NIS PROTOCOL (SECONDARY DATA USE)

TITLE:	**EVALUATION OF A REAL WORLD DATA COLLECTION FOR THE REASSESSMENT OF THE ADDITIONAL BENEFIT OF EVRYSDI® (RISDIPLAM)**
PROTOCOL NUMBER:	ML44661
VERSION NUMBER:	1.0
STUDIED MEDICINAL PRODUCT:	EVRYSDI® (RISDIPLAM)
PRODUCT REFERENCE NUMBER{S}	European Union (EU) marketing authorization number: EU/1/21/1531/001
AUTHOR:	[redacted]
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
31-Jul-2023 10:26:42	Company Signatory	[redacted]

MARKETING AUTHORIZATION HOLDER{S} (MAH) or STUDY INITIATOR:	Roche Registration GmbH Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany
RESEARCH QUESTION AND OBJECTIVES:	The objective of this study is to evaluate the comparative effectiveness and safety of risdiplam versus a therapy according to physician´s choice taking into account nusinersen and onasemnogene abeparvovec. The research questions are a result of the participation process with G-BA, the G-BA appraisal, the G-BA advice and discussions with medical experts regarding the evaluation of a real world data collection for the reassessment of the additional benefit of risdiplam. According to the requirements of the G-BA the study follows a non-randomized design comparing risdiplam with nusinersen and onasemnogene abeparvovec. Safety data is analyzed to allow a comparison of risdiplam versus a therapy according to physician´s choice taking into account nusinersen and onasemnogene abeparvovec.
COUNTRIES OF STUDY POPULATION:	Germany, Austria

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Es konnten keine Einträge für ein Abbildungsverzeichnis gefunden werden.

PROTOCOL ACCEPTANCE FORM

-not applicable-

TITLE:	**EVALUATION OF A REAL WORLD DATA COLLECTION FOR THE REASSESSMENT OF THE ADDITIONAL BENEFIT OF EVRYSDI® (RISDIPLAM)**
PROTOCOL NUMBER:	ML44661
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STUDIED MEDICINAL PRODUCT{S}:	EVRYSDI® (RISDIPLAM)
MARKETING AUTHORIZATION HOLDER{S} (MAH), or STUDY INITIATOR:	Roche Registration GmbH Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany

I agree to conduct the study in accordance with the current protocol.

_____
Treating Physician's Name (print)

_____ _____
Treating Physician's Signature Date

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Events
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	Confidence Interval
CRO	Contract Research Organization
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GPP	Good Pharmacoepidemiological Practice
HFMSE	Hammersmith Functional Motor Scale Expanded
ICH	International Conference on Harmonization
ICSR	Individual Case Safety Report
IRB	Institutional Review Board
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities,
NBS	Newborn Screening
RULM	Revised Upper Limb Module
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SMA	Spinal Muscular Atrophy
SMN 1/2	Survival Motor Neuron 1/2
SmPC	Summary of Product Characteristics
WHO	World Health Organization

2. RESEARCH TEAM

External Scientific Leader

[redacted]

Scientific Responsible

[redacted]

NIS Data Science Responsible

[redacted]

Protocol Development Responsible

[redacted]

Complementary information is given in Appendix 1

3. SYNOPSIS

TITLE:	**EVALUATION OF A REAL WORLD DATA COLLECTION FOR THE REASSESSMENT OF THE ADDITIONAL BENEFIT OF EVRYSDI® (RISDIPLAM)**
PROTOCOL NUMBER:	ML44661
VERSION NUMBER:	1.0
DATE OF SYNOPSIS:	07.07.2023
STUDIED MEDICINAL PRODUCT	EVRYSDI® (RISDIPLAM)
MAIN AUTHOR:	[redacted]
INDICATION:	Spinal Muscular Atrophy (SMA)
MARKETING AUTHORIZATION HOLDER:	Roche Registration GmbH Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany
Rationale and background	The objective of this study is to evaluate the comparative effectiveness and safety of risdiplam versus a therapy according to physician´s choice taking into account nusinersen and onasemnogene abeparvovec. The described study design is based on the previous exchange with the Gemeinsamer Bundesausschuss (G-BA, Federal Joint Committee) and scientific experts (1–6). Based on the previous assumptions on the specifics of the disease, the regulatory requirements and the novelty of this project, futility will be checked in the interim analysis.
Research question and objectives	The primary objectives for this study are as follows (presented by population): **Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the survival motor neuron 2 (*SMN2*) gene:** • To evaluate the safety of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as number of unplanned hospitalizations over time

Symptomatic patients with a clinically diagnosed SMA type 1:

- To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as time to death or permanent ventilation

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene:

- To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of the Revised Upper Limb Module (RULM) total score at 12 months after treatment start

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:

- To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of RULM total score at 12 months after treatment start

The secondary objectives for this study are as follows:

- To assess the oral treatment with risdiplam compared to nusinersen or onasemnogene abeparvovec for
    - Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene
    - Symptomatic patients with a clinically diagnosed SMA type 1
    - Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene
    - Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene

  including the following variables:
- Mortality
    - Death
- Morbidity
    - Motorfunction (assessed with age-appropriate instruments)
    - Achievement of motor milestones (World Health Organization (WHO) motor development milestones)
    - Respiratory function (need for permanent ventilation)
    - Bulbar function (ability to swallow, need for non-oral nutritional support, ability to speak)

- Other complications of disease (e.g. pain, orthopedic complications)

The safety objectives for this study are as follows:

- To assess the safety and tolerability of oral treatment with risdiplam compared to nusinersen or onasemnogene abeparvovec for
  - Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene
  - Symptomatic patients with a clinically diagnosed SMA type 1
  - Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene
  - Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene

including the following safety variables:

- Number of unplanned hospitalizations over time
- Time to first serious adverse event (SAE)
- Time to first adverse event (AE) leading to hospitalization
- Time to first selected SAE: retinopathy, effect on epithelial tissue, thrombocytopenia, nephropathy, hydrocephalus, hepatopathy, cardiac events, sensory neuropathy

Study design

Registry-based study, comparative, non-interventional, multicentric, multinational, open-label. As the treatment start date differs there will be simultaneously enrolled controls and not simultaneously enrolled controls.

Start Date of Study:
The planned start date of this study is Q4/2023 after confirmation of the submitted study protocol and statistical analysis plan by the G-BA.

Start of treatment with risdiplam is March 26, 2021 at the earliest. Start of treatment with nusinersen is May 30, 2017 at the earliest. Start of treatment with onasemnogene abeparvovec is May 18, 2020 at the earliest.

End of Study
The planned end of study date is January 01, 2026. Data that is documented in the study database after that time point will not be taken into account.

	Length of Study Interim analysis are planned 12 and 24 months after start of the study and will be handed in to G-BA latest 18 and 30 months after the start of the study. Final analysis will take place in January 2026.
Data sources	This registry-based study is based on the data of the SMArtCARE registry. The SMArtCARE project (www.smartcare.de) provides a platform to collect longitudinal clinical routine data on SMA patients in Germany, Austria and Switzerland. Data from Germany and Austria will be used for this analysis. Patients' data will be recorded on case report forms (CRFs). The degree of detail and completeness of data collected is dependent on local clinical practice. Data from patient notes should be entered on the CRF as soon as they become available. An electronic data capture (EDC) system will be used in this registry. Each patient will be identified in the registry by a unique patient identification code (patient number) that is assigned when the patient is registered and is retained as the primary identifier for the patient throughout entire participation in the registry and also in case the patient returns to registry participation after a temporary discontinuation.
Population	Patients must meet the following criteria for study entry: *For all populations*: • Signed informed consent form (if applicable by legal representative) to participate in the study • Genetically confirmed 5q-autosomal recessive SMA • Treatment according to the Summary of Product Characteristics (SmPC) with risdiplam OR nusinersen OR onasemnogene abeparvovec with treatment starting not earlier than March 26, 2021 for risdiplam, not earlier than May 30, 2017 for nusinersen and not earlier than May 18, 2020 for onasemnogene abeparvovec *Specific to the indicated populations:* **Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene:** • Pre-symptomatic diagnosis • *SMN2* copy number is ≤ 3 **Symptomatic patients with a clinically diagnosed SMA type 1:** • Not pre-symptomatic at time of diagnosis • Onset of symptoms < 6 months OR never achieved ability to sit unaided

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene:

- Not pre-symptomatic at time of diagnosis
- *SMN2* copy number is ≤ 3
- Onset of symptoms > 6 months and < 18 months OR never achieved ability to walk unaided

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:

- Not pre-symptomatic at time of diagnosis
- *SMN2* copy number is ≤ 3
- Onset of symptoms > 18 months
- Patient is able to walk unaided OR was able to walk unaided but has lost that ability

Patients who meet any of the following criteria will be excluded from study entry:

- Prior treatment with disease-modifying therapy before the patient was included in the registry (risdiplam, nusinersen OR onasemnogene abeparvovec)
- Current treatment with therapies which effectiveness is being tested for the treatment of SMA: e.g. salbutamol, riluzole, phenylbutyrate, valproate, hydroxyurea
- Current or previous participation in clinical trials

Variables

Primary Variables

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Number of unplanned hospitalizations over time	Time to death or permanent ventilation (> 16 hours/day, for longer than 21 consecutive days)	Change from baseline of RULM total score at 12 months after treatment start	Change from baseline of RULM total score at 12 months after treatment start

Secondary Variables

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Time to death or permanent ventilation (> 16 hours/day, for longer than 21 consecutive days) Time to death Time to permanent ventilation (> 16 hours/day, for longer than 21 consecutive days) Time to any respiratory support	Time to death Time to permanent ventilation (> 16 hours/day, for longer than 21 consecutive days) Time to any respiratory support	Time to death or permanent ventilation (> 16 hours/day, for longer than 21 consecutive days) Time to death Time to permanent ventilation (> 16 hours/day, for longer than 21 consecutive days) Time to any respiratory support	Time to death or permanent ventilation (> 16 hours/day, for longer than 21 consecutive days) Time to death Time to permanent ventilation (> 16 hours/day, for longer than 21 consecutive days) Time to any respiratory support
Proportion of patients reaching the WHO motor development milestone “sitting without support” at an appropriate age Proportion of patients reaching the WHO motor development milestone “walking without support” at an appropriate age Proportion of patients	Proportion of patients reaching the WHO motor development milestone “sitting without support” at an appropriate age Proportion of patients reaching the WHO motor development milestone “walking without support” at an appropriate age Proportion of patients	Proportion of patients reaching the WHO motor development milestone “walking without support” at an appropriate age Proportion of patients reaching the WHO motor development milestone “walking without support”	-

reaching the WHO motor development milestone "walking without support"	reaching the WHO motor development milestone "walking without support"		
-	Proportion of patients with a CHOP-INTEND score ≥ 40 at 12 months of age Change from baseline in CHOP-INTEND total score at 12, 24 and 36 months of age	Change from baseline in HFMSE total score at 12, 24, 36 months after treatment start Change from baseline in RULM total score at 24 and 36 months after treatment start	Change from baseline HFMSE total score 12, 24, 36 months after treatment start Change from baseline in RULM total score at 24 and 36 months after treatment start
The total score of the Bayley III scores in the subscales "Gross Motorskills" at 12, 24 and 36 months of age Proportion of patients with age-appropriate Bayley III scores in the subscales "Expressive Language" and "Receptive Language" at 12, 24 and 36 months of age	The total score of the Bayley III scores in the subscales "Gross Motorskills" at 12, 24 and 36 months of age Proportion of patients with age-appropriate Bayley III scores in the subscales "Expressive Language" and "Receptive Language" at 12, 24 and 36 months of age	-	**For ambulatory patients:** Proportion of patients with an improvement in walking distance > 30m at 12, 24 and 36 months after treatment start Proportion of patients with a worsening in walking distance > 30m at 12, 24 and 36 months after treatment start Change from baseline in walking distance at 12, 24 and 36 months after treatment start Relative change from baseline in walking distance at 12, 24 and 36 months after treatment start
Proportion of patients with deterioration of swallowing function at 12, 24, 36 months of age	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months of age	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months

Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months of age	Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months of age	after treatment start Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after treatment start	after treatment start Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after treatment start
Time to first documentation of severe scoliosis (≥ 40°Cobb angle) or orthopedic surgery Time to first documentation of severe scoliosis (≥ 40°Cobb angle) Time to first documentation of orthopedic surgery	Time to first documentation of severe scoliosis (≥ 40°Cobb angle) or orthopedic surgery Time to first documentation of severe scoliosis (≥ 40°Cobb angle) Time to first documentation of orthopedic surgery	Time to first documentation of severe scoliosis (≥ 40°Cobb angle) or orthopedic surgery Time to first documentation of severe scoliosis (≥ 40°Cobb angle) Time to first documentation of orthopedic surgery	Time to first documentation of severe scoliosis (≥ 40°Cobb angle) or orthopedic surgery Time to first documentation of severe scoliosis (≥ 40°Cobb angle) Time to first documentation of orthopedic surgery
Proportion of patients with regular pain at 12, 24, 36 months of age Proportion of patients experiencing fatigue at months 12, 24, 36 of age	Proportion of patients with regular pain at 12, 24, 36 months of age Proportion of patients experiencing fatigue at months 12, 24, 36 of age	Proportion of patients with regular pain at 12, 24, 36 months after treatment start Proportion of patients experiencing fatigue at 12, 24, 36 months after treatment start	Proportion of patients with regular pain at 12, 24, 36 months after treatment start Proportion of patients experiencing fatigue at 12, 24, 36 months after treatment start
Number of planned hospitalizations over time (excluding hospitalizations for SMA treatment administration)	Number of planned hospitalizations over time (excluding hospitalizations for SMA treatment administration)	Number of planned hospitalizations over time (excluding hospitalizations for SMA treatment administration)	Number of planned hospitalizations over time (excluding hospitalizations for SMA treatment administration)

CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, HFMSE = Hammersmith Functional Motor Scale Expanded

Safety Variables

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Time to first SAE Time to first AE leading to hospitalization Time to first selected SAE: retinopathy, effect on epithelial tissue, thrombocytopenia, nephropathy, hydrocephalus, hepatopathy, cardiac events, sensory neuropathy	Number of unplanned hospitalizations over time Time to first SAE Time to first AE leading to hospitalization Time to first selected SAE: retinopathy, effect on epithelial tissue, thrombocytopenia, nephropathy, hydrocephalus, hepatopathy, cardiac events, sensory neuropathy	Number of unplanned hospitalizations over time Time to first SAE Time to first AE leading to hospitalization Time to first selected SAE: retinopathy, effect on epithelial tissue, thrombocytopenia, nephropathy, hydrocephalus, hepatopathy, cardiac events, sensory neuropathy	Number of unplanned hospitalizations over time Time to first SAE Time to first AE leading to hospitalization Time to first selected SAE: retinopathy, effect on epithelial tissue, thrombocytopenia, nephropathy, hydrocephalus, hepatopathy, cardiac events, sensory neuropathy

Study size

In this study patients will be enrolled across the German and Austrian SMArtCARE centers (according to the SMArtCARE homepage, there are currently 49 centers in Germany and 13 centers in Austria).

The described study design is based on the previous exchange with the G-BA and scientific experts (ref.). Based on the previous assumptions on the specifics of the disease, the regulatory requirements and the novelty of this project, the first assumptions are translated into patient numbers in the following, which may have to be adapted in the course of this project. As stated in the G-BA decision the sample size calculations will be re-assessed at the first interim analysis based on the observed effects and recruiting rates (section 8.7.5) and considering all relevant endpoints. In addition futility will be checked in the interim analysis.

Comparison to nusinersen or onasemnogene abeparvovec:

- Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene:
  Currently there is no data available. It is therefore not possible to plan the number of cases at this time. Based on the interim analysis, a final sample

size estimate will be made using observed effect assumptions.

- Symptomatic patients with a clinically diagnosed SMA type 1:

  Approx. 8839 patients per arm, assuming an effect of HR=0.45 in favor of risdiplam, a one-sided alpha of 2.5%, a power of 80%, and a shifted null hypothesis of HR ≥ 0.5.

- Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene:

  Approx. 6280 patients per arm, assuming an effect size of 0.55 in favor of risdiplam, a one-sided alpha of 2.5%, a power of 80%, and a shifted null hypothesis of Cohen's d ≤ 0.5.

- Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:

  Currently there is no data available. It is therefore not possible to plan the number of cases at this time. Based on the interim analysis, a final sample size estimate will be made using observed effect assumptions.

Data Analysis

All analyses are based on the full analysis set (FAS), including all enrolled patients. The participants will be included in the analyses according to the treatment they received at enrollment. To adjust for differences in the confounder variables between the treatment groups, propensity score weighting will be applied if sufficient overlap and balance between the scores is given. Depending on the amount of missing data for the confounder variables, a complete case analysis or multiple imputation prior to propensity score calculation are considered according to the rules defined in the statistical analysis plan (SAP).
All primary estimands as defined in Section 8.3 will be evaluated following the treatment-policy strategy to handle intercurrent events (e.g. early discontinuation from the study treatment or treatment switch), with the exception of the primary estimand for presymptomatic patients, where treatment switches will be handled with the hypothetical strategy. Additionally, supplementary estimands with other strategies will be investigated as well, as described in the SAP. For hypothesis testing, statistical significance is controlled at the 1-sided, 0.025 alpha level and the shifted

	null hypothesis. Point estimators will be presented with 2-sided 95% confidence intervals.
Milestones	**First Data Extraction:** The first data extraction is the date from which the variables used for the analysis as per protocol start to be extracted. For details, see section 5. MILESTONES **Last Data Extraction:** The last data extraction is the date from which the minimum set of data required to perform the statistical analyses leading to the results for the primary objective(s) is completely available. The planned last data extraction date is January 2026.

4. AMENDMENTS AND UPDATES

none

5. MILESTONES

Milestone	Planned Date
First Data Extraction	At study start
Last Data Extraction	January 2026
Status report	6, 18 and 30 months after study start
Interim report	18 and 30 months after study start
Final report of study results (CSR)	Not applicable
Publication submission	August 2026

6. RATIONALE AND BACKGROUND

Spinal muscular atrophy (SMA) is a rare autosomal recessive neuromuscular disorder characterized by the progressive loss of proximal motor neurons leading to muscle weakness and profound neuromotor disability. It is primarily characterized by degeneration of the anterior horn cells of the spinal cord resulting in muscle atrophy and proximal muscle weakness. It is caused by a homozygous deletion in the survival motor neuron 1 (*SMN1*) gene on chromosome 5q13. The severity of the disease is highly variable and correlates with the age of onset and *SMN2* copy number. For classification purposes, patients are usually categorized into three main subtypes based on clinical criteria, including achieving (or failing to achieve) physical motor milestones, age of onset, and expected life span:

- Type 1 SMA (severe infantile type with onset before 6 months of age; infants never sit without support, with death due to respiratory distress usually within 2 years),
- Type 2 SMA (intermediate chronic infantile type with onset after the age of 6 months, children unable to stand or walk without support),
- Type 3 SMA (chronic juvenile type with onset around the age of 18 months, children able to walk until the disease progresses)

For the best possible development or preservation of motor function, it is particularly important that treatment is started as early as possible. In October 2021, the newborn screening (NBS) for SMA was therefore implemented in Germany. This will allow newborns with SMA to be diagnosed immediately after birth. One consequence of the introduction of the NBS for SMA is that fewer symptomatic patients will be diagnosed in the long term.

In all types of SMA, as the disease progresses, clinical symptoms include hypotonia, symmetrical muscle weakness and atrophy (predominantly of the proximal muscles of the shoulder and pelvic girdle), diminished or absent deep tendon reflexes, tremor of fingers and hands, fasciculation of the tongue muscles, and hyporeflexia with orthopedic deformities (contractures, scoliosis). Progressive respiratory failure and frequent pulmonary infections and superinfections are common in Types 1 and 2 SMA. Other common comorbidities include failure to thrive, pneumonia, osteopenia and osteoporosis with pathological fractures, poor cough and secretion clearance, reduced vital capacity, gastroesophageal dysmotility, urinary incontinence, hip dislocation, and joint and muscle pain.

6.1 STUDY RATIONALE

On the basis of the ongoing or completed studies on risdiplam considered for approval, the) identified evidence gaps, particularly comparative data of a treatment with risdiplam versus existing appropriate therapy alternatives are missing for patients.

Thus, the G-BA initiated a procedure to require an evaluation of a real world data collection for the reassessment of the additional benefit of risdiplam with the following PICO scheme requirements.

Population:

- Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene
- Symptomatic patients with a clinically diagnosed SMA type 1
- Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene
- Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene

Intervention:

- Risdiplam

Treatment according to the Summary of Product Characteristics (SmPC).

Comparator:

- Therapy according to physician’s choice taking into account nusinersen und onasemnogene abeparvovec.

Treatment according to the respective SmPC.

Outcome

- Mortality: Number of deaths

- Morbidity:

  Motorfunction (assessed with age-appropriate instruments)

  Achieving the motor milestones (World Health Organization (WHO) motor development milestones)

  Respiratory function (need for permanent ventilation)

  Bulbar function (ability to swallow, , need for non-oral nutritional support, ability to speak)

  Other complications of the disease (e.g. pain, orthopedic complications)
- Number of unplanned hospitalizations over time
- Adverse events:

  Time to first SAE

  Time to first AE leading to hospitalization

  Time to first selected SAE: retinopathy, effect on epithelial tissue, thrombocytopenia, nephropathy, hydrocephalus, hepatopathy, cardiac events, sensory neuropathy

7. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to evaluate the comparative effectiveness and safety of risdiplam versus a therapy according to physician´s choice taking into account nusinersen and onasemnogene abeparvovec. The research questions are a result of the participation process with G-BA, the G-BA appraisal, the G-BA advice and discussions with medical experts regarding the evaluation of a real world data collection for the reassessment of the additional benefit of risdiplam. The research questions will be addressed using registry data from the SMArtCARE registry.

Primary Objectives

The primary objectives for this study are as follows:

- **Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene:**

  To evaluate the safety of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as number of unplanned hospitalization over time

- **Symptomatic patients with a clinically diagnosed SMA type 1:**

  To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as time to death or permanent ventilation

- **Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene:**

  To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of Revised Upper Limb Module (RULM) total score at 12 months after treatment start

- **Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:**

  To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of RULM total score at 12 months after treatment start

Secondary objectives

The secondary objectives for this study are as follows:

- **Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene:**

  To assess the impact of treatment on time to death or permanent ventilation

  To assess the impact of treatment on time to death

  To assess the impact of treatment on time to permanent ventilation

  To assess the time to any respiratory support

To evaluate the proportion of patients reaching the WHO motor development milestone “sitting without support” at an appropriate age

To evaluate the proportion of patients reaching the WHO motor development milestone “walking without support” at an appropriate age

To evaluate the proportion of patients reaching the WHO motor development milestone “walking without support”

To evaluate the total score of the Bayley III in the subscale “Gross Motorskills” at 12, 24 and 36 months of age

To evaluate the proportion of patients with age-appropriate Bayley III scores in the subscales “Expressive Language” and “Receptive Language” at 12, 24 and 36 months of age

To evaluate the proportion of patients with deterioration of swallowing function at 12, 24 and 36 months of age

To evaluate the proportion of patients with need of non-oral nutritional support at 12, 24 and 36 months of age

To assess orthopedic complications by measuring the time to first documentation of severe scoliosis (≥ 40° Cobb angle) or orthopedic surgery

To assess orthopedic complications by measuring the time to first documentation of severe scoliosis (≥ 40° Cobb angle)

To assess orthopedic complications by measuring the time to first documentation of orthopedic surgery

To evaluate the proportion of patients with regular pain at 12, 24 and 36 months of age

To evaluate the proportion of patients with fatigue at 12, 24 and 36 months of age

To assess the number of planned hospitalizations over time (excluding hospitalizations for SMA treatment administration)

- **Symptomatic patients with a clinically diagnosed SMA type 1:**

To assess the impact of treatment on time to death

To assess the impact of treatment on time to permanent ventilation

To assess the time to any respiratory support

To evaluate the proportion of patients reaching the WHO motor development milestone “sitting without support” at an appropriate age

To evaluate the proportion of patients reaching the WHO motor development milestone “walking without support” at an appropriate age

To evaluate the proportion of patients reaching the WHO motor development milestone “walking without support”

To evaluate the proportion of patients with a Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score ≥ 40 at 12 months of age

To assess the change from baseline in CHOP-INTEND total score at 12, 24 and 36 months of age

To evaluate the total score of the Bayley III in the subscale "Gross Motor Skills" at 12, 24 and 36 months of age

To evaluate the proportion of patients with age-appropriate Bayley III scores in the subscales "Expressive Language" and "Receptive Language" at 12, 24 and 36 months of age

To evaluate the proportion of patients with deterioration of swallowing function at 12, 24 and 36 months of age

To evaluate the proportion of patients with need of non-oral nutritional support at 12, 24 and 36 months of age

To assess orthopedic complications by measuring the time to first documentation of severe scoliosis (≥ 40° Cobb angle) or orthopedic surgery

To assess orthopedic complications by measuring the time to first documentation of severe scoliosis (≥ 40° Cobb angle)

To assess orthopedic complications by measuring the time to first documentation of orthopedic surgery

To evaluate the proportion of patients with regular pain at 12, 24 and 36 months of age

To evaluate the proportion of patients with fatigue at 12, 24 and 36 months of age

To assess the number of planned hospitalizations over time (excluding hospitalizations for SMA treatment administration)

- **Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene:**

  To assess the impact of treatment on time to death or permanent ventilation

  To assess the impact of treatment on time to death

  To assess the impact of treatment on time to permanent ventilation

  To assess the time to any respiratory support

  To assess the proportion of patients reaching the WHO motor development milestone "walking without support" at an appropriate age

  To evaluate the proportion of patients reaching the WHO motor development milestone "walking without support"

  To assess the change from baseline in Hammersmith Functional Motor Scale Expanded (HFMSE) total score at 12, 24 and 36 months after treatment start

To assess the change from baseline in RULM total score at 24 and 36 months after treatment start

To evaluate the proportion of patients with deterioration of swallowing function at 12, 24 and 36 months after treatment start

To evaluate the proportion of patients with need of non-oral nutritional support at 12, 24 and 36 months after treatment start

To assess orthopedic complications by measuring the time to first documentation of severe scoliosis (≥ 40° Cobb angle) or orthopedic surgery

To assess orthopedic complications by measuring the time to first documentation of severe scoliosis (≥ 40° Cobb angle)

To assess orthopedic complications by measuring the time to first documentation of orthopedic surgery

To evaluate the proportion of patients with regular pain at 12, 24 and 36 months after treatment start

To evaluate the proportion of patients with fatigue at 12, 24 and 36 months after treatment start

To assess the number of planned hospitalizations over time (excluding hospitalizations for SMA treatment administration)

- **Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:**

  To assess the impact of treatment on time to death or permanent ventilation

  To assess the impact of treatment on time to death

  To assess the impact of treatment on time to permanent ventilation

  To assess the time to any respiratory support

  To assess the change from baseline in HFMSE total score at 12, 24 and 36 months after treatment start

  To assess the change from baseline in RULM total score at 24 and 36 months after treatment start

  For ambulatory patients: to assess the proportion of patients with an improvement in walking distance > 30m at 12, 24 and 36 months after treatment start

  For ambulatory patients: to assess the proportion of patients with a worsening in walking distance > 30m at 12, 24 and 36 months after treatment start

  For ambulatory patients: to assess the change from baseline in walking distance at 12, 24 and 36 months after treatment start

  For ambulatory patients: to assess the relative change from baseline in walking distance at 12, 24 and 36 months after treatment start

  To evaluate the proportion of patients with deterioration of swallowing function at 12, 24 and 36 months after treatment start

To evaluate the proportion of patients with need of non-oral nutritional support at 12, 24 and 36 months after treatment start

To assess orthopedic complications by measuring the time to first documentation of severe scoliosis (≥ 40° Cobb angle) or orthopedic surgery

To assess orthopedic complications by measuring the time to first documentation of severe scoliosis (≥ 40° Cobb angle)

To assess orthopedic complications by measuring the time to first documentation of orthopedic surgery

To evaluate the proportion of patients with regular pain at 12, 24 and 36 months after treatment start

To evaluate the proportion of patients with fatigue at 12, 24 and 36 months after treatment start

To assess the number of planned hospitalizations over time (excluding hospitalizations for SMA treatment administration)

Safety Objectives

The safety objectives of this study are as follows:

- **To assess the safety and tolerability of oral treatment with risdiplam compared to nusinersen or onasemnogene abeparvovec:**
  including the following safety variables:

  Number of unplanned hospitalizations over time

  Time to first SAE

  Time to first AE leading to hospitalization

  Time to first selected SAE: retinopathy, effect on epithelial tissue, thrombocytopenia, nephropathy, hydrocephalus, hepatopathy, cardiac events, sensory neuropathy

8. RESEARCH METHODS

8.1 STUDY DESIGN

This study is a registry-based, comparative, non-interventional, multicentric, multinational, open-label study. As the treatment start date differs, there will be simultaneously enrolled controls and not simultaneously enrolled controls.This registry-based study is based on the data of the SMArtCARE registry. The SMArtCARE project (www.smartcare.de) provides a platform to collect longitudinal clinical routine data on SMA patients in Germany, Austria, and Switzerland.

The registry collects data from SMA patients since 2017. Retrospective data for patients treated with nusinersen will be analyzed since the beginning of the registry (May 30, 2017 at the earliest), data for patients treated with onasemnogene abeparvovec since approval in 2020 (May 18, 2020 at the earliest) and data for patients treated with risdiplam since approval in 2021 (March 26, 2021 at the earliest). Details of the registry are given in the SMArtCARE protocol.

Start Date of Study:

The planned start date is Q4/2023 after confirmation of the submitted study protocol and statistical analysis plan by the G-BA.

Interim Analysis

Interim analysis are planned 12 and 24 months after start of the study and will be handed in to G-BA latest after 18 and 30 months after the start of the study. Based on these interim analysis, a final sample size estimate will be made using more precise effect assumptions. Final analysis will take place in January 2026.

End of Study:

The planned end date is January 01, 2026. Data that is documented in the study database after that time point will not be taken into account.

8.1.1 Rationale for Study Design

According to the requirements of the G-BA the study follows a non-randomized design comparing risdiplam with nursinersen and onasemnogene abeparvovec. Since the treatment start date differs there will be simultaneously enrolled controls and not simultaneously enrolled controls. The described study design is based on the previous exchange with the G-BA and scientific experts experts (1–6). Based on the previous assumptions on the specifics of the disease, the regulatory requirements and the novelty of this project, the first assumptions are translated into patient numbers in the following, which may have to be adapted in the course of this project. As stated in the G-BA Beschluss the sample size calculations will be re-assessed at the first interim analysis based on the observed effects and recruiting rates (Section 8.7.5) and considering all relevant endpoints. In addition, futility will be checked in the interim analysis (4).

8.1.2 Number of Patients Observed in the Study

In this study patients will be enrolled across the German and Austrian SMArtCARE centers.

- **Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene:**

- Currently there is no data available. It is therefore not possible to plan the number of cases. Based on the interim analysis, a sample size estimate will be made using the observed effect assumptions.

- **Symptomatic patients with a clinically diagnosed SMA type 1:**
  - Approx. 8839 patients per arm (see section 8.5).
- **Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene:**
  - Approx. 6280 patients per arm (see section 8.5).
- **Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:**
  - Currently there is no data available. It is therefore not possible to plan the number of cases. Based on the interim analysis, a sample size estimate will be made using the observed effect assumptions.

8.1.3 Sites

The registry collects data of patients from Germany and Austria (according to the SMArtCARE homepage, https://www.smartcare.de/).

8.2 SETTING

8.2.1 Selection Criteria

Patients must meet the following criteria for study entry:

For all populations:

- Signed informed consent form (by legal representative) to participate in the study
- Genetically confirmed 5q-autosomal recessive SMA
- Treatment according to the SmPC with risdiplam OR nusinersen OR onasemnogene abeparvovec with treatment starting no earlier than March 26, 2021 for risdiplam, not earlier than May 30, 2017 for nusinersen and not earlier than May 18, 2020 for onasemnogene abeparvovec.)
- Visit that will be used as baseline visit has to take place between six weeks before and three weeks after the first administration.

Specific to the indicated populations:

- **Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene:**

  Pre-symptomatic at time of diagnosis

  SMN2 copy number is $\leqslant$ 3

- **Symptomatic patients with a clinically diagnosed SMA type 1:**

Not pre-symptomatic at time of diagnosis

Onset of symptoms < 6 months OR never achieved ability to sit unaided

- **Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene:**

  Not pre-symptomatic at time of diagnosis

  SMN2 copy number is $\leqslant$ 3

  Onset of symptoms > 6 months and < 18 months OR never achieved ability to walk unaided

- **Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:**

  Not pre-symptomatic at time of diagnosis

  SMN2 copy number is $\leqslant$ 3

  Onset of symptoms > 18 months

  Patient is able to walk unaided OR was able to walk unaided but has lost that ability

Patients who meet any of the following criteria will be excluded from the evaluation of the real world data collection for the reassessment of the additional benefit of Evrysdi®:

- Prior treatment with disease-modifying therapy before the patient was included in the registry (risdiplam, nusinersen, or onasemnogene abeparvovec)
- Current treatment with therapies whose effectiveness is being tested for the treatment of SMA: e.g. salbutamol, riluzole, phenylbutyrate, valproate, hydroxyurea
- Current or previous participation in clinical trials

8.2.2 Treatment

8.2.2.1 Dosage, Administration, and Compliance

Dosing and treatment duration of any studied medicinal products are according to the respective SmPC.

Risdiplam

The recommended once daily dose of risdiplam is determined by age and body weight (see Table 1). Risdiplam is taken orally once a day after a meal at approximately the same time each day.

Table 1: Dosing regimen by age and body weight

Age and body weight	Recommended daily dose
< 2 months of age	0.15 mg/kg
2 months to < 2 years of age	0.20 mg/kg
≥ 2 years of age (< 20 kg)	0.25 mg/kg
≥ 2 years of age (≥ 20 kg)	5 mg

Risdiplam is taken orally once a day after a meal at approximately the same time each day, using the reusable oral syringe provided. In infants who are breastfed, risdiplam should be administered after breastfeeding. Risdiplam should not be mixed with milk or formula milk. Risdiplam should be taken immediately after it is drawn up into the oral syringe. If it is not taken within 5 minutes, it should be discarded from the oral syringe and a new dose be prepared. If risdiplam spills or gets on the skin, the area should be washed with soap and water. The patient should drink water after taking risdiplam to ensure the medicinal product has been completely swallowed. If the patient is unable to swallow and has a nasogastric or gastrostomy tube in situ, risdiplam can be administered via the tube. The tube should be flushed with water after delivering risdiplam.

Nusinersen

The recommended dosage of nusinersen 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.

Nusinersen is for intrathecal use by lumbar puncture. Treatment should be administered by health care professionals experienced in performing lumbar punctures. Nusinersen is administered as an intrathecal bolus injection over 1 to 3 minutes, using a spinal anesthesia needle. The injection must not be administered in areas of the skin where there are signs of infection or inflammation. It is recommended that the volume of cerebral spinal fluid, equivalent to the volume of nusinersen to be injected, is removed prior to administration of nusinersen. Sedation may be required to administer nusinersen, 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.

Onasemnogene abeparvovec

Onasemnogene abeparvovec is administered as a single-dose intravenous infusion. Patients will receive a dose of nominal 1.1×10^{14} vg/kg onasemnogene abeparvovec. The total volume is determined by patient body weight.

Onasemnogene abeparvovec 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. Insertion of a secondary (‘back-up’) catheter is recommended in case of blockage in the primary catheter. Following completion of infusion, the line should be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection. Starting 24 hours prior to infusion of onasemnogene abeparvovec it is recommended to initiate an immunomodulatory regimen. Prior to initiation of the

immunomodulatory regimen and prior to administration of onasemnogene abeparvovec, the patient must be checked for symptoms of active infectious disease of any nature.

8.2.3 Concomitant Medication and Treatment

Concomitant medication will be allowed except for treatments defined as exclusion criterion.

Medication taken on a regular basis is documented in the SMArtCARE database.

8.3 ENDPOINTS AND ESTIMANDS

8.3.1 Primary Objectives and Corresponding Estimands

Table 2: Primary Objectives and Corresponding Estimands

Primary Objective	Estimand Definition
To evaluate the safety of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as the number of unplanned hospitalization over time	Population: Presymptomatic patients with a 5q-associated SMA and up to three copies of the SMN2 gene as defined by the study inclusion and exclusion criteria (see Section 8.2.1 of the protocol) Endpoint: number of unplanned hospitalization over time Treatment (see Section 8.2.2of the protocol): Experimental arm: Risdiplam according to SmPC Control arm: Nusinersen or onasemnogene abeparvovec according to SmPC Intercurrent events and handling strategies: Early discontinuation from study treatment: Treatment-policy strategy Treatment switch: Hypothetical strategy Population-level summary: Rate ratio
To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as time to death or permanent ventilation	Population: Symptomatic patients with a clinically diagnosed SMA type 1 (see Section 8.2.1of the protocol) Endpoint: Time to death or permanent ventilation (> 16 hours/day, for longer than 21 consecutive days) Treatment: as defined above Intercurrent events and handling strategies: Early discontinuation from study treatment: Treatment-policy strategy Treatment switch: Treatment-policy strategy Population-level summary: hazard ratio
To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of RULM total score	Population: Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene (see Section 8.2.1 of the protocol). Only patients with a baseline value and a value at month 12 after treatment start are included.

Primary Objective	Estimand Definition
	Endpoint: Change from baseline of RULM total score at 12 months after treatment start Treatment: as defined above Intercurrent events and handling strategies: Early discontinuation from study treatment: Treatment-policy strategy Treatment switch: Treatment-policy strategy Population-level summary: Cohen's d
To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of RULM total score	Population: Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the SMN2 gene (see Section 6.1 of the protocol). Only patients with a baseline value and a value at month 12 after treatment start are included. Endpoint: as defined above Treatment: as defined above Intercurrent events and handling strategies: as defined above Population-level summary: as defined above

8.3.2 Secondary Variables

Table 3: Secondary Variables

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Time to death or permanent ventilation[a] Time to death Time to permanent ventilation[a] Time to any respiratory support	Time to death Time to permanent ventilation[a] Time to any respiratory support	Time to death or permanent ventilation[a] Time to death Time to permanent ventilation[a] Time to any respiratory support	Time to death or permanent ventilation[a] Time to death Time to permanent ventilation[a] Time to any respiratory support
Proportion of patients reaching the WHO motor development milestone "sitting without support" at an appropriate age Proportion of patients reaching the WHO motor development milestone "walking	Proportion of patients reaching the WHO motor development milestone "sitting without support" at an appropriate age Proportion of patients reaching the WHO motor development milestone "walking	Proportion of patients reaching the WHO motor development milestone "walking without support" at an appropriate age Proportion of patients reaching the WHO motor development milestone "walking without support"	-

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
without support" at an appropriate age Proportion of patients reaching the WHO motor development milestone "walking without support"	without support" at an appropriate age Proportion of patients reaching the WHO motor development milestone "walking without support"		
-	Proportion of patients with a CHOP-INTEND score ≥ 40 at 12 months of age Change from baseline in CHOP-INTEND total score at 12, 24 and 36 months of age	Change from baseline in HFMSE total score at 12, 24, 36 months after treatment start Change from baseline in RULM total score at 24 and 36 months after treatment start	Change from baseline HFMSE total score 12, 24, 36 months after treatment start Change from baseline in RULM total score at 24 and 36 months after treatment start
The total score of the Bayley III scores in the subscales "Gross Motorskills" at 12, 24 and 36 months of age Proportion of patients with age-appropriate Bayley III scores in the subscales "Expressive Language" and "Receptive Language" at 12, 24 and 36 months of age	The total score of the Bayley III scores in the subscales "Gross Motorskills" at 12, 24 and 36 months of age Proportion of patients with age-appropriate Bayley III scores in the subscales "Expressive Language" and "Receptive Language" at 12, 24 and 36 months of age	-	For ambulatory patients: Proportion of patients with an improvement in walking distance > 30m at 12, 24 and 36 months after treatment start Proportion of patients with a worsening in walking distance > 30m at 12, 24 and 36 months after treatment start Change from baseline in walking distance at 12, 24 and 36 months after treatment start Relative change from baseline in walking distance at 12, 24 and 36 months after treatment start
Proportion of patients with deterioration of swallowing function at 12, 24, 36 months of age Proportion of patients with need of non-oral nutritional support at	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months of age Proportion of patients with need of non-oral nutritional support at	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after treatment start Proportion of patients with need of non-oral nutritional support at	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after treatment start Proportion of patients with need of non-oral nutritional support at

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
12, 24, 36 months of age	12, 24, 36 months of age	12, 24, 36 months after treatment start	12, 24, 36 months after treatment start
Time to first documentation of severe scoliosis[b] or orthopedic surgery Time to first documentation of severe scoliosis[b] Time to first documentation of orthopedic surgery	Time to first documentation of severe scoliosis[b] or orthopedic surgery Time to first documentation of severe scoliosis[b] Time to first documentation of orthopedic surgery	Time to first documentation of severe scoliosis[b] or orthopedic surgery Time to first documentation of severe scoliosis[b] Time to first documentation of orthopedic surgery	Time to first documentation of severe scoliosis[b] or orthopedic surgery Time to first documentation of severe scoliosis[b] Time to first documentation of orthopedic surgery
Proportion of patients with regular pain at 12, 24, 36 months of age Proportion of patients experiencing fatigue at months 12, 24, 36 months of age	Proportion of patients with regular pain at 12, 24, 36 months of age Proportion of patients experiencing fatigue at 12, 24, 36 months of age	Proportion of patients with regular pain at 12, 24, 36 months after treatment start Proportion of patients experiencing fatigue at 12, 24, 36 months after treatment start	Proportion of patients with regular pain at 12, 24, 36 months after treatment start Proportion of patients experiencing fatigue at 12, 24, 36 months after treatment start
Number of planned hospitalizations over time (excluding hospitalizations for SMA treatment administration)	Number of planned hospitalizations over time (excluding hospitalizations for SMA treatment administration)	Number of planned hospitalizations over time (excluding hospitalizations for SMA treatment administration)	Number of planned hospitalizations over time (excluding hospitalizations for SMA treatment administration)

[a] permanent ventilation is defined as ventilation > 16 hours/day, for longer than 21 consecutive days, [b] severe scoliosis is defined as a Cobb angle $\geqslant 40^{\circ}$

8.3.3 Safety Variables

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Time to first SAE Time to first AE leading to hospitalization Time to first selected SAEs[a]	Number of unplanned hospitalizations over time Time to first SAE Time to first AE leading to hospitalization Time to first selected SAEs[a]	Number of unplanned hospitalizations over time Time to first SAE Time to first AE leading to hospitalization Time to first selected SAEs[a]	Number of unplanned hospitalizations over time Time to first SAE Time to first AE leading to hospitalization Time to first selected SAEs[a]

[a] selected SAEs are: retinopathy, effect on epithelial tissue, thrombocytopenia, nephropathy, hydrocephalus, hepatopathy, cardiac events, sensory neuropathy

8.4 DATA SOURCE(S)

8.4.1 Collection of Data on the CRF

All clinical data for this project is collected 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 (see also SMArtCARE protocol). Further registries may be included.

At enrollment and baseline the SMA confirmation including the genetic details (*SMN2* copy numbers) are documented together with date of birth and gender. The following baseline data are documented: pre-symptomatic /age at onset of symptoms, motor function, pulmonary function, nutrition, scoliosis surgery in the past, other medical history, (previous) treatment of SMA, participation in clinical studies currently/in the past.

At each visit a detailed medical assessment will be performed and documented in the eCRF giving also details on the SMA treatment and other concomitant medication. In addition, the adverse events eCRF will be completed at each visit. The eCRF pages documenting the main inclusion criteria, and effectiveness and safety variables are given in the following table.

Special documentation is available for administration of nusinersen and onasemnogene abeparvovec.

Table 4: CRF pages documenting the main inclusion criteria and effectiveness and safety variables

Variable	eCRF page
Main inclusion criterion	
Pre-symptomatic diagnosis / no pre-symptomatic diagnosis	Baseline – Results of the genetic examination Baseline – Clinical diagnosis
Onset of symptoms < 6 months Onset of symptoms > 6 months and < 18 months Onset of symptoms > 18 months	Baseline – Clinical diagnosis
Never achieved ability to sit unaided Never achieved ability to walk unaided Patient is able to walk unaided OR was able to walk unaided but has lost that ability	Baseline– Clinical diagnosis
SMN2 copy number is ≤ 3	Baseline– Results of the genetic examination
Primary effectiveness variables	

Variable	eCRF page
Unplanned hospitalizations	Medical assessment - Hospitalization
Time to death or time to permanent ventilation (> 16 hours/day, for longer than 21 consecutive days)	Adverse events / End of data collection Medical assessment – Pulmonary function and support
RULM total score	Physiotherapeutic evaluation - RULM
Secondary effectiveness variables	
WHO motor development milestones	Medical assessment
HFMSE score	Physiotherapeutic evaluation - HFMSE
CHOP INTEND score	Physiotherapeutic evaluation - CHOP INTEND
Bayley score	Physiotherapeutic evaluation – Bayley Scale
Respiratory support	Baseline and Medical assessment– Pulmonary function and support
Swallowing function	Medical assessment - Nutrition
Non-oral nutritional support	Baseline and Medical assessment - Nutrition
Scoliosis	Medical assessment - Orthopedic symptoms
Orthopedic surgery	Baseline and Medical assessment - Orthopedic symptoms
Walking distance	Walk test - „distance_na“ (Total distance)
Fatigue	Medical assessment - Orthopedic symptoms
Hospitalizations	Medical assessment - Hospitalization
Safety variables	
Adverse events	Adverse events
Treatment of SMA	Medical assessment– Medication

8.4.2 Safety Data Collection

All adverse events and serious adverse will be collected at every visit and documented in the CRF in a specific AE section. For regular follow-up patients adverse events include events with unplanned or prolonged hospitalization and additionally unexpected events without hospitalization.

For specific medications, selected AE will be collected, e.g. possible treatment-related medical occurrences such as lumbar puncture associated AE.

Death will be documented in the “End of data collection” CRF.

8.5 SAMPLE SIZE

Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene.

The current evidence for pre-symptomatic patients treated with risdiplam, nursinersen or onasemnogene abeparvovec is still limited. There is no evidence to date, for making assumptions on differences between treatments. It is therefore not possible to calculate the sample size yet.

The primary endpoint for pre-symptomatic patients is the number of unplanned hospitalization over time. A negative binomial regression model will be used to estimate the rate ratio. Based on the first interim analyses (see section 8.7.5), the sample size for a shifted null hypothesis (RR ≥ 0,5), an one-sided alpha of 2.5% and a power of 80% will be calculated using the observed effect size.

Symptomatic patients with a clinically diagnosed SMA type 1:

For patients with a clinically diagnosed SMA type 1, the sample size estimation is based on the endpoint time to death or permanent ventilation.

The probability of the event death or permanent ventilation of patients treated with nusinersen is assumed to be 40 %, while the probability for patients treated with onasemnogene abeparvovec is assumed to be 9 % (7). Since the distribution between patients receiving nusinersen and patients receiving onasemnogene abeparvovec is not yet known, assumptions for the probability of the comparison arm cannot be derived.

To be able to provide a rough sample size as a first orientation, a probability of the event death or permanent ventilation of 22% for the comparison arm and an effect of a HR=0.45 in favor of risdiplam will be assumed. The assumptions of an one-sided alpha of 2.5 %, a power of 80 %, an observation period of 36 months and a shifted null hypothesis (HR ≥ 0,5) are leading to 2828 events and 8839 patients per treatment arm.

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene

In the population of patients with clinically diagnosed SMA type 2, sample size estimation is based on the endpoint change from baseline in RULM total score.

Based on the CHERISH study, one can expect a change from baseline to month 12 of 3.7 points in the RULM total score for patients treated with Nusinersen (7). At the time of submission, there is no data published showing the performance in RULM total score for onasemnogene abeparvovec. For orientation, a change of 3.7 points in RULM total score is assumed for the comparison arm.

To be able to provide a rough sample size for a first orientation an effect size of 0.55 in favor of risdiplam with and standard deviation of 11 will be assumed (change of 9.75 points in RULM total score for the risdiplam arm). The assumptions of an one-sided alpha of 2.5%, a power of 80% and a shifted null hypothesis (Cohen's d ≤ 0,5) are leading to 6280 patients per group. The threshold was chosen with regard to Cohen's rule of thumb for interpreting results (Medium Effect = 0.5) (8).

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene

Currently data available on SMA type 3 patients treated with Nursinersen or onasemnogene abeparvovec is not sufficient to calculate the sample size.

The primary endpoint for the pre-symptomatic patients is the change from baseline in RULM total score. Based on the first interim analyses, the sample size will be calculated for a shifted null hypothesis (Cohen's d ≤ 0,5), an one-sided alpha of 2.5% and a power of 80% using the observed effect size.

8.6 DATA MANAGEMENT

Following the extraction from the data source, anonymized data will be stored at Chrestos Concept GmbH & Co. KG (named Chrestos in the following). Access to the data will be restricted to members of Chrestos. No personal data will be provided to Roche/Genentech.

8.6.1 Data Quality Assurance

Data used for this study is collected and stored in the SMArtCARE registry.

The clinical sites are responsible for implementing and maintaining quality assurance and quality control systems with written SOPs. Data are entered at the site into an eCRF. SMArtCARE uses SAS software to review the data for completeness, consistency and plausibility. All programs which can be used to influence data or data quality are validated.

8.6.2 Electronic Case Report Forms

SMArtCARE uses an electronic data capture (EDC) system. This system is implemented and maintained by Open Applications Consulting Ltd. SAS software is used to review the data for completeness, consistency and plausibility. Query resolution processes are implemented. All programs which can be used to influence data or data quality are validated (e.g. data validation programs, programs for CRF/query tracking, programs for import of EDC data into SAS or for import of external data, etc.).

8.6.3 Source Data Documentation

Source data verification (SDV) is performed by SMArtCARE according to protocol in order to verify the accuracy and completeness of the entries on the eCRF by comparing them with the source data, and to ensure and increase the quality of the data (SMArtCARE protocol).

In addition, SDV for 100% of patients for the primary endpoint and for at least 10% of randomly selected patients for all other endpoints over the period since the start of data collection will be performed by Clinische Studien Gesellschaft (CSG).

8.7 DATA ANALYSIS

All analyses are based on the Full Analysis Set (FAS), including all enrolled patients. The participants will be included in the analyses according to the treatment they received at enrollment. Relevant confounders have been specified according to the description in Section 8.7.4. To adjust for differences in the confounder variables between the treatment groups, propensity score weighting will be applied if sufficient overlap and balance between the scores is given. Depending on the amount of missing data for the confounder variables, a complete case analysis or multiple imputation prior to propensity score calculation are considered according to the rules defined in the statistical analysis plan (SAP).

8.7.1 Primary Objectives Analyses

All primary estimands will be evaluated following the treatment-policy strategy to handle intercurrent events (e.g. early discontinuation from the study treatment or treatment switch), with the exception of the primary estimand for presymptomatic patients, where treatment switches will be handled with the hypothetical strategy. The rationale of using the hypothetical strategy for the primary estimand for presymptomatic patients is to provide a picture of a treatment effect on the safety foreseen in clinical practice when treatment is actually administered. Additionally, supplementary estimands with other strategies will be investigated as well, as described in the SAP. For hypothesis testing, statistical significance is controlled at the 1-sided, 0.025 alpha level and the shifted null hypothesis. Point estimators will be presented with 2-sided 95% confidence intervals.

The comparison of the number of unplanned hospitalizations over time between the arms will be performed using a negative binomial regression model, which accounts for different follow-up times, with the patient’s number of hospitalizations as a function of treatment arm and the time that each patient stays in the included as an offset in the model. This analytic model estimates the rate ratio, which quantifies the risk of hospitalization associated with risdiplam in comparison to the control arm.

Time to death or permanent ventilation will be presented graphically using Kaplan-Meier curves and with the median and 25% quantiles. To quantify the treatment effect, the hazard ratio (and the 2-sided 95% confidence interval (CI) will be estimated.

For the change from baseline of RULM total score, a MMRM analysis will be performed and Cohen's d will be estimated as a measure of the effect size. The estimated treatment difference in the mean change from baseline will be presented with a 95% CI. The score and change from baseline score will also be summarized using descriptive statistics. The mean absolute scores and change from baseline scores over time will also be presented graphically using a line plot.

8.7.2 Safety Analyses

The analysis of safety outcomes/variables is based on all SAE, AE leading to hospitalization and selected SAE. The time to onset of the first episode of (serious) adverse event in each category will be summarized using Kaplan Meier approach and presented graphically.

All SAE, AE leading to hospitalization and selected SAE term entered by the physician describing the event (the "verbatim term") will be assigned to a standardized term (the "preferred term") based on the most up-to-date version of Medical Dictionary for Regulatory Activities (MedDRA). Summary statistics of SAE, AE leading to hospitalization and selected SAE will be performed using preferred terms and their according system organ class.

The time to onset SAE, AE leading to hospitalization and selected SAE will be summarized according to the preferred term and their according system organ class.

The number of unplanned hospitalizations over time will be analyzed separately using negative binomial regression models.

8.7.3 Subgroups

Subgroup analyses will be performed to investigate the generalizability of the results when comparing risdiplam to the control arm. Analyses will be presented for the following subgroups:

Table 5: Subgroups

Subgroups	Categories	Populations
Sex	Male, female	All
Age at diagnosis	0 to 18 months, 18 months to 5 years, 6 to 11 years, 12 to 17 years, and 18 to 25 years, > 25 years	SMA3
Age at enrollment	2 to 5 years, 6 to 11 years, 12	SMA2, SMA3

	to 17 years, and 18 to 25 years, > 25 years	
Age at enrollment	≤ median age, > median age	presymptomatic
Geographic region	Germany, Austria	All
History of scoliosis surgery	Yes, no	SMA2, SMA3
Highest motor milestone at baseline (disease severity)	None, Sitting without support, Crawl on hands and knees, Standing without support, Walking without support, Climb stairs	All
Nutrition support	Yes – exclusively, yes – supplementary, no	All
Ventilation support	Yes, no	All
Contractures	Yes, no	SMA1, SMA2, SMA3
SMN2 Copy Number	1, 2, 3	All
Baseline CHOP-INTEND	≤ median score, > median score	SMA1, presymptomatic
Baseline HFMSE score	≤ median score, > median score	SMA2, SMA3
Baseline CMAP amplitude	<1.5mV, ≥1.5mV	presymptomatic
Time between first treatment and onset of symptoms	≤ 3 months, > 3 months	SMA1

8.7.4 Confounder

For the real world data collection for the reassessment of the additional benefit of risdiplam all confounders should be identified in advance through systematic research and prespecified for the analyses.

A search to identify confounders was already conducted for the real world data collection for the reassessment of the additional benefit of onasemnogene abeparvovec on March 23, 2021 (9).

Additionally a search for prognostic factors and treatment effect modifiers has already been conducted and published as part of the Matching-Adjusted-Indirect-Comparison (MAIC) presented in the risdiplam benefit dossier (10, 11). Publications published by April 30, 2019, were included.

The two sources are in agreement about the important confounders for patients with SMA. Therefore, the confounder definition used for the real world data collection for the reassessment of the additional benefit of onasemnogene abeparvovec will be adopted

for the real world data collection for the reassessment of the additional benefit of risdiplam. This will also help to make the two data collections more consistent.

G-BA and IQWiG agreed in the consultation 2022-B-215 on November 3rd 2022 regarding the real world data collection for the reassessment of the additional benefit of risdiplam that this approach and the use of the two sources is appropriate to identify the relevant confounders (1, 2, 9, 12).

The following adaptations to the confounders proposed in the advisory request 2022-B-215 should be considered:

1. Because of the approved indication of onasemnogene abeparvovec, the real world data collection for the reassessment of the additional benefit of onasemnogene abeparvovec collects data for pre-symptomatic patients and those with type 1 and type 2 SMA. The real world data collection for the reassessment of the additional benefit of risdiplam will also collect data for patients with type 3 SMA. The extent to which the analysis of data on type 3 SMA should take into account additional confounders should be reviewed.

2. The importance of the various confounders should be adequately described for the different patient populations included in the real world data collection for the reassessment of the additional benefit of risdiplam.

3. The requirement of the G-BA for the adaptation of the study protocol (version 2.02) of the real world data collection for the reassessment of the additional benefit of onasemnogene abeparvovec regarding the significance of the confounder "age at symptom onset" should be taken into account.

Ad 1.

The search for prognostic factors and treatment effect modifiers that has been conducted and published as part of the Matching-Adjusted-Indirect-Comparison (MAIC) presented in the risdiplam benefit dossier also includes SMA type 3 patients (11). The identified confounders are *SMN2* copy number, baseline motor function, baseline bulbar function, baseline respiratory function, age of symptom onset, age at study enrollment in natural history studies, clinical disease severity and SMA type, the implementation of supportive care, disease duration before DMT initiation and age at treatment initiation. These are in agreement with the confounders identified for the real world data collection for the reassessment of of onasemnogene abeparvovec. The division pre-symptomatic vs. symptomatic is not relevant, as this aspect is already reflected in the definition of the patient populations to be analyzed (stratification factor).

Ad 2.

Please see Table 6: Confounders.

Ad 3.

Please see Table 6: Confounders.

Table 6: Confounders

Confounder (9)	Clinical relevance (9)	Included in study	Definition (9)	Operationalization in SMArtCARE eCRF	Applicable to analysis population
SMN2 copy number*	Very important	Yes	SMN2 copy number	Genetic Test Result: SMN2 copy number	All
Age at symptom onset	Less important	Yes	Age of symptom onset in months for symptomatic patients	Clinical Diagnosis: Age at symptom onset	SMA type 1, SMA type 2, SMA type 3
Age at treatment initiation	Very important	Yes	Age in weeks at treatment initiation	Registries, Clinical Trials: Age at visit AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN(Date of treatment)	Pre-symptomatic patients: directly SMA type 1, SMA type 2, SMA type 3: Derived (treatment delay defined as time from symptom onset to treatment initiation)
Nutrition support	Very important	Yes	Gastric tube or nasal feeding tube (exclusive/ supplemental/ no ne) at treatment initiation	Nutrition: Does the patient use a gastric or nasal feeding tube? AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN(Date of treatment)	SMA type 1, SMA type 2, SMA type 3
Ventilation support	Very important	Yes	Duration of ventilator use (nighttime/inter mittent/ permanent (≥16h/day) at treatment	Pulmonary: Does the patient receive ventilator support? = Yes AND Pulmonary: Time of	SMA type 1, SMA type 2, SMA type 3

Confounder (9)	Clinical relevance (9)	Included in study	Definition (9)	Operationalization in SMArtCARE eCRF	Applicable to analysis population
			initiation	ventilator use 1. Night (during sleep) 2. Intermittent day time and continuous at night 3. Continuous (>16h/day) AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	
Contractures	Less important	Yes	Contractures limiting function (yes/no) at treatment initiation	Clinical Examination: Are any contractures present? = Yes AND Registries, Clinical Trials: Type of limitation = Severe (imposing limits to function) AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	SMA type 1, SMA type 2, SMA type 3
Motoric function: Highest motor milestone (at treatment initiation)	Very important	Yes	Highest motor milestone at treatment initiation: None/n.a. Sitting without support Crawl on hands and knees Standing without support	Best current motor function: Best current motor function AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	All

Confounder (9)	Clinical relevance (9)	Included in study	Definition (9)	Operationalization in SMArtCARE eCRF	Applicable to analysis population
			Walking without support Climb stairs		
Motoric Function CHOP-INTEND	Very important	Yes	CHOP-INTEND score at treatment initiation	CHOP-INTEND: Score AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	Pre-symptomamatic patients, SMA type 1
Motoric Function: HFMSE score	Very important	Yes	Mean Hammersmith score treatment initiation	HFMSE: total AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	SMA type 2, SMA type 3
Ulnar CMAP (compound muscle action potential) (only for sensitivity analysis)	n.a.	Sensitivity analysis only	Ulnar CMAP at treatment initiation Response, amplitude > 1mV No response or response ≤ 1mV Unknown	Neurophysiology: CMAP amplitude (mV): Ulnar AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	All
*In the AbD to onasemnogene abeparvovec SMN2 copy number is used as a stratification factor					

8.7.5 Planned interim analyses and status reports

First status report (submission 6 months after study start):

Disposition, summaries of demographics / baseline characteristics, exposure and patient-related observation period will be analyzed as described in the SAP and will be presented in the status report. Further analyses might be conducted and presented if appropriate. The data cut for this analysis will be at study start (retrospective enrolled patients only).

Second status report and first interim analysis (submission 18 months after study start):

Disposition, summaries of demographics / baseline characteristics, exposure and patient-related observation period will be analyzed as described in the SAP. The primary endpoints (and secondary endpoints if appropriate) will be analyzed as described in the SAP. Module 4 of the dossier template will be used to submit the results. Based on this interim analysis, the sample size will be re-calculated using observed effect sizes and recruitment rates as assumptions. If the expected power is less than 60% for a primary endpoint (and relevant secondary endpoints) the enrollment might be stopped due to futility in the respective population. The data cut for this analysis will be 12 months after study start.

Third status report and second interim analysis (submission 30 months after study start):

Disposition, summaries of demographics / baseline characteristics, exposure and patient-related observation period will be analyzed as described in the SAP. The primary endpoints (and secondary endpoints if appropriate) will be analyzed as described in the SAP. Module 4 of the dossier template will be used to submit the results. If the expected power is less than 60% for a primary endpoint (and relevant secondary endpoints) the enrollment might be stopped due to futility in the respective population. The data cut for this analysis will be 24 months after study start.

8.8 DATA QUALITY ASSURANCE AND QUALITY CONTROL

The Marketing Authorization Holder (MAH) must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, and documentation of Institutional Review Board/Ethics Committee (IRB/EC) and governmental approval/notification (if necessary).

Chrestos, a Contract research Organization (CRO) commissioned by MAH, shall ensure that the datasets and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

Data not held within MAH systems will be periodically transferred electronically from SMArtCARE registry to Chrestos. SMArtCARE registry will comply with the MAH procedures as written in the contract regarding content, archiving and records management of process documents.

Retention of Records

Archiving at the study site has to be for at least five years after final study report or first publication of study results, whichever comes later; or according to local regulation.

Records and documents pertaining to the conduct of this study must be retained by SMArtCARE for at least 25 years after completion of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the SMArtCARE. Written notification should be provided to the SMArtCARE prior to transferring any records to another party or moving them to another location.

8.9 LIMITATIONS OF THE RESEARCH METHOD

As any observational research this study is subject to a risk of bias. The data collected in this study is dependent on routine clinical practice and the level of data collected may differ between participating sites. Consequently, the data obtained in this study will be less comprehensive than data obtained from a prospective, interventional clinical study.

To minimize the bias, certain measurements will be performed (detailed description in the SAP). Missing confounder values will be addressed (complete case, multiple imputation or exclusion of variables). Propensity score weighting will be applied to adjust for differences in the confounder variables between the treatment groups. Data reporting will be conducted in a consistent way to avoid bias in the data collection process.

9. PROTECTION OF HUMAN PATIENTS

Data will be collected as part of routine clincal practice. The responsibility lies with the treating physician.

9.1 INFORMED CONSENT

The patients have explicitly agreed to any secondary use of their data.

9.2 CONFIDENTIALITY

The SMArtCARE registry maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in datasets that are transmitted to any SMArtCARE registry location. Only aggregated data from the registry are available and are used in this study.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or

separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, CSG monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

9.3 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for Good Pharmacoepidemiological Practice (GPP) published by the International Society of Pharmacoepidemiology (ISPE) and the laws and regulations of the country in which the research is conducted.

9.4 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol and relevant supporting information must be submitted to the EC, and reviewed and approved by the EC before the study is initiated.

SMArtCARE is responsible for providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS

All adverse events extracted from the data source for the study as specified in the protocol will be summarized as part of any interim analyses and in the final value dossier submission in scope of the reassessment of the additional benefit of risdiplam by G-BA (4).

11. PLANS FOR DISSEMINATION AND COMMUNICATION OF STUDY RESULTS

Study results will be published in scope of the reassessment of the additional benefit of risdiplam by G-BA (4).

12. REFERENCES

1. Roche. Beratungsantrag zum Wirkstoff Risdiplam in dem Anwendungsgebiet Spinale Beratungsantrag zum Wirkstoff Risdiplam in dem Anwendungsgebiet Spinale Muskelatrophie - Anwendungsbegleitende Datenerhebung; 19.8.2022.
2. G-BA. Niederschrift (finale Fassung) zum Beratungsgespräch gemäß § 8 AM-NutzenV Beratungsanforderung 2022-B-215 Risdiplam zur Behandlung der 5q-assiziierten spnalen Muskelatrophie (SMA); 28.11.2022.
3. IQWiG. A21-131 - Anwendungsbegleitende Datenerhebung Risdiplam - Rapid Report - Version 1.0: Stand: 15.02.2022; 2022.
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5. G-BA. Zusammenfassende Dokumentation über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Risdiplam (Spinale Muskelatrophie) Forderung einer anwendungsbegleitenden Datenerhebung und von Auswertungen; 21.7.2022.
6. G-BA. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über die Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Risdiplam (spinale Muskelatrophie); Forderung einer anwendungsbegleitenden Datenerhebung und von Auswertungen: Vom 21. Juli 2022; 2022.
7. Ribero VA, Daigl M, Martí Y, Gorni K, Evans R, Scott DA et al. How does risdiplam compare with other treatments for Types 1-3 spinal muscular atrophy: a systematic literature review and indirect treatment comparison. J Comp Eff Res; 11(5):347–70, 2022. doi: 10.2217/cer-2021-0216.
8. Jacob Cohen, Hrsg. Statistical Power Analysis for the Behavioral Sciences (Revised Edition): The t Test for Means; 1977.
9. Novartis. Routine data collection and evaluations of onasemnogene abeparvovec in Germany: Study Protocol; Protocol Number: COAV101A1DE01; Version: 2.02; November 18, 2021; 2021.
10. Roche. Dossier zur Nutzenbewertung gemäß § 35a SGB V, Risdiplam (Evrysdi®), Modul 4A, 5q-assoziierte spinale Muskelatrophie (SMA) bei Patienten ab einem Alter von zwei Monaten, mit einer klinisch diagnostizierten SMA Typ I, Typ II oder Typ III oder mit einer bis vier Kopien des SMN2-Gens: Medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen; 2021.

11. Baranello G, Darras BT, Day JW, Deconinck N, Klein A, Masson R et al. Risdiplam in Type 1 Spinal Muscular Atrophy. N Engl J Med; 384(10):915–23, 2021. doi: 10.1056/NEJMoa2009965.
12. Baranello G, Gorni K, Daigl M, Kotzeva A, Evans R, Hawkins N et al. Prognostic Factors and Treatment-Effect Modifiers in Spinal Muscular Atrophy. Clin Pharmacol Ther, 2021. doi: 10.1002/cpt.2247.

Appendix 1
List of Stand-Alone Documents Not Included in the Protocol

STATISTICAL ANALYSIS PLAN

STUDY TITLE:	**EVALUATION OF A REAL WORLD DATA COLLECTION FOR THE REASSESSMENT OF THE ADDITIONAL BENEFIT OF EVRYSDI® (RISDIPLAM)**
STUDY NUMBER:	ML44661
VERSION NUMBER:	1.0
ROCHE COMPOUND(S):	EVRYSDI® (RISDIPLAM)
PLAN PREPARED BY:	[redacted]
MARKETING AUTHORIZATIONHOLDER (MAH):	Roche Registration GmbH
LEGAL REGISTERED ADDRESS:	Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany
DATE FINAL:	See electronic date stamp above

STATISTICAL ANALYSIS PLAN APPROVAL

Sponsor Signature(s) and Date(s): 10 August 2023

[redacted]

CONFIDENTIAL

STATISTICAL ANALYSIS PLAN VERSION HISTORY

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	see electronic date stamp on title page	1.0, 31-Jul-2023

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

Initial version.

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LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
AE	adverse event
AR	autoregressive
BSID	Bayley scale of infant development
CHOP-INTEND	Children's hospital of Philadelphia infant test of neuromuscular disorders
eCRF	electronic case report form
EDC	electronic data capture
FAS	full analysis set
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HFMSE	Hammersmith functional motor scale expanded
HR	hazard ratio
ICH	International Council on Harmonization
IPTW	inverse probability of treatment weights
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MICE	multiple imputation by chained equations
MMRM	mixed model repeated measures
NBS	newborn screening
RULM	Revised upper limb module
SAE	serious adverse events
SAP	Statistical Analysis Plan
SD	standard deviation
SDV	source data verification
SMA	spinal muscular atrophy
SMN 1/2	survival motor neuron 1/2
SmPC	summary of product characteristics
SOP	standard operating procedures
WHO	World health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analysis of the data collected within the framework of study ML44661. It is based on the final study protocol, version 1.0, dated 31 Jul 2023 and follows the principles of the Guideline ICH E9. It gives all details for the statistical analysis of this study. The statistical analysis will be carried out according to Chrestos standard operating procedures (SOP).

The SAP contains a more technical and detailed elaboration of the procedures described in the study protocol for conducting the statistical analyses.

This SAP was written and finalized prior to database hard lock and data analysis.

Spinal muscular atrophy (SMA) is a rare autosomal recessive neuromuscular disorder characterized by the progressive loss of proximal motor neurons leading to muscle weakness and profound neuromotor disability. It is primarily characterized by degeneration of the anterior horn cells of the spinal cord resulting in muscle atrophy and proximal muscle weakness. It is caused by a homozygous deletion in the survival motor neuron 1 (*SMN1*) gene on chromosome 5q13. The severity of the disease is highly variable and correlates with the age of onset and *SMN2* copy number. For classification purposes, patients are usually categorized into three main subtypes based on clinical criteria, including achieving (or failing to achieve) physical motor milestones, age of onset, and expected life span:

- Type 1 SMA (severe infantile type with onset before 6 months of age; infants never sit without support, with death due to respiratory distress usually within 2 years),
- Type 2 SMA (intermediate chronic infantile type with onset after the age of 6 months, children unable to stand or walk without support),
- Type 3 SMA (chronic juvenile type with onset around the age of 18 months, children able to walk until the disease progresses)

For the best possible development or preservation of motor function, it is particularly important that treatment is started as early as possible. In October 2021, the newborn screening (NBS) for SMA was therefore implemented in Germany. This will allow newborns with SMA to be diagnosed immediately after birth. One consequence of the introduction of the NBS for SMA is that fewer symptomatic patients will be diagnosed in the long term.

In all types of SMA, as the disease progresses, clinical symptoms include hypotonia, symmetrical muscle weakness and atrophy (predominantly of the proximal muscles of the shoulder and pelvic girdle), diminished or absent deep tendon reflexes, tremor of fingers and hands, fasciculation of the tongue muscles, and hyporeflexia with orthopedic deformities (contractures, scoliosis). Progressive respiratory failure and frequent pulmonary infections and superinfections are common in Types 1 and 2 SMA. Other common comorbidities include failure to thrive, pneumonia, osteopenia and osteoporosis

with pathological fractures, poor cough and secretion clearance, reduced vital capacity, gastroesophageal dysmotility, urinary incontinence, hip dislocation, and joint and muscle pain.

On the basis of the ongoing or completed studies on risdiplam considered for approval, the) identified evidence gaps, particularly comparative data of a treatment with risdiplam versus existing appropriate therapy alternatives are missing for patients.

Thus, the G-BA initiated a procedure to require an evaluation of a real world data collection for the reassessment of the additional benefit of risdiplam.

1.1 OBJECTIVES AND ENDPOINTS AND ESTIMANDS

1.1.1 Primary Objectives and corresponding Estimands

Table 1: Primary Objectives / Estimands

Primary Objective	Estimand Definition
To evaluate the safety of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as the number of unplanned hospitalization over time	Population: Presymptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene as defined by the study inclusion and exclusion criteria (see protocol for details) Endpoint: Number of unplanned hospitalization over time Treatment (see protocol for details): Experimental arm: Risdiplam according to Summary of Product Characteristics (SmPC) Control arm: Nusinersen or onasemnogene abeparvovec according to SmPC Intercurrent events and handling strategies: Early discontinuation from study treatment: Treatment-policy strategy Treatment switch: Hypothetical strategy Population-level summary: Rate ratio
To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as time to death or permanent ventilation	Population: Symptomatic patients with a clinically diagnosed SMA type 1 (see protocol for details) Endpoint: Time to death or permanent ventilation (> 16 hours/day, for longer than 21 consecutive days) Treatment: as defined above Intercurrent events and handling strategies: Early discontinuation from study treatment: Treatment-policy strategy Treatment switch: Treatment-policy strategy Population-level summary: Hazard ratio
To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec	Population: Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene (see protocol for details). Only patients with

Primary Objective	Estimand Definition
measured as change from baseline of RULM total score	a baseline value and a value at month 12 after treatment start are included. Endpoint: Change from baseline of RULM total score at 12 months after treatment start Treatment: as defined above Intercurrent events and handling strategies: Early discontinuation from study treatment: Treatment-policy strategy Treatment switch: Treatment-policy strategy Population-level summary: Cohen's d
To evaluate the efficacy of risdiplam compared to nusinersen or onasemnogene abeparvovec measured as change from baseline of RULM total score	Population: Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene (see protocol for details). Only patients with a baseline value and a value at month 12 after treatment start are included. Endpoint: as defined above Treatment: as defined above Intercurrent events and handling strategies: as defined above Population-level summary: as defined above

Abbreviations; RULM = revised upper limb module

1.1.2 Secondary Objectives and Endpoints

Table 2: Secondary Endpoints

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Time to death or permanent ventilation[a] Time to death Time to permanent ventilation[a] Time to any respiratory support	Time to death Time to permanent ventilation[a] Time to any respiratory support	Time to death or permanent ventilation[a] Time to death Time to permanent ventilation[a] Time to any respiratory support	Time to death or permanent ventilation[a] Time to death Time to permanent ventilation[a] Time to any respiratory support
Proportion of patients reaching the WHO motor development milestone "sitting without support" at an appropriate age Proportion of patients reaching the WHO motor development milestone "walking without support" at an appropriate age	Proportion of patients reaching the WHO motor development milestone "sitting without support" at an appropriate age Proportion of patients reaching the WHO motor development milestone "walking without support" at an appropriate age	Proportion of patients reaching the WHO motor development milestone "walking without support" at an appropriate age Proportion of patients reaching the WHO motor development milestone "walking without support"	-

Pre-symptomatic patients	**Patients with SMA Type 1**	**Patients with SMA Type 2**	**Patients with SMA Type 3**
Proportion of patients reaching the WHO motor development milestone “walking without support”	Proportion of patients reaching the WHO motor development milestone “walking without support”		
-	Proportion of patients with a CHOP-INTEND score ⩾ 40 at 12 months of age Change from baseline in CHOP-INTEND total score at 12, 24 and 36 months of age	Change from baseline in HFMSE total score at 12, 24, 36 months after treatment start Change from baseline in RULM total score at 24 and 36 months after treatment start	Change from baseline HFMSE total score 12, 24, 36 months after treatment start Change from baseline in RULM total score at 24 and 36 months after treatment start
Change from baseline in the total score of the Bayley III scores in the subscales “Gross Motorskills” at 12, 24 and 36 months of age Proportion of patients with age-appropriate Bayley III scores in the subscales “Expressive Language” and “Receptive Language” at 12, 24 and 36 months of age	Change from baseline in the total score of the Bayley III scores in the subscales “Gross Motorskills” at 12, 24 and 36 months of age Proportion of patients with age-appropriate Bayley III scores in the subscales “Expressive Language” and “Receptive Language” at 12, 24 and 36 months of age	-	For ambulatory patients: Proportion of patients with an improvement in walking distance > 30m at 12, 24 and 36 months after treatment start Proportion of patients with a worsening in walking distance > 30m at 12, 24 and 36 months after treatment start Change from baseline in walking distance at 12, 24 and 36 months after treatment start Relative change from baseline in walking distance at 12, 24 and 36 months after treatment start
Proportion of patients with deterioration of swallowing function at 12, 24, 36 months of age Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months of age	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months of age Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months of age	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after treatment start Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after treatment start	Proportion of patients with deterioration of swallowing function at 12, 24, 36 months after treatment start Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months after treatment start
Time to first documentation of	Time to first documentation of	Time to first documentation of	Time to first documentation of

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
severe scoliosis[b] or orthopedic surgery Time to first documentation of severe scoliosis[b] Time to first documentation of orthopedic surgery	severe scoliosis[b] or orthopedic surgery Time to first documentation of severe scoliosis[b] Time to first documentation of orthopedic surgery	severe scoliosis[b] or orthopedic surgery Time to first documentation of severe scoliosis[b] Time to first documentation of orthopedic surgery	severe scoliosis[b] or orthopedic surgery Time to first documentation of severe scoliosis[b] Time to first documentation of orthopedic surgery
Proportion of patients with regular pain at 12, 24, 36 months of age Proportion of patients experiencing fatigue at months 12, 24, 36 months of age	Proportion of patients with regular pain at 12, 24, 36 months of age Proportion of patients experiencing fatigue at 12, 24, 36 months of age	Proportion of patients with regular pain at 12, 24, 36 months after treatment start Proportion of patients experiencing fatigue at 12, 24, 36 months after treatment start	Proportion of patients with regular pain at 12, 24, 36 months after treatment start Proportion of patients experiencing fatigue at 12, 24, 36 months after treatment start
Number of planned hospitalizations over time (excluding hospitalizations for SMA treatment administration)	Number of planned hospitalizations over time (excluding hospitalizations for SMA treatment administration)	Number of planned hospitalizations over time (excluding hospitalizations for SMA treatment administration)	Number of planned hospitalizations over time (excluding hospitalizations for SMA treatment administration)

[a] permanent ventilation is defined as ventilation > 16 hours/day, for longer than 21 consecutive days, [b] severe scoliosis is defined as a Cobb angle $\geqslant 40^{\circ}$

Abbreviations: CHOP-INTEND – Children's hospital of Philadelphia infant test of neuromuscular disorders, HFMSE – Hammersmith functional motor scale expanded, WHO – World Health Organization

Table 3: Safety Endpoints

Pre-symptomatic patients	Patients with SMA Type 1	Patients with SMA Type 2	Patients with SMA Type 3
Time to first SAE Time to first AE leading to hospitalization Time to first selected SAEs[a]	Number of unplanned hospitalizations over time Time to first SAE Time to first AE leading to hospitalization Time to first selected SAEs[a]	Number of unplanned hospitalizations over time Time to first SAE Time to first AE leading to hospitalization Time to first selected SAEs[a]	Number of unplanned hospitalizations over time Time to first SAE Time to first AE leading to hospitalization Time to first selected SAEs[a]

[a] selected SAEs are: retinopathy, effect on epithelial tissue, thrombocytopenia, nephropathy, hydrocephalus, hepatopathy, cardiac events, sensory neuropathy

Abbreviations: AE – adverse event, SAE – serious adverse event

1.2 STUDY DESIGN

This study is a registry-based, comparative, non-interventional, multicentric, multinational, open-label study. As the treatment start date differs, there will be simultaneously enrolled controls and not simultaneously enrolled controls.This registry-based study is based on the data of the SMArtCARE registry. The SMArtCARE project (www.smartcare.de) provides a platform to collect longitudinal clinical routine data on SMA patients in Germany, Austria, and Switzerland.

The registry collects data from SMA patients since 2018. Retrospective data for patients treated with nusinersen will be analyzed since the beginning of the registry (May 30, 2017 at the earliest), data for patients treated with onasemnogene abeparvovec since approval in 2020 (May 18, 2020 at the earliest) and data for patients treated with risdiplam since approval in 2021 (March 26, 2021 at the earliest). Details of the registry are given in the SMArtCARE protocol (1).

Start Date of Study:

The planned start date is Q4/2023 after confirmation of the submitted study protocol and statistical analysis plan by the G-BA.

Interim Analyses

Interim analyses are planned 12 and 24 months after start of the study and will be handed in to G-BA latest after 18 and 30 months after the start of the study. Based on these interim analysis, a final sample size estimate will be made using more precise effect assumptions. Final analysis will take place in January 2026.

End of Study:

The planned end date is January 01, 2026. Data that is documented in the study database after that time point will not be taken into account.

1.2.1 Data Monitoring

Data used for this study are collected and stored in the SMArtCARE registry.

The clinical sites are responsible for implementing and maintaining quality assurance and quality control systems with written SOPs. Data are entered at the site into an electronic case report form (eCRF). SMArtCARE uses SAS software to review the data for completeness, consistency and plausibility. All programs which can be used to influence data or data quality are validated.

SMArtCARE uses an electronic data capture (EDC) system (1). This system is implemented and maintained by Open Applications Consulting Ltd. SAS software is used to review the data for completeness, consistency and plausibility. Query resolution processes are implemented. All programs which can be used to influence data or data

quality are validated (e.g. data validation programs, programs for CRF/query tracking, programs for import of EDC data into SAS or for import of external data, etc.).

Source data verification (SDV) is performed by SMArtCARE according to protocol in order to verify the accuracy and completeness of the entries on the eCRF by comparing them with the source data, and to ensure and increase the quality of the data (SMArtCARE protocol (1)).

In addition, SDV for 100% of patients for the primary endpoint and for at least 10% of randomly selected patients for all other endpoints over the period since the start of data collection will be performed by Clinische Studien Gesellschaft (CSG).

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene.

The comparison of the number of unplanned hospitalizations over time between both arms will be performed using a negative binomial regression model. This analytic model estimates the rate ratio, λ_e / λ_c, which quantifies the risk of unplanned hospitalization associated with risdiplam (λ_e) in comparison to nusinersen or onasemnogene abeparvovec (λ_c). Statistical significance is controlled at the 1-sided, 0.025 alpha (α) level. The Wald test will be performed via the following hypothesis:

$$H_0: \text{Rate Ratio} \geq 0.5 \text{ versus } H_1: \text{Rate Ratio} < 0.5$$

Symptomatic patients with a clinically diagnosed SMA type 1:

Treatment comparison of the time to death or permanent ventilation will be based on the Cox-regression test. Statistical significance is controlled at the 1-sided, 0.025 alpha (α) level. The shifted null and alternative hypotheses can be phrased as:

$$H_0: \text{Hazard Ratio} \geq 0.5 \text{ versus } H_1: \text{Hazard Ratio} < 0.5$$

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the SMN2 gene:

The Change from baseline of RULM total score change from baseline endpoints a mixed model repeated measures (MMRM) analysis will be performed and Cohen's d will be estimated as a measure of the effect size. Statistical significance is controlled at the 1-sided, 0.025 alpha (α) level. The hypothesis to be tested is that the difference in the mean change from baseline in the total RULM score at Month 12 between risdiplam and nusinersen or onasemnogene abeparvovec (δ) is:

$$H_0: \delta \leq 0.5 \text{ versus } H_1: \delta > 0.5$$

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:

See SMA type 2 and up to three copies of the *SMN2* gene.

2.2 SAMPLE SIZE DETERMINATION

Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene.

The current evidence for pre-symptomatic patients treated with risdiplam, nursinersen or onasemnogene abeparvovec is still limited. There is no evidence to date, for making assumptions on differences between treatments. It is therefore not possible to calculate the sample size yet.

The primary endpoint for pre-symptomatic patients is the number of unplanned hospitalization over time. A negative binomial regression model will be used to estimate the rate ratio. Based on the first interim analyses (see Section 4.7.1), the sample size for a shifted null hypothesis (RR ≥ 0.5), an one-sided alpha of 2.5% and a power of 80% will be calculated using the observed effect size.

Symptomatic patients with a clinically diagnosed SMA type 1:

For patients with a clinically diagnosed SMA type 1, the sample size estimation is based on the endpoint time to death or permanent ventilation.

The probability of the event death or permanent ventilation of patients treated with nusinersen is assumed to be 40 % (2), while the probability for patients treated with onasemnogene abeparvovec is assumed to be 9 % (3). Since the distribution between patients receiving nusinersen and patients receiving onasemnogene abeparvovec is not yet known, assumptions for the probability of the comparison arm cannot be derived.

To be able to provide a rough sample size as a first orientation, a probability of the event death or permanent ventilation of 22% for the comparison arm and an effect of a hazard ration (HR) = 0.45 in favor of risdiplam will be assumed. The assumptions of an one-sided alpha of 2.5 %, a power of 80 %, an observation period of 36 months and a shifted null hypothesis (HR ≥ 0.5) are leading to 2828 events and 8839 patients per treatment arm.

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene

In the population of patients with clinically diagnosed SMA type 2, sample size estimation is based on the endpoint change from baseline in RULM total score.

Based on the CHERISH study, one can expect a change from baseline to month 12 of 3.7 points in the RULM total score for patients treated with nusinersen (4). At the time of submission, there is no data published showing the performance in RULM total score for

onasemnogene abeparvovec. For orientation, a change of 3.7 points in RULM total score is assumed for the comparison arm.

To be able to provide a rough sample size for a first orientation an effect size of 0.55 in favor of risdiplam with and standard deviation of 11 will be assumed (change of 9.75 points in RULM total score for the risdiplam arm). The assumptions of an one-sided alpha of 2.5%, a power of 80% and a shifted null hypothesis (Cohen's d ≤ 0,5) are leading to 6280 patients per group. The threshold was chosen with regard to Cohen's rule of thumb for interpreting results (medium effect = 0.5) (5).

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene

Currently data available on SMA type 3 patients treated with nursinersen or onasemnogene abeparvovec is not sufficient to calculate the sample size.

The primary endpoint for the pre-symptomatic patients is the change from baseline in RULM total score. Based on the first interim analyses, the sample size will be calculated for a shifted null hypothesis (Cohen's d ≤ 0,5), an one-sided alpha of 2.5% and a power of 80% using the observed effect size.

3. ANALYSIS SETS

The participant analysis sets for the purposes of analyses are defined in Table 4.

Table 4 Participant Analysis Sets

Participant Analysis Set	Description
FAS	All enrolled participants; participants will be included in the analyses according to the treatment they received at enrollment.

FAS = full analysis set

4. STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

All clinical data will be downloaded and transferred into SAS® datasets. All statistical analyses will be carried out using SAS®, version 9.4 or higher and R, version 4.3.0 or higher.

If not specified otherwise, descriptive statistics will be presented by treatment group and time point, where appropriate. For continuous data the sample size, mean, standard deviation (SD), median, range (min, max) and interquartile range (Q1, Q3) will be presented. Categorical data will be displayed by absolute and relative frequencies (percentages). Percentages will be based on all non-missing values. Missing categories

might be displayed in addition (only by absolute frequencies). Exceptions to this rule are to be specified explicitly. In any case, the percent basis will be specified in a table footnote. Percentages will be rounded to one decimal place.

For hypothesis testing, statistical significance is controlled at the 1-sided, 0.025 alpha level and the shifted null hypothesis. Point estimators will be presented with 2-sided 95% confidence intervals.

For responder and change from baseline analyses planned to be conducted at a certain month of age/after treatment start (e.g. at 12m, 24m, 36m), the closest assessment within a time frame of ±2 months will be used for the analysis, unless otherwise specified. This time frame considers that visits take place every four months. If there was no assessment within this time frame, the value is assumed to be missing.The visit that will be used as baseline visit has to take place between six weeks before and three weeks after the first administration.

Every switch between the study medications risdiplam, nusinersen and onasemnogene abeparvovec will be considered a treatment switch, including switches between nusinersen and onasemnogene abeparvovec within the control arm.

4.1.1 Confounder

Confounders have been identified in advance through systematic research, as described in the Protocol Section 8.7.4. The following confounders will be considered.

Table 5: Confounders

Confounder (6)	Clinical relevance (6)	Included in study	Definition (6)	Operationalization in SMArtCARE eCRF	Applicable to analysis population
SMN2 copy number*	Very important	Yes	SMN2 copy number	Genetic Test Result: *SMN2* copy number	All
Age at symptom onset	Less important	Yes	Age of symptom onset in months for symptomatic patients	Clinical Diagnosis: Age at symptom onset	SMA type 1, SMA type 2, SMA type 3
Age at treatment initiation	Very important	Yes	Age in weeks at treatment initiation	Registries, Clinical Trials: Age at visit AT	Pre-symptomatic patients: directly SMA type 1, SMA type 2, SMA type 3: Derived (treatment delay defined as time from symptom onset to treatment initiation)

Confounder (6)	Clinical relevance (6)	Included in study	Definition (6)	Operationalization in SMArtCARE eCRF	Applicable to analysis population
				Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN(Date of treatment)	
Nutrition support	Very important	Yes	Gastric tube or nasal feeding tube (exclusive/ supplemental/ no ne) at treatment initiation	Nutrition: Does the patient use a gastric or nasal feeding tube? AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN(Date of treatment)	SMA type 1, SMA type 2, SMA type 3
Ventilation support	Very important	Yes	Duration of ventilator use (nighttime/intermittent/ permanent (≥16h/day) at treatment initiation	Pulmonary: Does the patient receive ventilator support? = Yes AND Pulmonary: Time of ventilator use 1. Night (during sleep) 2. Intermittent day time and continuous at night 3. Continuous (>16h/day) AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	SMA type 1, SMA type 2, SMA type 3

Confounder (6)	Clinical relevance (6)	Included in study	Definition (6)	Operationalization in SMArtCARE eCRF	Applicable to analysis population
Contractures	Less important	Yes	Contractures limiting function (yes/no) at treatment initiation	Clinical Examination: Are any contractures present? = Yes AND Registries, Clinical Trials: Type of limitation = Severe (imposing limits to function) AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	SMA type 1, SMA type 2, SMA type 3
Motoric function: Highest motor milestone (at treatment initiation)	Very important	Yes	Highest motor milestone at treatment initiation: None/n.a. Sitting without support Crawl on hands and knees Standing without support Walking without support Climb stairs	Best current motor function: Best current motor function AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	All
Motoric Function CHOP-INTEND	Very important	Yes	CHOP-INTEND score at treatment initiation	CHOP-INTEND: Score AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	Pre-symptomamatic patients, SMA type 1
Motoric Function: HFMSE score	Very important	Yes	Mean Hammersmith score treatment initiation	HFMSE: total AT	SMA type 2, SMA type 3

Confounder (6)	Clinical relevance (6)	Included in study	Definition (6)	Operationalization in SMArtCARE eCRF	Applicable to analysis population
				Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	
Ulnar CMAP (compound muscle action potential) (only for sensitivity analysis)	n.a.	Sensitivity analysis only	Ulnar CMAP at treatment initiation Response, amplitude > 1mV No response or response ≤ 1mV Unknown	Neurophysiology: CMAP amplitude (mV): Ulnar AT Registries, Clinical Trials: Visit date = Risdiplam/ nusinersen/ onasemnogene abeparvovec: MIN (Date of treatment)	All
*In the AbD to onasemnogene abeparvovec *SMN2* copy number is used as a stratification factor					

4.1.2 Propensity Score

To adjust for differences in the confounder variables between the treatment groups, propensity score weighting will be applied if sufficient overlap and balance between the scores is given, as detailed below.

The propensity score is the probability that a patient was assigned to a treatment conditional on the observed baseline covariates, $e(x) = \mathrm{pr}(z = 1 \mid x)$, and will be estimated using logistic regression (7).

After calculation of propensity scores for each patient, the overlap of propensity scores between the treatment groups will be evaluated. To date, there is no established criterion for sufficient overlap. Thus an overlap is considered sufficient if the overlap of propensity score distributions between the treatment groups is >50%, which is in accordance with the rules defined in the onasemnogene abeparvovec study protocol (8). If applicable guidelines are available at a later date, the criterion used might be amended. If the overlap is not sufficient for applying propensity score methods, only naïve comparisons will be performed.

In case of sufficient overlap, weights will be calculated based on the propensity scores. Two weighting methods will be considered, inverse probability of treatment weights (IPTW) and fine stratification weights (9). IPTW defines the weights for treated patients as $1/PS$ and weights for patients in the comparison arm as $1/(1 - PS)$. To avoid extreme

weights, propensity scores above 0.95 and below 0.05 will be truncated and set to the respective threshold. For fine stratification weights, the propensity scores are used to define fine stratums (10). A fixed width of 0.1 will be used to define stratums, resulting in 10 stratums total. Weights are then calculated based on the total number of patients within each stratum, for all stratums with at least one treated and one reference patient, and are defined as ($N_{\text{total in PS stratum i}}$ / N_{total}) / ($N_{\text{exposed in PS stratum i}}$ / $N_{\text{total exposed}}$) for treated patients, and as ($N_{\text{total in PS stratum i}}$ / N_{total}) / ($N_{\text{reference in PS stratum i}}$ / $N_{\text{total reference}}$) for the comparison.

For both weighting methods, the balance between treatment groups for each confounder variable will be evaluated by calculating standardized differences after weighting. The balance is sufficient for performing propensity score analyses if $abs(SMD) < 0.2$ is given for each confounder. Otherwise, only naïve comparisons are performed. If both weighting methods show sufficient balance between the treatment groups, the weighting method with the best overall confounder balance after weighting will be used for all analyses. As an overall measure of balance, the post-weighting C statistic can be used (11).

Baseline characteristics will be described for the population after propensity score weighting.

4.1.3 Handling of Missing Data

For efficacy variables, an incomplete event date will be replaced by the last day of the month, assuming the month and year are known. For safety variables, an incomplete event date will be replaced by the first day of the month (assuming the month and year are known), unless there is evidence that the patient was event-free within that month, in which case the date the patient was last known to be event-free within that month will be used as the event date. If the month is missing, the date the patient was last known to be event-free will be used.

The Sponsor will emphasize to investigators the importance of collecting complete data, both for outcome measures and for the confounder variables at baseline required for the propensity score analysis described above.

In case missing data are still present in the confounder variables, the following steps will be performed.

4.1.3.1 Descriptive Analysis of Missing Data

The patterns of missing data for the confounder variables will be summarized with upset-plots by population and treatment group. Furthermore, the number of complete cases will be summarized.

Depending on the percentage of missing data the method to deal with it will be chosen, as described below.

4.1.3.2 Dealing with Missing Data

There are different methods to deal with missing data. For this study complete case analysis and multiple imputation are considered. It is planned to align with the rules of thumb described by Jakobsen et al. (12). According to these rules missing data can be ignored, if the proportion of missing data is below 5%. On the other hand, it is not recommended to use multiple imputation, if more than 40% of the data is missing. With multiple confounder variables there are two ways to assess the proportion of missing data, at subject level and at variable level. It is planned to focus on the subject level first. If 95% or more of the subjects have no missing confounder variables the complete case analysis will be used, meaning that only patients without missing confounder variables will be included in the analysis. Otherwise the percentages of subjects with missing data per confounder variable will be considered. All variables with an amount of missing data below 40% percent will be included in the multiple imputation approach (described below). Variables with more than 40% of subjects with missing data are not imputed at all and are not used as confounder.

4.1.3.3 Multiple Imputation

The confounder variables to be included in the multiple imputation are selected as described before. The missing variables will be imputed by non-missing baseline covariates using the multiple imputation by chained equations (MICE, 13) algorithm. For numeric variables the Predictive mean matching method is used and for factorial variables the Logistic regression method (for 2 factors), the Multinomial logit model (for >2 factors) or the ordered logit model (for >2 ordered factors) is used.

1000 imputed datasets will be generated. For each dataset, propensity scores will be estimated using logistic regression, as described above. For each patient, propensity scores will be averaged across all imputed datasets, following the across-approach previously described (14, 15, 16). Based on the averaged propensity scores, the overlap between treatment groups will be evaluated, weights will be generated if appropriate and the balance of confounder variables will be evaluated (Section 4.1.2). All statistical analyses described in Sections 4.2 - 4.5 will be conducted with the chosen weights.

4.2 PRIMARY ENDPOINT ANALYSIS

4.2.1 Definition of Primary Enpoints

Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene:

The primary endpoint is the number of unplanned hospitalization over time. The primary estimand is defined as follows:

- Population: Presymptomatic patients with a 5q associated SMA and up to three copies of the *SMN2* gene as defined by the study inclusion and exclusion criteria (see Section 8.2.1 of the protocol)
- Endpoint: number of unplanned hospitalization over time

- Treatment (see Section 8.2.2 of the protocol):
  - Experimental arm: Risdiplam according to SmPC
  - Control arm: Nusinersen or onasemnogene abeparvovec according to SmPC
- Intercurrent events and handling strategies:
  - Early discontinuation from study treatment: Treatment-policy strategy
  - Treatment switch: Hypothetical strategy
- Population-level summary: Rate ratio

Symptomatic patients with a clinically diagnosed SMA type 1:

The primary endpoint is the time to death or permanent ventilation. The primary estimand is defined as follows:

- Population: Symptomatic patients with a clinically diagnosed SMA type 1 (see Section 8.2.1of the protocol)
- Endpoint: Time to death or permanent ventilation (> 16 hours/day, for longer than 21 consecutive days)
- Treatment (see Section 8.2.2 of the protocol):
  - Experimental arm: Risdiplam according to SmPC
  - Control arm: Nusinersen or onasemnogene abeparvovec according to SmPC
- Intercurrent events and handling strategies:
  - Early discontinuation from study treatment: Treatment-policy strategy
  - Treatment switch: Treatment-policy strategy
- Population-level summary: hazard ratio

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene:

The primary endpoint is the change from baseline of RULM total score at 12 months after treatment start. The primary estimand is defined as follows:

- Population: Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the *SMN2* gene (see Section 8.2.1 of the protocol). Only patients with a baseline value and a value at month 12 after treatment start are included.
- Endpoint: Change from baseline of RULM total score at 12 months after treatment start
- Treatment (see Section 8.2.2 of the protocol):
  - Experimental arm: Risdiplam according to SmPC
  - Control arm: Nusinersen or onasemnogene abeparvovec according to SmPC
- Intercurrent events and handling strategies:

  - Early discontinuation from study treatment: Treatment-policy strategy
  - Treatment switch: Treatment-policy strategy
- Population-level summary: Cohen's d

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:

The primary endpoint is the change from baseline of RULM total score at 12 months after treatment start. The primary estimand is defined as follows:

- Population: Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene (see Section 8.2.1 of the protocol). Only patients with a baseline value and a value at month 12 after treatment start are included.
- Endpoint: Change from baseline of RULM total score at 12 months after treatment start
- Treatment (see Section 8.2.2 of the protocol):
  - Experimental arm: Risdiplam according to SmPC
  - Control arm: Nusinersen or onasemnogene abeparvovec according to SmPC
- Intercurrent events and handling strategies:
  - Early discontinuation from study treatment: Treatment-policy strategy
  - Treatment switch: Treatment-policy strategy
- Population-level summary: Cohen's d

Table 6: Operationalization of primary endpoints in SMArtCARE eCRF

Primary Endpoint	Fields of SMArtCARE eCRF
Pre-symptomatic patients Number of unplanned hospitalization over time	• Nusinersen/onasemnogene abeparvovec/risdiplam: 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: Start date
Patients with SMA Type 1 Time to death or permanent ventilation (> 16 hours/day, for longer than 21 consecutive days)	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • End of data collection: Date of death • Medical assessment: Visit date • Medical assessment: Start of ventilator use • Medical assessment: Ongoing use of ventilator? • Medical assessment: End of ventilator use • Medical assessment: Time of ventilator use = Continuous (>16h/day)
Patients with SMA Type 2	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • RULM: Date of assessment

Change from baseline of RULM total score at 12 months after treatment start	• RULM: Total RULM score
Patients with SMA Type 3 Change from baseline of RULM total score at 12 months after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • RULM: Date of assessment • RULM: Total RULM score

4.2.2 Main Analytical Approach for Primary Endpoint(s)

Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the SMN2 gene:

The rationale of using FAS population and hypothetical strategy for the primary estimand is to provide a picture of a treatment effect on the safety foreseen in clinical practice when treatment is actually administered. Additional analysis applying treatment strategy to treatment switches (intercurrent events) will also be provided (details see Section 4.2.3).

The main analysis for the primary endpoint will be performed using a negative binomial regression model, which accounts for different follow-up times, with the patient's number of unplanned hospitalizations as a function of treatment arm and the time that each patient stays in the included as an offset in the model. This analytic model estimates the rate ratio, which quantifies the risk of unplanned hospitalization associated with risdiplam in comparison to the control arm. For patients that switch treatments (risdiplam, nusinersen, onasemnogene abeparvovec) only unplanned hospitalizations before the treatment switch will be included in the main analysis. The follow up times for these patients ends with the treatment switch.

Symptomatic patients with a clinically diagnosed SMA type 1:

The rationale of using FAS population and treatment policy strategy for the primary estimand is to provide a picture of a treatment effect foreseen in clinical practice when treatment (including treatment switches) is administered. Additional analysis applying hypothetical strategy to treatment switches (intercurrent events) will also be provided (details see Section 4.2.3).

The primary efficacy variable is time to death or permanent ventilation, defined as the time from first study treatment administration (risdiplam, nusinersen, onasemnogene abeparvovec) to the date death or the start date of permanent ventilation (whichever occurs first). Permanent ventilation is defined as ventilation for more than 16 hours/day, for longer than 21 consecutive days. Patients who have not had an event will be censored at the date they are last known to be alive and event free on or prior to the clinical cutoff date. Data for patients who are enrolled without any post baseline

assessments will be censored at the date of first study treatment administration plus 1 day.

The main analysis for the primary endpoint will be performed using a Cox proportional hazards model. A Cox-regression test will be performed and the hazard ratio (and 95% confidence interval (CI)) will be estimated.

Time to death or permanent ventilation will be presented graphically using Kaplan-Meier curves and with the median and 25% quantiles based on the Kaplan-Meier approach. Additionally, the p-value will be presented based on a 1-sided Logrank test.

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the SMN2 gene:

The rationale of using FAS population and treatment policy strategy for the primary estimand is to provide a picture of a treatment effect foreseen in clinical practice when treatment (including treatment switches) is administered. Additional analysis applying hypothetical strategy to treatment switches (intercurrent events) will also be provided (details see Section 4.2.3).

The main analysis for the primary endpoint will be performed using a MMRM. The model will include the change from baseline at the visits up to 12 months as response variable and will include the categorical covariates of treatment group, visit, visit-by-treatment group interaction, baseline RULM Total Score (continuous), as fixed effects. The MMRM model will assume an unstructured covariance structure. If there are convergence problems with the model, then a heterogeneous compound symmetry or an autoregressive (AR) (1) covariance structure may be fitted.

Cohen's d will be estimated as a measure of the effect size. The estimated treatment difference in the mean change from baseline will be presented with a 95% CI. The score and change from baseline score will also be summarized using descriptive statistics. The mean absolute scores and change from baseline scores over time will also be presented graphically using a line plot.

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the *SMN2* gene:

As described above for type 2 patients.

4.2.3 Supplementary Analyses

Pre-symptomatic patients with a 5q-associated SMA and up to three copies of the *SMN2* gene:

The analysis method, population, and definition of intercurrent events will be the same as the main analysis (Section 4.2.1). However, all treatment switches will follow a

treatment policy strategy, where all unplanned hospitalizations will be included in the main analysis and the follow up times for the respective do not end with the treatment switch.

Symptomatic patients with a clinically diagnosed SMA type 1:

The analysis method, population, and definition of intercurrent events will be the same as the main analysis (Section 4.2.1). However, all treatment switches will follow a hypothetical strategy, where the time to death or permanent ventilation will be censored at the date of treatment switch, to estimate a treatment effect in the absence of treatment switches.

Symptomatic patients with a clinically diagnosed SMA type 2 and up to three copies of the SMN2 gene:

The analysis method, population, and definition of intercurrent events will be the same as the main analysis (Section 4.2.1). However, all treatment switches will follow a hypothetical strategy, where all values will be censored after the occurrence of the intercurrent event, to estimate a treatment effect in the absence of treatment switches. Data censored after treatment switches following hypothetical strategy will be implicitly imputed by the MMRM model assuming missing at random (MAR).

Symptomatic patients with a clinically diagnosed SMA type 3 and up to three copies of the SMN2 gene:

As described above for type 2 patients.

4.3 SECONDARY ENDPOINTS ANALYSES

Time to event analyses will be presented graphically using Kaplan-Meier curves. The median time and the 25% quantile (and 95% CIs) will be presented. To quantify the treatment effect, the hazard ratio (and 95% 2-sided CI) will be estimated using a Cox proportional hazards model, p-values will be presented based on a 1-sided Cox Regression test. Additionally, p-values will be presented based on a 1-sided Logrank test.

Responder analyses will describe the number and percentage of patients who are classified as a responder. To compare between treatment arms, relative and absolute effect measures will be presented, including absolute risk reduction, odds ratio and relative risk with corresponding 95% CIs. P-values (1-sided) will be presented for the relative risk.

For analyses describing the change from baseline, an MMRM analysis will be performed as described in Section 4.2.2. Cohen's d will be estimated as a measure of the effect size. The estimated treatment difference in the mean change from baseline will be

presented with a 95% CI. The values and change from baseline values will also be summarized using descriptive statistics. The mean absolute values and change from baseline values over time will be presented graphically using a line plot.

4.3.1 Secondary Endpoints

Table 7: Operationalization of secondary endpoints in SMArtCARE eCRF

Variable	Fields of SMArtCARE eCRF
Secondary Variables (as applicable)	
Time to death	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN (Date of treatment) • End of data collection: Date of death
Time to permanent ventilation (>16 hours/day, for longer than 21 consecutive days)	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Start of ventilator use • Medical assessment: Ongoing use of ventilator? • Medical assessment: End of ventilator use • Medical assessment: Time of ventilator use = Continuous (>16h/day)
Time to death or permanent ventilation (> 16 hours/day, for longer than 21 consecutive days)	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • End of data collection: Date of death • Medical assessment: Visit date • Medical assessment: Start of ventilator use • Medical assessment: Ongoing use of ventilator? • Medical assessment: End of ventilator use • Medical assessment: Time of ventilator use = Continuous (>16h/day)
Time to any respiratory support	• Nusinersen/onasemnogene abeparvovec/risdiplam: 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
Proportion of patients reaching the WHO motor development milestone “sitting without support” at an appropriate age	• Medical assessment: Best current motor function = Sitting or higher 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)
Proportion of patients reaching the WHO motor development milestone “walking without support” at an appropriate age	• Medical assessment: Best current motor function = Walking without support • Medical assessment: Age gained of new motor milestone Medical assessment: Age at visit (if age gained of new motor milestone not filled)
Proportion of patients reaching the WHO motor development milestone “walking without support”	• Medical assessment: Best current motor function = Walking without support

Proportion of patients with a CHOP-INTEND score ≥ 40 at 12 months of age	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • CHOP-INTEND: Date of evaluation • CHOP-INTEND: Score
Change from baseline in CHOP INTEND total score at 12, 24 and 36 months of age	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • CHOP-INTEND: Date of evaluation CHOP-INTEND: Score
Change from baseline in HFMSE total score at 12, 24 and 36 months after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • HFMSE: Date of assessment • HFMSE: Extended Total HFMSE
Change from baseline in RULM total score at 24 and 36 months after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • RULM: Date of assessment • RULM: Total RULM score
For ambulatory patients: change from baseline in walking distance at 12, 24, 36 months after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Walk test: Date of assessment • Walk test: distance_na
For ambulatory patients: proportion of patients with a change of walking distance > 30m (improvement and worsening) at 12, 24 and 36 months after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Walk test: Date of assessment • Walk test: distance_na
For ambulatory patients: relative change from baseline in walking distance at 12, 24 and 36 months after treatment start	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Walk test: Date of assessment • Walk test: distance_na
Proportion of patients with deterioration of swallowing function at 12, 24, 36 months of age/after treatment start[a]	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Swallowing? = With difficulties • 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 of feeding tube not filled).
Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months of age/after treatment start[a]	• Nusinersen/onasemnogene abeparvovec/risdiplam: 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)
Change from baseline in the total score of the Bayley III scores in the subscales “Gross Motorskills” at 12, 24 and 36 months of age	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Bayley: Date of Evaluation • Bayley: Gross Motorskills
Proportion of patients with age-appropriate Bayley III scores in the subscales “Expressive Language” and “Receptive Language” at 12, 24 and 36 months of age	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Bayley: Date of Evaluation • Bayley: Expressive Language • Bayley: Receptive Language
Time to first documentation of severe scoliosis (≥ 40°Cobb angle) or orthopedic surgery	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Does the patient have scoliosis? • Medical assessment: Cobb angle • Medical assessment: Orthopedic surgery since last visit?
Time to first documentation of severe scoliosis (≥ 40°Cobb angle)	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Does the patient have scoliosis? • Medical assessment: Cobb angle
Time to first documentation of orthopedic surgery	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Orthopedic surgery since last visit?
Proportion of patients with regular pain at 12, 24, 36 months of age/after treatment start[a]	• Orthopedics: Visit date • Orthopedics: Does the patient suffer pain regularly? • Orthopedics: unknown/1=Yes
Proportion of patients experiencing fatigue at 12, 24, 36 months of age/after treatment start[a]	• Othopedics: Visit date • Orthopedics: Does the patient experience fatigue? • Othopedics: unknown/1=Yes
Number of planned hospitalizations over time (excluding hospitalizations for SMA treatment administration)	• Nusinersen/onasemnogene abeparvovec/risdiplam: MIN(Date of treatment) • Medical assessment: Visit date • Medical assessment: Planned hospitalization since last visit (except for treatment administration)? • Medical assessment: Admission date

Footnotes: a) Months of age for presymtomatic patients and patients with SMA type 1, months after treatment start for patients with SMA type 2 and 3.

4.3.1.1 Time to death

Time-to-death is defined as the time in months from the date of first treatment administration until the date of death from any cause. Patients with no death reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in

which they were known to be alive. Patients who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of withdrawal.

4.3.1.2 Time to permanent ventilation

Time to permanent ventilation is defined as the time from date of first treatment administration to the first documentation of permanent ventilation of at least 16 hours per day for longer than 21 consecutive days. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be without permanent ventilation. Patients who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of withdrawal.

4.3.1.3 Time to death or permanent ventilation

See Section 4.2.1.

4.3.1.4 Time to any respiratory support

Time to any respiratory support is defined as the time from date of first treatment administration to the first documentation of ventilator support. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be without any respiratory support. Patients who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of withdrawal.

4.3.1.5 Proportion of patients reaching the WHO motor development milestone “sitting without support” at an appropriate age

The proportion of patients who reach the motor milestone “sitting without support” at an appropriate age based on the windows of achievement for the WHO motor development milestones will be presented. Since healthy children usually achieve the milestone until 9.5 months of age and visits should take place every four months, the assessment at the first visit between 9.5 and 13.5 months of age will be used for this analysis. Patients who do not reach the motor milestone, or have not maintained the motor milestone, or have been withdrawn, or died, will be classified as non-responders for the analysis. Patients with a missing motor milestone assessment between 9.5 and 13.5 months of age will also be classified as non-responders, unless they reached the motor milestone at a visit before and after the given time window.

4.3.1.6 Proportion of patients reaching the WHO motor development milestone “walking without support” at an appropriate age

The proportion of patients who reach the motor milestone “walking without support” at an appropriate age based on the windows of achievement for the WHO motor development milestones will be presented. Since healthy children usually achieve the milestone until 18 months of age and visits should take place every four months, the assessment at the first visit between 18 months and 22 months of age will be used for this analysis. Patients who do not reach the motor milestone, or have not maintained the motor

milestone, or have been withdrawn, or died, will be classified as non-responders for the analysis. Patients with a missing motor milestone assessment at month 18 will also be classified as non-responders, unless they reached the motor milestone at a visit before and after the given time window.

4.3.1.7 Proportion of patients reaching the WHO motor development milestone "walking without support"

The proportion of patients who reach the motor milestone "walking without support" at any age will be presented. Patients who do not reach the motor milestone, or have not maintained the motor milestone, or have been withdrawn, or died, will be classified as non-responders for the analysis. Patients with only missing motor milestone assessment will also be classified as non-responders.

4.3.1.8 Proportion of patients with a CHOP-INTEND score ⩾ 40 at 12 months of age

The proportion of patients who achieve a score of 40 or higher in the CHOP-INTEND at 12 months of age will be presented. Patients who do not achieve a score of at least 40, or have not maintained an earlier achieved score of at least 40, or have been withdrawn, or died, will be classified as non-responders for the analysis. Patients with a missing CHOP-INTEND assessment at month 12 will also be classified as non-responders.

The CHOP-INTEND consists of 16 items scored from 0 to 4, with a higher score indicating better motor skills. Both the left and right sides are scored and the maximum score is selected for the final item score. The total score is calculated by summing the item scores to give a maximum possible score of 64. If an individual item is missing or 'Cannot Test (CNT)' is recorded, the item score will be set to 0.

4.3.1.9 Change from baseline in CHOP INTEND total score at 12, 24 and 36 months of age

The change from baseline in the CHOP INTEND total score at 12, 24 and 36 months of age will be presented. The CHOP INTEND score is defined as described above.

4.3.1.10 Change from baseline in HFMSE total score at 12, 24 and 36 months after treatment start

The change from baseline in the total score of HFMSE at 12, 24 and 36 months after treatment start will be presented.

The HFMSE was developed to assess the motor function ability of individuals aged two years or older, with Type 2 and 3 SMA (17). The scale contains 33 items which score on a 3-point Likert scale (0-2) and are summed to derive the total score, with lower scores indicating greater impairment. The HFMSE was designed to assess important functional abilities, including standing, transfer, ambulation, and proximal and axial function.

For items recorded as "Not Done" for the HFMSE scale, these items are considered as missing with missing item scores.

If 6 or fewer items are missing, the missing items will be imputed to be “0” (unable to perform the task) prior to the calculation of the total score of HFMSE. If more than 6 items are missing at an assessment time point, the total score of HFMSE at this assessment time point will not be calculated.

4.3.1.11 For ambulatory patients: proportion of patients with an improvement in walking distance > 30m at 12, 24 and 36 months after treatment start

The proportion of ambulatory patients with an improvement in walking distance > 30m at 12, 24 and 36 months after treatment start will be presented. Patients who do not show an improvement of at least 30m, or have not retained the improvement, or have been withdrawn, or died, will be classified as non-responders for the analysis. Patients with a missing assessment of walking distance will also be classified as non-responders.

Walking distance describes the distance walked in the 6-minute walking test. Ambulatory patients are defined as all patients who reached the motor milestone “walking without support” at baseline.

4.3.1.12 For ambulatory patients: Proportion of patients with a worsening in walking distance > 30m at 12, 24 and 36 months after treatment start

The proportion of ambulatory patients with a worsening in walking distance > 30m at 12, 24 and 36 months after treatment start will be presented. Patients who do not show a worsening of at least 30m, or have not retained the worsening, or have been withdrawn, or died, will be classified as non-responders for the analysis. Patients with a missing assessment of walking distance will also be classified as non-responders.

Walking distance describes the distance walked in the 6-minute walking test. Ambulatory patients are defined as all patients who reached the motor milestone “walking without support” at baseline.

4.3.1.13 For ambulatory patients: change from baseline in walking distance at 12, 24 and 36 months after treatment start

The change from baseline in walking distance at months 12, 24 and 36 after treatment start will be presented for ambulatory patients.

Walking distance describes the distance walked in the 6-minute walking test. Ambulatory patients are defined as all patients who reached the motor milestone “walking without support” at baseline.

4.3.1.14 For ambulatory patients: relative change in walking distance from baseline at 12, 24 and 36 months after treatment start

For the relative change from baseline in walking distance at months 12, 24 and 36 after treatment start, the mean relative distance and relative change from baseline distance at

each time point will be summarized using descriptive statistics and presented graphically using a line plot.

4.3.1.15 Proportion of patients with deterioration of swallowing function at 12, 24, 36 months of age/after treatment start

The assessed swallowing function is ordered as follows:

1. No feeding tube, swallowing = normal
2. No feeding tube, swallowing = with difficulties
3. Feeding tube (supplementary e.g. for fluids)
4. Feeding tube (exclusively fed by tube)

A shift table will present the number/percentage of patients per category at 12, 24 and 36 months of age (for presymptomatic and SMA type 1 patients) or after treatment start (for SMA type 2 and 3 patients) versus the corresponding swallowing function at baseline.

4.3.1.16 Proportion of patients with need of non-oral nutritional support at 12, 24, 36 months of age/after treatment start

Non-oral nutritional support includes the use of a gastral or nasal feeding tube, either exclusively or supplementary.

The proportion of patients with need of non-oral nutritional support at 12, 24 and 36 months of age (for presymptomatic and SMA type 1 patients) or after treatment start (for SMA type 2 and 3 patients) will be presented. Patients who have needed non-oral nutritional support at least once between the start of treatment and the respective time point will be classified as responders. Patients who have no need of non-oral nutritional support, or have been withdrawn, or died, will be classified as non-responders for the analysis. Patients with only missing assessments will also be classified as non-responders.

4.3.1.17 Change from baseline in the total score of the Bayley III scores in the subscales “Gross Motorskills” at 12, 24 and 36 months of age

The change from baseline in the total score of the Bayley III scores in the subscale “Gross Motorskills” at 12, 24 and 36 months of age will be presented.

The Bayley scale of infant development (BSID)-III assesses the developmental progress of infants and young children, and is primarily used to identify children with developmental delays and to evaluate the impact of intervention efforts. The BSID-III consists of a core battery of five scales: three scales are administered with child interaction, the Cognitive Scale, the Language Scale (Receptive Communication and Expressive Communication), and the Motor Scale (Fine Motor and Gross Motor); two additional scales (Social-Emotional and Adaptive Behavior) are conducted with parent/caregiver questionnaires (Bayley 2006, 18).

4.3.1.18 Proportion of patients with age-appropriate Bayley III scores in the subscales “Expressive Language” and “Receptive Language” at 12, 24 and 36 months of age

The proportion of patients with age-appropriate Bayley III scores in the subscales “Expressive Language” and “Receptive Language” at 12, 24 and 36 months of age will be presented. Patients who do not show age-appropriate Bayley III scores, or have not maintained age-appropriate scores, or have been withdrawn, or died, will be classified as non-responders for the analysis. Patients with a missing Bayley III score assessment will also be classified as non-responders.

Age-appropriate scores will be defined via the developmental age equivalents given in the BSID-III manual (18), which represent the average age in months at which a given total raw score is typical. The lowest score given for the respective ages ±2 months to account for visit windows will be used as the respective lower threshold.

4.3.1.19 Time to first documentation of severe scoliosis (≥ 40° Cobb angle) or orthopedic surgery

Time to first documentation of severe scoliosis or orthopedic surgery is defined as the time from date of first treatment administration to the first documentation of severe scoliosis, as defined via a Cobb angle of >= 40, or to the first documentation of orthopedic surgery, whichever comes first. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be without severe scoliosis or orthopedic surgery. Patients who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of withdrawal. Patients with severe scoliosis at the time of study entry will be excluded from the analysis.

4.3.1.20 Time to first documentation of severe scoliosis (≥ 40° Cobb angle)

Time to first documentation of severe scoliosis is defined as the time from date of first treatment administration to the first documentation of severe scoliosis, as defined via a Cobb angle of >= 40. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be without severe scoliosis. Patients who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of withdrawal. Patients with severe scoliosis at the time of study entry will be excluded from the analysis.

4.3.1.21 Time to first documentation of orthopedic surgery

Time to first documentation of orthopedic surgery is defined as the time from date of first treatment administration to the first documentation of orthopedic surgery. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be without any orthopedic surgery. Patients who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of withdrawal. Patients with severe scoliosis at the time of study entry will be excluded from the analysis.

4.3.1.22 Proportion of patients with regular pain at 12, 24, 36 months of age/after treatment start

The proportion of patients with regular pain at months 12, 24 and 36 of age (for presymptomatic and SMA type 1 patients) or after treatment start (for SMA type 2 and 3 patients) will be presented. Patients who do not have regular pain, or have been withdrawn, or died, will be classified as non-responders for the analysis. Patients with a missing assessment for regular pain will also be classified as non-responders.

4.3.1.23 Proportion of patients experiencing fatigue at 12, 24, 36 months of age/after treatment start

The proportion of patients who experience fatigue at months 12, 24 and 36 months of age (for presymptomatic and SMA type 1 patients) or after treatment start (for SMA type 2 and 3 patients) will be presented. Patients who do not experience fatigue, or have been withdrawn, or died, will be classified as non-responders for the analysis. Patients with a missing assessment for fatigue will also be classified as non-responders.

4.3.1.24 Number of planned hospitalizations over time (excluding hospitalizations for SMA treatment administration)

The comparison of the number of planned hospitalization over time between the arms will be performed using a negative binomial regression model, which accounts for different follow-up times, with the patient's number of planned hospitalizations as a function of the treatment arm and the time that each patient stays in the hospital included as an offset in the model. This analytic model estimates the rate ratio, which quantifies the risk of planned hospitalization associated with risdiplam in comparison to the control arm.

Hospitalizations for SMA treatment administration are excluded as they are not recorded in the SMArtCARE registry.

4.4 SUBGROUP ANALYSES

Subgroup analyses will be performed to investigate the generalizability of the results when comparing risdiplam to the control arm. Analyses will be presented for the following subgroups:

Table 8: Subgroups

Subgroups	Categories	Populations
Sex	Male, female	All
Age at diagnosis	0 to 18 months, 18 months to 5 years, 6 to 11 years, 12 to 17 years, and 18 to 25 years, > 25 years	SMA3
Age at enrollment	2 to 5 years, 6 to 11 years, 12 to 17 years, and 18 to 25 years, > 25 years	SMA2, SMA3

Subgroups	Categories	Populations
Age at enrollment	⩽ median age, > median age	presymptomatic
Geographic region	Germany, Austria	All
History of scoliosis surgery	Yes, no	SMA2, SMA3
Highest motor milestone at baseline (disease severity)	None, Sitting without support, Crawl on hands and knees, Standing without support, Walking without support, Climb stairs	All
Nutrition support	Yes – exclusively, yes – supplementary, no	All
Ventilation support	Yes, no	All
Contractures	Yes, no	SMA1, SMA2, SMA3
SMN2 Copy Number	1, 2, 3	All
Baseline CHOP-INTEND	⩽ median score, > median score	SMA1, presymptomatic
Baseline HFMSE score	⩽ median score, > median score	SMA2, SMA3
Baseline CMAP amplitude	<1.5mV, ⩾1.5mV	presymptomatic
Time between first treatment and onset of symptoms	⩽ 3 months, > 3 months	SMA1

4.5 SAFETY ANALYSES

4.5.1 Adverse Events

Table 9: Operationalization of safety endpoints in SMArtCARE eCRF

Variable	Fields of SMArtCARE eCRF
Safety Variables	
Number of unplanned hospitalizations over time	• Nusinersen/onasemnogene abeparvovec/risdiplam: 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 hospitalization? • Adverse events: Start date
Time to first SAE	• Nusinersen/onasemnogene abeparvovec/risdiplam: 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 hospitalization? • Adverse event: Start date • Adverse event: Description of adverse event

Variable	Fields of SMArtCARE eCRF
Safety Variables	
Time to first AE leading to hospitalization	• Nusinersen/onasemnogene abeparvovec/risdiplam: 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 hospitalization? • Adverse event: Start date
Time to first selected SAE (each of the of the following): • retinopathy • effect on epithelial tissue • thrombocytopenia • nephropathy • hydrocephalus • hepatopathy • cardiac events • sensory neuropathy	• Nusinersen/onasemnogene abeparvovec/risdiplam: 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 hospitalization? • Adverse events: Any unexpected events without hospitalization? • Adverse events: Type of unexpected event • Adverse events: Start date • Adverse event: Description of adverse event

The analysis of safety outcomes/variables is based on SAE, AE leading to hospitalization and selected SAE. The time to onset of the first episode of (serious) adverse event in each category will be summarized using KM approach and presented graphically.

All SAE, AE leading to hospitalization and selected SAE term entered by the physician describing the event (the “verbatim term”) will be assigned to a standardized term (the “preferred term”) based on the most up-to-date version of MedDRA. Data displays of SAE and selected SAE will be performed using the preferred terms and their according system organ class.

The time to onset SAE, AE leading to hospitalization and SAE will be summarized using the preferred terms and their according system organ class.

The number of unplanned hospitalizations over time will be analyzed separately using negative binomial regression models.

All safety analyses will follow the hypothetical strategy for treatment switches, where all time to event analyses will be censored at the date of the treatment switch. For the number of unplanned hospitalizations over time, only unplanned hospitalizations before

the treatment switch will be included and follow up times for these patients end with the treatment switch.

4.6 OTHER ANALYSES

4.6.1 Patient Disposition

All summaries will be done by treatment group and by retrospective / prospective enrolled patients.

Population details will be presented based on the total population in terms of:

- Number of patients enrolled (= FAS)
- Number of patients treated

The disposition will be summarized as the overall count and percentage of patients who completed respectively discontinued the study prematurely including the categories for the primary reason for withdrawal as specified in the CRF.

4.6.2 Summaries of Demographics and Baseline Characteristics

Demographic and baseline characteristics such as age, sex, geographic region, and baseline disease characteristics (such as history of scoliosis surgery, highest motor milestone, HFMSE score, nutrition support, ventilation support, contractures, SMN2 Copy Number, CHOP-INTEND, CMAP amplitude, time between first treatment and onset of symptoms, pre-existing illness, need for wheelchair, participation in other registries) will be summarized by treatment group and by retrospective / prospective enrolled patients using means, SDs, medians, and ranges for continuous variables, and counts and proportions for categorical variables, as appropriate.

4.6.3 Concomitant medication/ Therapy interventions

Concomitant medication on regular basis (treatment names), Therapy interventions (Physiotherapy, Feeding/Speech therapy, Occupational therapy, Other) and will be summarized by treatment group.

4.6.4 Extent of Exposure

The exposure (duration of treatment) to SMA-Medication (risdiplam, nusinersen,) will be summarized by treatment group. Dose and number of interruptions (> 4 weeks) for risdiplam will be summarized. The number of subjects treated with onasemnogene abeparvovec will be summarized.

The number of subjects that switched treatment will be summarized by treatment group. The exposure (duration of treatment) for the switched treatments will be summarized as well.

4.6.5 Orthoses/Devices/Wheelchair use

The use, location and type of orthoses, the use and type of devices and the use and type of wheelchairs will be summarized by treatment group and visit.

4.6.6 Observation period

The patient-related observation period will be summarized (median, min, max) by treatment group and by retrospective / prospective enrolled patients (overall and end-point specific if applicable).

4.7 INTERIM ANALYSES / STATUS REPORTS

4.7.1 Planned interim analyses and status reports

First status report (submission 6 months after study start):

Disposition, summaries of demographics / baseline characteristics, exposure and patient-related observation period will be analyzed as described above and will be presented in the status report. Further analyses might be conducted and presented if appropriate. The data cut for this analysis will be at study start (retrospective enrolled patients only).

Second status report and first interim analysis (submission 18 months after study start):

Disposition, summaries of demographics / baseline characteristics, exposure and patient-related observation period will be analyzed as described above. The primary endpoints (and secondary endpoints if appropriate) will be analyzed as described above. Module 4 of the dossier template will be used to submit the results. Based on this interim analysis, the sample size will be re-calculated using observed effect sizes and recruitment rates as assumptions considering all relevant endpoints.. If the expected power is less than 60% for a primary endpoint (and relevant secondary endpoints) the enrollment might be stopped due to futility in the respective population. The data cut for this analysis will be 12 months after study start.

Third status report and second interim analysis (submission 30 months after study start):

Disposition, summaries of demographics / baseline characteristics, exposure and patient-related observation period will be analyzed as described above. The primary endpoints (and secondary endpoints if appropriate) will be analyzed as described above. Module 4 of the dossier template will be used to submit the results. If the expected power is less than 60% for a primary endpoint (and relevant secondary endpoints) the enrollment might be stopped due to futility in the respective population. The data cut for this analysis will be 24 months after study start.

4.8 CHANGES TO PROTOCOL-PLANNED ANALYSES

Not applicable.

5. SUPPORTING DOCUMENTATION

This section is not applicable, since there is no additional supporting document.

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