üblichen Präsentation der Ergebnisse in Form von Effektschätzungen mit Konfidenzintervall in der späteren Nutzenbewertung bei der Interpretation der Ergebnisse dieser Ansatz zur Anwendung kommen.

2.2.17 Auswertung der Datenerhebung: Subgruppenanalysen

Position des G-BA

Aufgrund der zu erwartenden geringen Fallzahlen wird vorgeschlagen, alle relevanten Subgruppenanalysen ohne die Anforderung einer statistisch signifikanten Interaktion zu rechnen und darzustellen.

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

Entfernung des Kriteriums einer statistisch signifikanten Interaktion für die Berichterstattung von Subgruppenergebnissen.

Bewertung der vom pU vorgenommenen Änderungen durch das IQWiG

In den überarbeiteten Versionen des Protokolls und des SAP wird die Anforderung einer statistisch signifikanten Interaktion für die relevanten Subgruppenanalysen entfernt. Dieses Vorgehen erscheint sachgerecht.

2.2.18 Auswertung der Datenerhebung: Umgang mit fehlenden Confoundern

Position des G-BA

Für die Berücksichtigung von Daten sollten die entsprechenden Register/ Datensätze grundsätzlich Informationen zu allen relevanten Baseline-Confoundern enthalten. Ein Ausschluss von einzelnen Personen mit verbleibenden fehlenden Daten aus allen Analysen, die diese Confounder berücksichtigen, erscheint in Anbetracht geringer Fallzahlen jedoch nicht sachgerecht.

Es wird vorgeschlagen, verbleibende fehlende Werte bei einzelnen Personen durch den Ansatz der Multiplen Imputation zu ersetzen. Darüber hinaus sollten Angaben, in welchem Umfang bzw. aus welchen Gründen fehlende Daten zu erwarten sind, und Angaben zum Umgang mit unplausiblen Daten bzw. Ausreißern ergänzt werden.

Des Weiteren sollte eine Beschreibung der Anteile fehlender Daten vorgesehen werden.

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

Präspezifikation einer Imputation von Fehlwerten mittels multipler Imputation für Confounder bzw. Baseline- Charakteristika.

Hinsichtlich des Umgangs mit Fehlwerten bei historischen Daten wird auf die Niederschrift zum Beratungstermin am 11. August 2021 verwiesen (Frage 7). Rückfragen zur Kongruenz der Positionen hinsichtlich einer Fehlwertsubstitution einerseits und Anforderungen an die Eignung historischer Daten andererseits wurden durch Novartis Gene Therapies mündlich im und schriftlich nach dem Beratungstermin vorgetragen. Mangels näherer Ausführungen des G-BA erfolgte eine bestmögliche Umsetzung der G-BA-Positionen ohne weitere Diskussion von Konsistenzaspekten.

Bewertung der vom pU vorgenommenen Änderungen durch das IQWiG

In der überarbeiteten Version des SAP wird ergänzt, dass beim Auftreten von fehlenden Daten eine multiple Imputation vorgenommen wird. Es wird zudem ergänzt, wie mit unplausiblen Daten umgegangen werden soll. Dieses Vorgehen erscheint sachgerecht unter der Voraussetzung, dass die Angaben zu fehlenden Werten ausreichend detailliert sind und insbesondere Umfang der fehlenden Daten, Gründe für die fehlenden Daten und Anteile fehlender Daten beschrieben werden.

2.2.19 Auswertung der Datenerhebung: Umgang mit Behandlungswechseln 1

Position des G-BA

Die Aufteilung der Patienten in die vorgeschlagenen „Behandlungsgruppen“ sollte geändert werden, da eine adäquate Aufteilung der Patienten durch Informationen erfolgen muss, die zu Studienbeginn vorliegen.

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

Allokation von Patienten in zwei Behandlungsarme anhand der Ersttherapie im Rahmen des G-BA-Ansatzes.

Bewertung der vom pU vorgenommenen Änderungen durch das IQWiG

Die geforderte Zuordnung aller therapie-naiven Patienten zur Erstbehandlung wird in den überarbeiteten Versionen des Protokolls und des SAP vorgenommen. Dieses Vorgehen erscheint sachgerecht.

2.2.20 Auswertung der Datenerhebung: Umgang mit Behandlungswechseln 2

Position des G-BA

Ein Cox-Modell mit zeitabhängigen Kovariablen wird im vorliegenden Fall nicht als adäquate Methode für den Umgang mit Behandlungswechseln erachtet.

Es wird eine Zuordnung therapienaiver Patientinnen und Patienten zur jeweiligen Erstbehandlung (New-User-Design) empfohlen. Als Sensitivitätsanalyse sollten ergänzende Auswertungen mit Zensierungen bei Behandlungswechseln erfolgen, wobei der Zeitpunkt der Zensierung variiert werden sollte, um „Carry-over"-Effekte für die vorherige Behandlung zu berücksichtigen.

Sofern die Ausgangsfragestellung aufgrund eines zu hohen Anteils an Behandlungswechseln nicht mehr beantwortet werden kann, kann ggf. alternativ ein Prevalent-New-User-Design für die Auswertung genutzt werden. Ob diese Option herangezogen werden sollte, kann jeweils nach Übermittlung von Daten zum Verlauf der AbD (siehe nachfolgenden Punkt) an den G-BA entschieden und in einem Amendment zum Protokoll und SAP implementiert werden

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

Abbildung einer Zuordnung von Patienten zur Erstbehandlung ohne Berücksichtigung von Therapiewechseln im Rahmen der Hauptanalyse und unter alleiniger Betrachtung von Therapiewechseln mittels Zensierung im Rahmen von Sensitivitätsanalysen im Rahmen des G-BA-Ansatzes.

Bewertung der vom pU vorgenommenen Änderungen durch das IQWiG

Die geforderte Zuordnung aller therapie-naiven Patienten zur Erstbehandlung wird in den überarbeiteten Versionen des Protokolls und des SAP vorgenommen. Als Sensitivitätsanalyse werden ergänzende Auswertungen mit Zensierungen bei Behandlungswechseln geplant, sowie eine Variation des Zeitpunkts der Zensierung, um „Carry-over"-Effekte zu berücksichtigen. Dieses Vorgehen erscheint sachgerecht.

2.2.21 Auswertung der Datenerhebung: Umgang mit Behandlungswechseln 3

Position des G-BA

Angaben zur Anzahl von Patienten, die die Behandlung wechseln einschließlich der jeweils vorliegenden Zeiten unter den verschiedenen Behandlungen, sollten Bestandteil der regelmäßig dem G-BA vorzulegenden Angaben zum Verlauf der AbD sein.

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

Berichterstattung über Therapiewechsel und -zeitpunkte mit jeder Einreichung beim G-BA.

Bewertung der vom pU vorgenommenen Änderungen durch das IQWiG

Der pU beabsichtigt gemäß Studienprotokoll, zu den unterschiedlichen Berichtszeitpunkten (siehe auch Abschnitt 2.2.22) jeweils auch Informationen zum Therapiewechsel bereitzustellen („extend of treatment switching on a study level"). Das Vorgehen erscheint sachgerecht unter der Voraussetzung, dass diese Angaben ausreichend detailliert sind und beispielsweise auch Angaben zur Beobachtungsdauer (Mittelwert, Median, Minimum, Maximum, Quartile) enthalten.

2.2.22 Auswertung der Datenerhebung: Geplante Analysen

Position des G-BA

Die geplanten Zeitpunkte für die Interimsanalysen und die finale Analyse weichen von den im Beschluss genannten Zeitpunkten ab.

Die vorzulegenden Analysen sollten in Relation zum Beschlussdatum, nicht in Relation zum Studienstart geplant und entsprechend der Angaben im Beschluss durchgeführt werden. Zu jeder Zwischenanalyse sollte entsprechend auch eine Prüfung auf Abbruch wegen Vergeblichkeit vorgenommen werden.

Anmerkung des pU (aus seiner Zusammenfassung der vorgenommenen Änderungen)

Anpassung der Analyse- und Berichtzeitpunkte an die Vorgaben des G-BA-Beschlusses vom 4. Februar 2021 mit Verweis auf die in beiden Beratungsterminen dargelegten Auswirkungen auf die Datenverfügbarkeit und daraus resultierende Belastbarkeit von Zwischenergebnissen.

Prüfung eines Abbruchs wegen Vergeblichkeit mit zweiter und dritter Zwischenanalyse. Deskriptive Diskussion von Patientenzahlen und Ergebnissen der aktualisierten Fallzahlplanungen im Rahmen der ersten Zwischenanalyse, jedoch keine formale Abbruchentscheidung aufgrund erheblicher Unsicherheit von Zwischenergebnissen auf Grundlage einer erwartbar eingeschränkten Datengrundlage.

Für eine detaillierte Darstellung des Sachverhalts wird auf Abschnitt 8.2.2.4 und 8.4 des Studienprotokolls verwiesen.

Bewertung der vom pU vorgenommenen Änderungen durch das IQWiG

Zur Beschreibung der geplanten Analysen hat der pU das Studienprotokoll und den SAP weitreichend geändert und die Abschnitte 8.4 und 8.5 im Studienprotokoll sowie das Kapitel 6 im SAP grundlegend überarbeitet. Die Änderungen umfassen neben den vom G-BA adressierten Punkten weitere Aspekte. Die im Zusammenhang mit der AbD relevanten und über die in den vorhergehenden Abschnitten des vorliegenden Dokuments hinausgehend beschriebenen Aspekte werden nachfolgend bewertet.

Analyse- und Berichtszeitpunkte

Der pU hat in der neuen Version des Studienprotokolls wie gefordert die einzelnen Berichts- und Analysezeitpunkte in Relation zum Datum des G-BA-Beschlusses (04.02.2021) und nicht mehr in Relation zum Studienstart geplant. Dies erscheint grundsätzlich sachgerecht.

Da im vorliegenden Fall das Studienprotokoll und der SAP aufgrund weitreichender Mängel der ersten Versionen erneut geprüft werden müssen, liegen zwischen möglichem Beginn der AbD auf Basis eines finalen Studienprotokolls und SAPs sowie erstem Berichtzeitpunkt nur wenige Monate (Freigabe der Dokumente nicht vor Anfang 2022, erster Berichtszeitpunkt August 2022 geplant). Der pU beschreibt, dass die erste Zwischenanalyse mit Berichtszeitpunkt August 2022 (18 Monate nach Beschlussfassung) daher keine aussagekräftigen Ergebnisse

enthalten werde. Er schlägt daher vor, dass zu diesem Zeitpunkt entgegen der Beschlussfassung des G-BA auf eine Prüfung auf Vergeblichkeit verzichtet wird.

Die Argumentation des pU erscheint inhaltlich sachgerecht, betrifft allerdings auch die Zwischenanalyse selbst. Es wird daher im vorliegenden Fall vorgeschlagen, auf die erste Zwischenanalyse inklusive Prüfung auf Vergeblichkeit zum Zeitpunkt 18 Monate nach Beschlussfassung zu verzichten und zu diesem Zeitpunkt lediglich einen Statusreport vorzulegen.

Zur weiteren Vereinfachung könnte darüber hinaus erwogen werden, die verbleibende zweite (ehemals dritte) Zwischenanalyse um 6 Monate vorzuziehen (von Februar 2026 auf August 2025) und dadurch mit dem dritten Statusreport zusammenzulegen. Die Anzahl der Berichtszeitpunkte könnte dadurch von 5 auf 4 ohne relevanten Informationsverlust verringert werden.

Insgesamt werden daher aufgrund des derzeitigen Verlaufs der Protokollerstellung für die AbD zu Onasemnogen-Abeparvovec folgende Berichtszeitpunkte vorgeschlagen:

- August 2022 (18 Monate nach Beschlussdatum): Statusreport
- Februar 2024 (36 Monate nach Beschlussdatum): erste Zwischenanalyse und Prüfung auf Vergeblichkeit, Statusreport
- August 2025 (54 Monate nach Beschlussdatum): zweite Zwischenanalyse und Prüfung auf Vergeblichkeit, Statusreport
- 1. Juli 2027: Finale Analyse

Zeitpunkt des Datenschnitts für Zwischenanalysen

Der pU gibt im Studienprotokoll an, dass der Datenschnitt für die Analysen etwa 6 Monate vor dem jeweiligen Berichtszeitpunkt erfolgen sollte, damit die Zeit für die Berichtserstellung jeweils ausreichend ist.

Dies ist für die finale Analyse nachvollziehbar, da hierfür ein vollständiges Dossier zur Nutzenbewertung zu erstellen ist. Für die weniger aufwändigen Berichte zu Zwischenanalysen erscheint dies jedoch nicht erforderlich und widerspricht auch dem eigenen Vorschlag des pU in den Beratungsgesprächen mit dem G-BA, in denen er 4 Monate als erforderlich Latenzzeit angegeben hatte. Die Datenschnitte sollten für die Zwischenanalysen daher jeweils 4 Monate, nicht 6 Monate, vor dem jeweiligen Berichtszeitpunkt erfolgen.

Berichtsformat und -inhalt

Der pU beschreibt für die Berichte zu Zwischenanalysen und zur Prüfung auf Vergeblichkeit, dass er diese auf Basis des Moduls 4 der Dossiervorlagen für Nutzenbewertungen nach § 35a SGB V erstellen wird. Dies erscheint sachgerecht. Allerdings sollte in Studienprotokoll und SAP auf eine konkrete Benennung zu befüllender Abschnitte der Dossiervorlagen verzichtet

werden. Denn es ist offen, ob die Struktur und der Inhalt der Dossiervorlagen zum jeweiligen Berichtszeitpunkt dem heutigen Stand entsprechen werden.

Für die finale Analyse sollte klargestellt werden, dass diese zwar mit dem vollständigen Dossier zur Nutzenbewertung übermittelt wird, das Dossier aber darüber hinaus den Anforderungen an ein Dossier zur Nutzenbewertung nach § 35a SGB V genügen muss (unter anderem vollständige Darstellung der relevanten Evidenz zu Onasemnogen-Abeparvovec im Vergleich zur jeweiligen zweckmäßigen Vergleichstherapie).

Prüfung auf Vergeblichkeit

Im Zusammenhang mit der Prüfung auf Vergeblichkeit gibt der pU an, dass eine nicht ausreichende Fallzahl ggf. bereits für einen einzelnen „key endpoint“ ausreichend ist, um die Beobachtung für die jeweilige Population zu beenden. In einem solchen Fall sollen die Ergebnisse nicht ausgewertet werden. Beides erscheint nicht sachgerecht.

Die Prüfung auf Vergeblichkeit sollte die Gesamtschau aller Daten umfassen. Sie ist daher auch nur sinnvoll möglich, wenn dieser Prüfung eine vollständige Auswertung der Ergebnisse zum jeweiligen Zeitpunkt zugrunde liegt. Die entsprechenden Berichte zu den Zwischenanalysen müssen daher alle bis dahin erhobenen Ergebnisse und die zugehörigen Analysen vollständig enthalten.

Darüber hinaus erscheint es sinnvoll, die Entscheidung für oder gegen eine Fortsetzung der Beobachtung der Population in Abstimmung mit dem G-BA auf Basis des jeweiligen Zwischenberichts zu treffen.

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