Routine data collection and evaluations of onasemnogene abeparvovec in Germany

Study Protocol

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Signature Page

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

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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

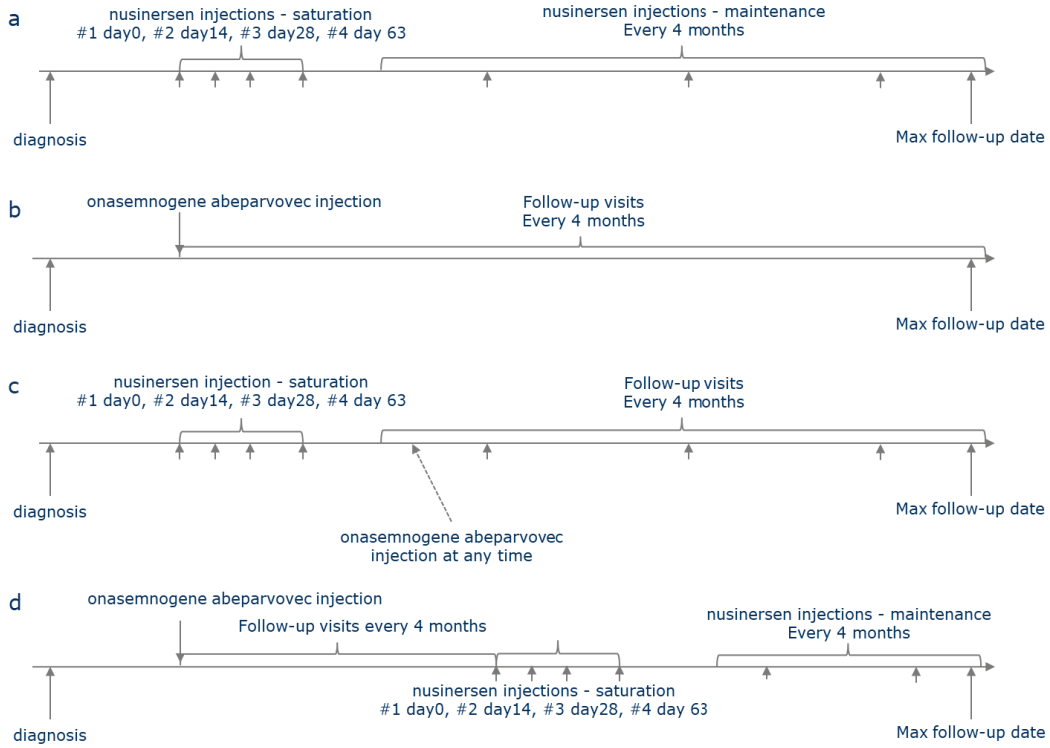
Study design aspect	NGT approach	G-BA approach
Inclusion and exclusion criteria	Key inclusion criteria: ▪ Presymptomatic patients with 5q-associated SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene OR ▪ Symptomatic patients with 5q-associated SMA with a biallelic mutation 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.

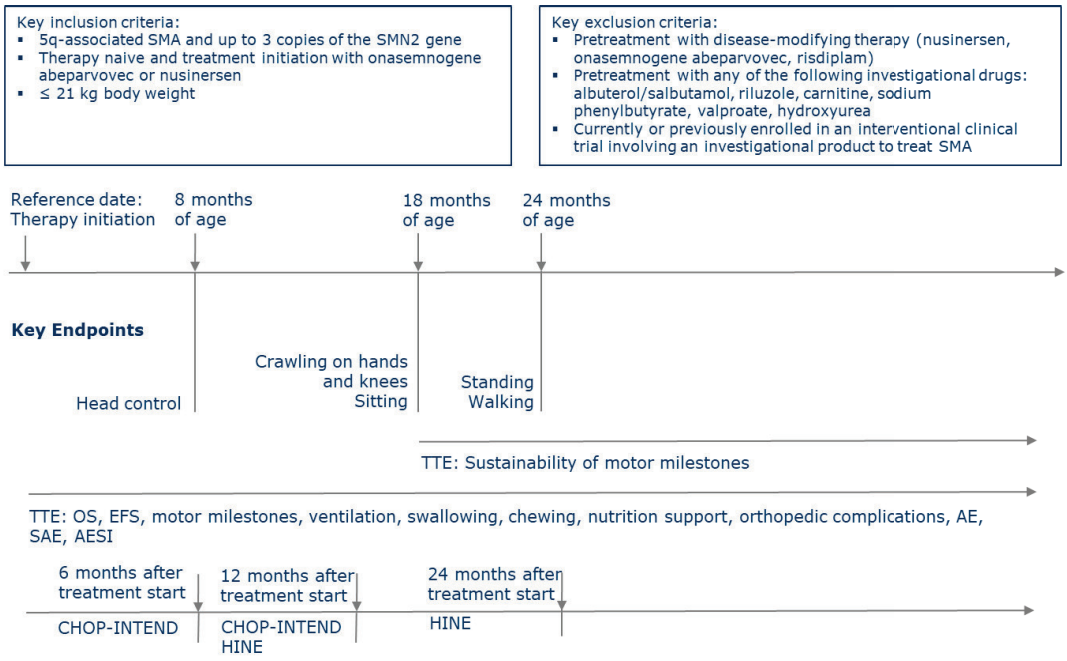
Furthermore, switches from nusinersen to risdiplam and risdiplam to onasemnogene abeparvovec as well as combination therapy of onasemnogene abeparvovec and risdiplam are expected. These will not be investigated, as only nusinersen was defined as the comparator for this study (28). Subjects switching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

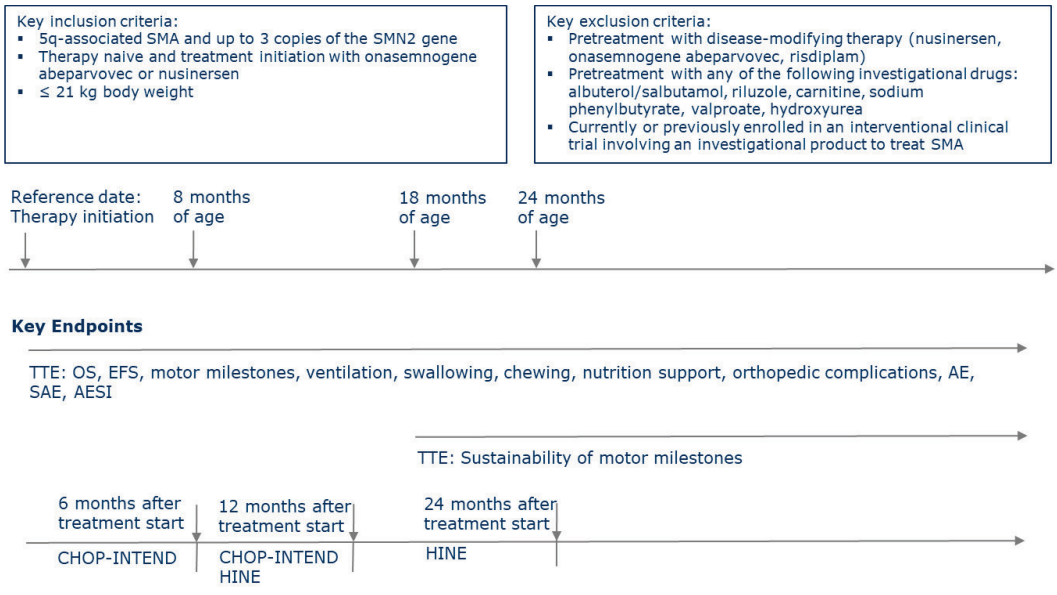
As per change requests No. 10, 19, 20, and 21 (Table 6), main analysis will allocate patients into two treatment arms depending on their initial treatment: 1) nusinersen or 2) onasemnogene abeparvovec. Patients initially treated with risdiplam and switched to nusinersen or onasemnogene abeparvovec violate 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).

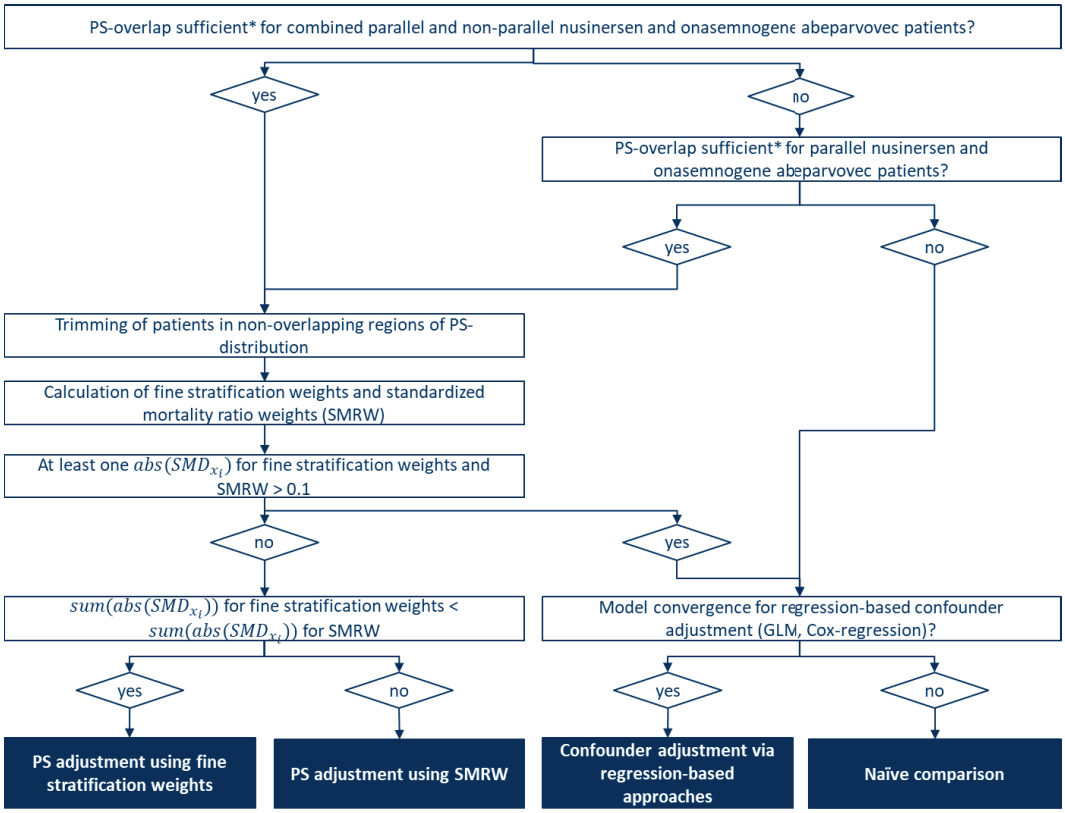
For sensitivity analysis, ulnar compound muscle action potential (CMAP) amplitude will be included in baseline confounders (see section 8.5 of SAP).

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.

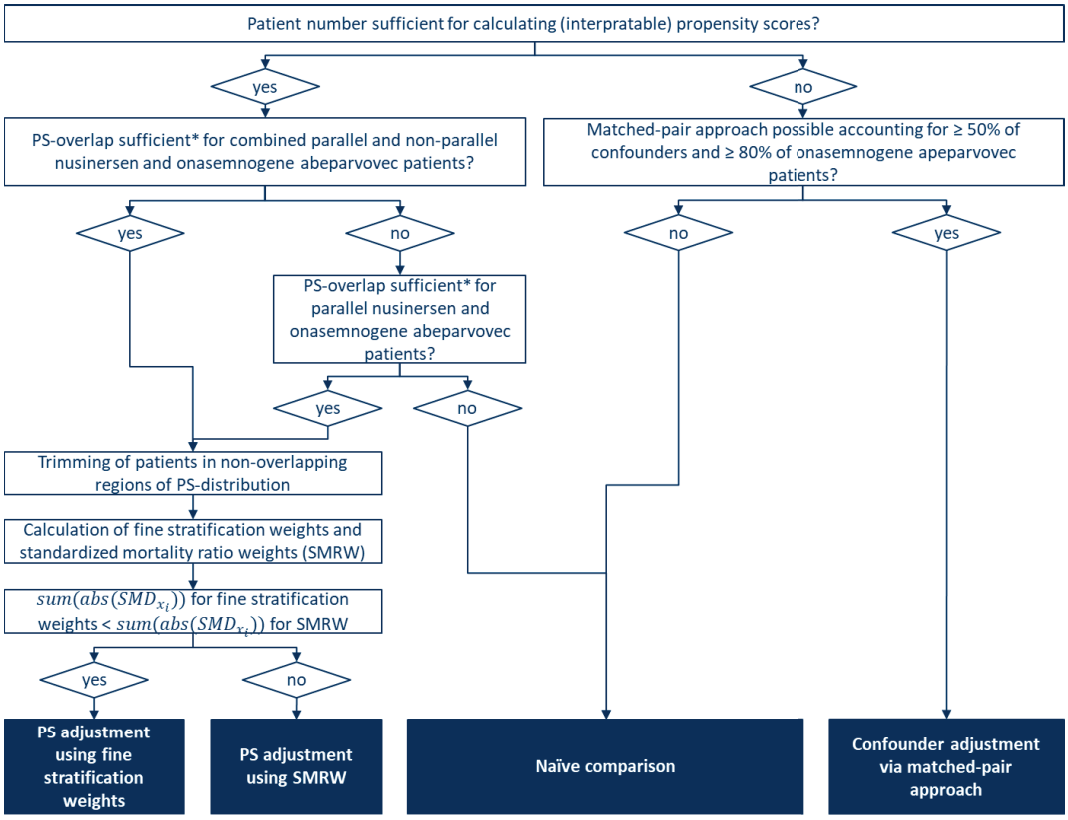
For both NGT and G-BA approaches, adjustment of confounders will take place using appropriate methods following a pre-specified decision tree. Figure 4 illustrates the decision tree for NGT approach, Figure 5 illustrates the decision tree for G-BA approach. See SAP section 8.1 for details.

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

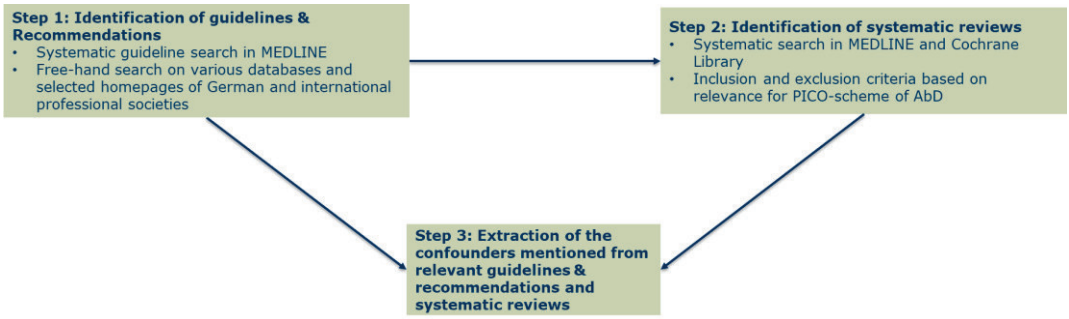
1. Methodical approaches for identifying confounders in SMA

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

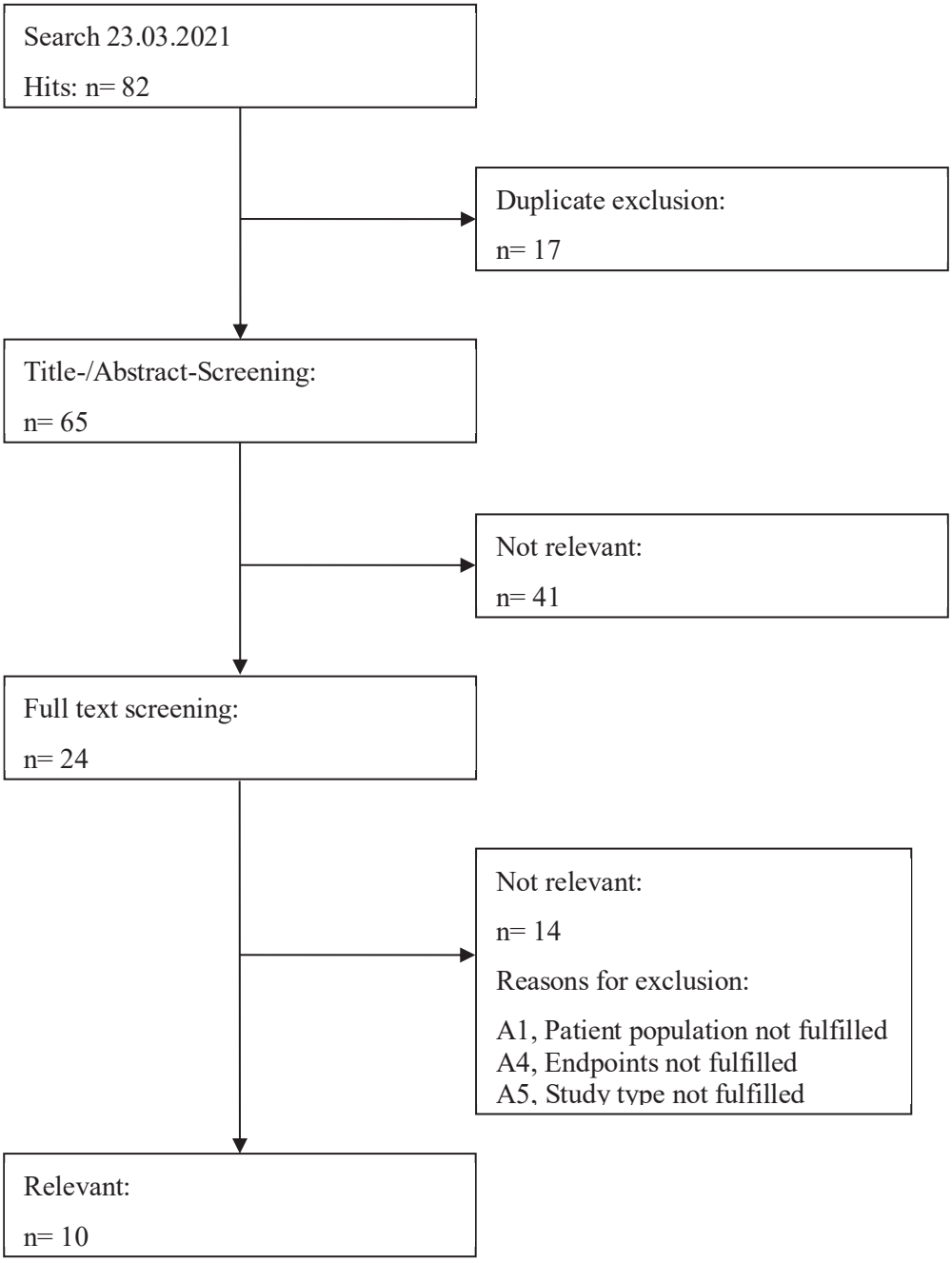
2.4 Results – Guidelines and recommendations

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

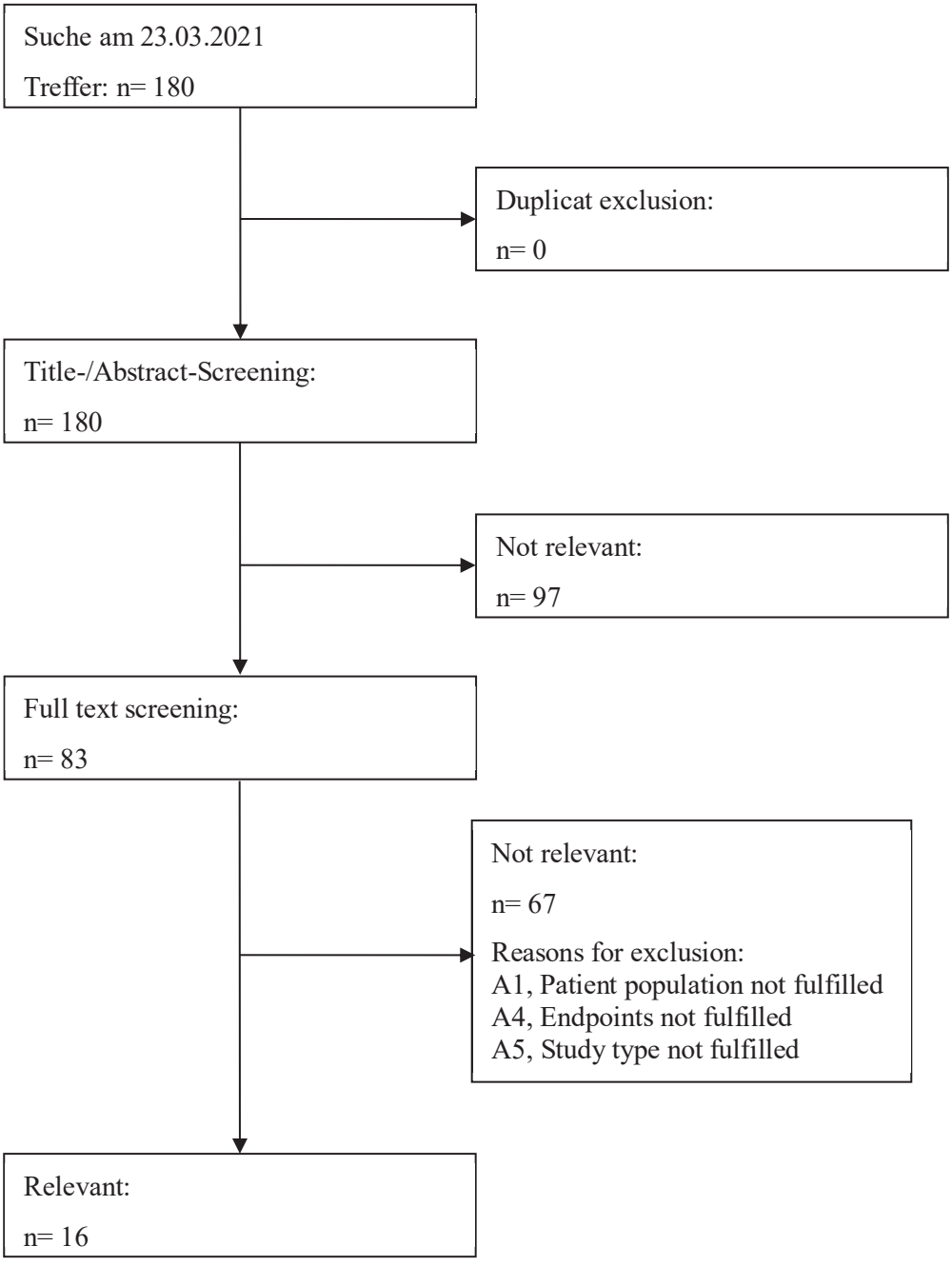
The PRISMA diagram shown in Figure A8 illustrates the screening and selection process for relevant systematic reviews and meta-analyses, which form the second basis for the identification of confounders.

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
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
61	Uchitel et al. Viral-Mediated Gene Replacement Therapy in the Developing Central Nervous System: Current Status and Future Directions.Pediatr Neurol 2020:110():5-19.	A5, Study type not fulfilled
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63	Van Geel et al. Measuring walking-related performance fatigability in clinical practice: a systematic review. Eur J Phys Rehabil Med 2020:56(1):88-103.	A1, Patient population not fulfilled
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65	Wei et al. Notable Carrier Risks for Individuals Having Two Copies of SMN1 in Spinal Muscular Atrophy Families with 2-copy Alleles: Estimation Based on Chinese Meta-analysis Data. J Genet Couns 2017:26(1):72-78.	A1, Patient population not fulfilled
66	Wiffen et al. Systematic Reviews Published in the Cochrane Library January-March 2017. J Pain Palliat Care Pharmacother 2017:31(2):167-169.	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