# NI PAES PROTOCOL (SECONDARY AND PRIMARY DATA COLLECTION)

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|---|---|
| **TITLE:** | A Prospective, Observational, Post-Authorisation Efficacy Study to Assess Long-term Effectiveness of Risdiplam in Patients with Genetically Confirmed 5q SMA |
| **PROTOCOL NUMBER:** | BN43428 |
| **VERSION NUMBER:** | 1.0 ; 30 JUL 2021 |
| **AUTHOR:** | [redacted], PharmD, Ph.D.<br>[redacted]<br>Roche Products Ltd.<br>6 Falcon Way<br>Welwyn Garden City AL7 1TW<br>United Kingdom<br><br>[redacted], MD, MscPH<br>[redacted]<br>Evidera<br>27-35, rue Victor Hugo<br>94200 Ivry-sur-Seine<br>France |
| **EU PAS REGISTER NUMBER:** | To be registered |
| **STUDIED MEDICINAL PRODUCT:** | Risdiplam (Evrysdi®) |
| **DATE FINAL:** | See electronic date stamp below |

## FINAL PROTOCOL APPROVAL

| Date and Time (UTC) | Title | Approver's Name |
|---|---|---|
| 30-Jul-2021 13:00:37 | Company Signatory | [redacted] |

**CONFIDENTIAL**

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|---|---|
| **ACTIVE SUBSTANCE:** | M09AX10: Risdiplam |
| **PRODUCT REFERENCE NUMBER:** | European Union (EU) marketing authorisation number: EU/1/21/1531/001 |
| **PROCEDURE NUMBER:** | EMEA/H/C/005145 |
| **RESEARCH QUESTION AND OBJECTIVES:** | This prospective, observational study aims to evaluate disease progression in patients with genetically confirmed 5q spinal muscular atrophy (SMA; both pre-symptomatic and symptomatic) who have been treated with risdiplam and to compare disease progression with that observed in patients not receiving any disease-modifying therapy (DMT) for SMA, i.e., DMT-naive patients. Symptomatic status and *SMN2* copy number are key subgroups for consideration in this study, as they represent potential effect modifiers for the level of effectiveness of risdiplam. All treatment decisions will be made during routine care and will be independent of the study. |
| **COUNTRIES OF STUDY POPULATION:** | Several European countries with potential addition of non-European countries |
| **MARKETING AUTHORIZATION HOLDER (MAH):** | Roche Registration GmbH<br>Emil-Barell-Strasse 1<br>D-79639 Grenzach-Wyhlen<br>Germany |
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I agree to conduct the study in accordance with the current protocol.

_____

Treating Physician's Name (print)

_____ _____

Treating Physician's Signature Date

Please return a copy of this form to Roche or its designee.

Please retain the signed original for your study files.

# 1. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| 6MWT | 6-Minute Walk Test |
| 10MWT | 10-Metre Walk Test |
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminotransferase |
| BSID-III | Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) |
| CDM | Common Data Model |
| CHMP | Committee for Medicinal Products for Human Use |
| CHOP-INTEND | Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders |
| CIs | Confidence Intervals |
| CMP | Clinical Monitoring Plan |
| CRO | Contract Research Organisation |
| DMT | Disease-Modifying Therapy |
| EC | Ethics Committee |
| eCRF | electronic Case Report Form |
| EDC | Electronic Data Capture |
| EMA | European Medicines Agency |
| EMR | Electronic Medical Records |
| ENCePP | European Network of Centres for Pharmacoepidemiology And Pharmacovigilance |
| EU | European Union |
| GLM | Generalised Linear Model |
| GPP | Good Pharmacoepidemiological Practice |
| GVP | EU Guideline on Good Pharmacovigilance Practices |
| HCP | Health Care Professional |
| HFMSE | Hammersmith Functional Motor Scale Expanded |
| HINE-2 | Hammersmith Infant Neurological Examination−Module 2 |
| HR | Hazard Ratio |
| IPW | Inverse Probability Weighting |
| IRB | Institutional Review Board |
| ISPE | International Society of Pharmacoepidemiology |
| KM | Kaplan Meier |
| MAH | Marketing Authorisation Holder |

| Abbreviation | Definition |
|---|---|
| 6MWT | 6-Minute Walk Test |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MFM32 | Motor function measure 32 |
| MMRM | Mixed Model for Repeated Measures |
| mRNA | Pre-Messenger Ribonucleic Acid |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NMiS | Neuromuskulära Sjukdomar i Sverige |
| OR | Odds Ratio |
| PAES | Post-Authorisation Efficacy Study |
| PDC | Primary Data Collection |
| PNCR | Paediatric Neuromuscular Clinical Research |
| RHS | Revised Hammersmith Scale |
| RULM | Revised Upper Limb Module |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SDU | Secondary Data Use |
| SMA | Spinal Muscular Atrophy |
| SMAIS | SMA Independence Scale |
| SMN1 | Survival Motor Neuron 1 |
| SMN2 | Survival Motor Neuron 2 |
| TREAT-NMD | Translational Research in Europe for the Assessment and Treatment of Neuromuscular Disorders |
| TUG | Timed Up and Go |
| ULN | Upper Limit of Normal |
| WHO | World Health Organization |

## 2. RESPONSIBLE PARTIES

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## 3. SYNOPSIS

| | |
|---|---|
| **TITLE:** | A Prospective, Observational, Post-Authorisation Efficacy Study to Assess Long-term Effectiveness of Risdiplam in Patients with Genetically Confirmed 5q SMA |
| **ROTOCOL NUMBER:** | BN43428 |
| **VERSION NUMBER:** | 1.0 |
| **DATE OF SYNOPSIS:** | 30 JUL 2021 |
| **STUDIED MEDICINAL PRODUCT:** | Risdiplam (Evrysdi®) |
| **SCIENTIFIC RESPONSIBLE:** | [redacted], M.D., Ph.D.<br>[redacted]<br>F. Hoffmann-La Roche<br>4070 Basel<br>Switzerland<br>E-mail: [redacted] |
| **MAIN AUTHOR:** | [redacted], PharmD, Ph.D.<br>[redacted]<br>Roche Products Ltd.<br>6 Falcon Way<br>Welwyn Garden City AL7 1TW<br>United Kingdom<br>E-mail: [redacted] |
| **PHASE:** | IV, non-interventional study |
| **INDICATION:** | Risdiplam (Evrysdi®) is indicated for the treatment of 5q spinal muscular atrophy (SMA) in patients 2 months of age and older, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four *SMN2* copies |
| **MARKETING AUTHORIZATION HOLDER:** | Roche Registration GmbH<br>Emil-Barell-Strasse 1<br>D-79639 Grenzach-Wyhlen<br>Germany |

## Rationale and Background

Spinal muscular atrophy (SMA) is an autosomal recessive disorder. Complex and comprehensive multidisciplinary care is often required for the clinical care of SMA. Risdiplam (Evrysdi®) is an orally administered, *SMN2* pre-messenger ribonucleic acid (mRNA) splicing modifier that directly targets the underlying molecular deficiency of the disease.

On 26 February 2021, the Committee for Medicinal Products for Human Use (CHMP) recommended granting a marketing authorisation in the European Union for Evrysdi, the first oral treatment for 5q SMA. As a requirement of the marketing authorisation, the CHMP mandated that the Marketing Authorisation Holder (MAH) conduct a post-authorisation efficacy study (PAES): a long-term, prospective, observational study to further evaluate disease progression in patients with SMA (both pre-symptomatic and symptomatic) who have 1 to 4 *SMN2* copies and who are being treated with risdiplam and to compare the data collected with natural history data collected from untreated patients.

The PAES will provide further data on maintenance of effectiveness in the long-term in risdiplam-treated patients.

## Research Question and Objectives

This prospective, observational study aims to evaluate disease progression in patients with genetically confirmed 5q SMA (both pre-symptomatic and symptomatic) who have been treated with risdiplam and to compare disease progression with that observed in patients not receiving any disease-modifying therapy (DMT) for SMA, i.e., DMT-naive patients. Symptomatic status and *SMN2* copy numbers are key subgroups for consideration in this study, as they represent potential effect modifiers for the level of effectiveness of risdiplam. All treatment decisions will be made during routine care and will be independent of the study.

The primary objectives for this study are as follows:

- To describe the real-world, long-term effectiveness of risdiplam on disease progression and to compare the impact of potential effect modifiers (symptomatic status, *SMN2* copy number) on long-term effectiveness
- To compare the real-world, long-term effectiveness outcomes between a cohort of risdiplam-treated patients and a cohort of DMT-naive patients (untreated with any DMT approved for SMA)

## Study Design

This study is a multi-country, non-interventional, prospective, longitudinal cohort study that will use a hybrid method of 2 sources of data collection:

- Secondary data use (SDU): Data will be extracted from existing SMA patient registries.
- Primary data collection (PDC): Data will be collected de novo from sites in countries not covered by the SDU.

Study countries will be primarily in Europe, although non-European countries (e.g., those in North America or Australasia) can be included in order to achieve the target sample size. The study design intends that SDU will be prioritized in terms of the selection of the countries to be included: in the first case, selection of countries for the study will be driven by the patient SMA registries that participate in this study. PDC will be included to complement the SDU, and in order to avoid overlap of patients in both SDU and PDC and to increase the coverage of patients with SMA, PDC sites will be selected from countries not covered by SDU for this study.

**Study Period**

An eligibility period (enrolment/cohort entry period) of up to 3 years is planned in order to reach the target sample size. If the target sample size is reached in less than three years, the eligibility period will end earlier. The study aims to collect up to 5 years of follow-up data per patient. Due to the rare disease context of this study, data collection will be maximised. If patients are enrolled at the start of the eligibility period, they could potentially have up to 8 years of follow-up data.

**Studied Medicinal Product**

Risdiplam; an orally administered, *SMN2* mRNA splicing modifier.

**Population**

The study population will consist of 2 study cohorts:

1) Risdiplam cohort
2) DMT-naive cohort

Both study cohorts will include patients with SMA (pre-symptomatic and symptomatic).

**Risdiplam Cohort Eligibility Criteria**

At the index date (see Section 8.2.2), patients must meet all of the following inclusion criteria and none of the exclusion criteria to be enrolled in the risdiplam cohort.

- **Risdiplam Cohort Inclusion Criteria**
  - **Risdiplam cohort from SDU**
    1. Patients are alive, with genetically confirmed 5q SMA (pre-symptomatic or symptomatic)
    2. New users of risdiplam: Patients have a start date for risdiplam treatment that is within the eligibility period
    3. Patients are included in a registry at the index date (risdiplam start) or are included in a registry up to 6 months* after the index date and have retrospective study data available for the time period between the index date and registry entry (*the rationale for this criterion is to maximize the size of the study population, due to the rare disease area)
  - **Risdiplam cohort from PDC**
    1. Patients are alive, with genetically confirmed 5q SMA (pre-symptomatic or symptomatic)

2. New users of risdiplam: Patients have initiated risdiplam at cohort entry or have initiated risdiplam up to 6 months* before cohort entry and have retrospective study data available for the time period between risdiplam initiation and cohort entry (*the rationale for this criterion is to maximize the size of the study population, due to the rare disease area)
3. Patients are being treated at participating study sites by physicians who are prescribing risdiplam as part of routine practice
4. Patients have signed the informed consent (or assent), as required by local regulations, at cohort entry

- **Risdiplam Cohort Exclusion Criteria**
  - **For both SDU and PDC,** patients will be excluded if they meet the following criterion:
    1. Patients who previously received risdiplam outside of a commercial setting (routine care), for example as part of a clinical trial or an Early Access Program

Note: Patients who have received a DMT, other than risdiplam, for SMA previously or concurrently to risdiplam are eligible for inclusion in the risdiplam cohort from SDU and PDC.

**DMT-naive Cohort Eligibility Criteria**

At the index date (see Section 8.2.2), patients must meet all of the following inclusion criteria and none of the exclusion criteria to be enrolled in the DMT-naive cohort.

- **DMT-naive Cohort Inclusion Criteria**
  - **DMT-naive Cohort from SDU**
    1. Patients are alive, with genetically confirmed 5q SMA (pre-symptomatic or symptomatic)
  - **DMT-naive Cohort from PDC**
    1. Patients are alive, with genetically confirmed 5q SMA (pre-symptomatic or symptomatic)
    2. Patients are being treated at participating study sites by physicians as part of routine practice
    3. Patients have signed the informed consent (or assent), as required by local regulations, at cohort entry
- **DMT-naive Cohort Exclusion Criteria**
  - **For both SDU and PDC,** patients will be excluded if they meet the following criteria:
    - Patients have a record of any treatment with an approved DMT for SMA (see Section 6.1.2)

**Variables**

For variables collected directly from study sites, only variables obtained according to routine clinical practice and collected according to the study objectives will be documented in this study. For variables extracted from patient registries, only variables collected according to the study objectives will be documented in this study.

- **Demographic and Clinical Characteristic Variables**
    - Socio-demographic information
    - Height and weight
    - Medical history
    - Level of respiratory support
    - Comorbidities
    - Prior and concomitant treatments (incl. SMA DMT)
    - Symptomatic status, either:
        - Symptomatic (date of SMA symptoms onset and presenting symptom(s), or
        - Pre-symptomatic
    - SMA genetic diagnosis and other information:
        - Genetic diagnosis date, *SMN1* pathogenic mutation
        - Number of *SMN2* gene copies, method for identification of *SMN2* copies
    - Family history of SMA
- **Exposure Variables**
    - Risdiplam treatment characteristics (risdiplam cohort)
    - SMA DMT after the index date (including any change in risdiplam treatment)
- **Effectiveness Outcomes**

The effectiveness outcomes for this study have been divided into primary, secondary, and tertiary effectiveness outcomes and are based on data recording in routine care and patient registries, likely accuracy of measurement, and relevance to the whole study population.

    - **Primary effectiveness outcomes**
        - Survival
        - Prolonged/permanent ventilation-free survival
        - Developmental motor milestone achievement
        - Motor function assessed using Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), Hammersmith Functional Motor Scale Expanded (HFMSE) or Revised Upper Limb Module (RULM)

- **Secondary effectiveness outcomes**
  - Onset of symptoms (within the pre-symptomatic group)
  - Need for nutritional support/tube feeding
  - Hospitalisations and reasons for hospitalisations
  - Withdrawal of risdiplam treatment and reasons for withdrawal of treatment (risdiplam cohort only)

- **Tertiary effectiveness outcomes**
  - Motor function measure 32 (MFM32)
  - Revised Hammersmith Scale (RHS)
  - Timed function tests (e.g., 6-Minute Walk Test [6MWT], 10-Metre Walk Test [10MWT], Timed Up and Go [TUG] Test)
  - SMA Independence Scale (SMAIS)

- **Other Variables**
  - AE and SAEs (only for PDC patients within the risdiplam cohort and for routine pharmacovigilance; not for analysis)

**Data Sources**

Two data sources will be used in this study: SDU and PDC (see previous sections).

- **SDU: Existing SMA Patient Registries**

A database feasibility assessment is being conducted in parallel with the development of this protocol to provide in-depth evaluation of existing patient registries.

There are well-established existing SMA patient registries that represent an important source of information regarding patients, treatments, standard of care, and outcomes over time.

Within Europe, the patient registries included in the database feasibility include, but are not limited to, the following:

- Translational Research in Europe for the Assessment and Treatment of Neuromuscular Disorders (TREAT-NMD): An EU–funded network of excellence for genetic neuromuscular diseases that has an SMA-specific dataset that collects data from multiple national/regional registries. The countries in Europe included in the network are Austria, Bulgaria, Czech Republic, Denmark, Finland, Germany, Hungary, Ireland, Italy, Lithuania, Norway, the Netherlands, Poland, Russian Federation, Serbia, Slovakia, Spain, Switzerland, Ukraine, and the United Kingdom.
- SMArtCARE: A prospective, multi-centre non-randomized registration and outcome study, created in 2017 to collect real-world longitudinal data in Germany, Switzerland and Austria on all available patients with SMA independent of their actual treatment regimen.
- SMA Research and Clinical Hub (REACH UK): A new initiative in collaboration with existing SMA registries in the United Kingdom such as the UK SMA Patient Registry and SMArtNet Clinical Network UK.
- French Register of Patients with Spinal Muscular Atrophy (R-SMA France): A prospective observational study that aims to obtain clinically meaningful data on treatment, survival and outcomes of all the patients with 5q SMA.
- Neuromuscular Diseases in Sweden – Neuromuskulära Sjukdomar i Sverige (NMiS): A Swedish national registry.

Study countries will be primarily in Europe; however, non-European patient registries have also been evaluated and may be included in order to maximise recruitment. The non-European patient registries included in the database feasibility include, but are not limited to, the following:

- The Australian Neuromuscular Disease Registry: a nationwide registry of people diagnosed with neuromuscular diseases, including SMA.
- The Canadian Neuromuscular Disease Registry: a nationwide registry of people diagnosed with neuromuscular diseases, including SMA.
- CureSMA: There are 3 databases: CureSMA Membership Database, Pediatric Neuromuscular Clinical Research (PNCR), and the Clinical Care Network. The CureSMA membership database is worldwide, patient-reported data provided through personal communications and surveys. The PNCR dataset in the United states covers SMA and includes 5 sites: Columbia University Medical Center, Boston Children's Hospital, Children's Hospital of Philadelphia (CHOP), Stanford Health Care, and Nemours Children's Health System. The Clinical Care network has national coverage.

The final list of patient registries will depend on the availability and accessibility of data and their potential to reach the target sample size.

- **PDC: Prospective Site-based Data Collection**

Data will be collected de novo from sites in countries not covered by the SDU.

For PDC, the data from enrolled patients will be recorded via electronic CRFs (eCRF) using a web-based electronic data capture (EDC) system. The eCRF will be designed to optimise consistency of data collection with those of existing patient registries. Data from patient notes should be entered into the eCRF as soon as they become available.

The final list of countries for PDC will depend on the availability and accessibility of patient registries and their potential to reach the target sample size.

**Study Size/Determination of Sample Size**

The study aims to enrol patients with genetically confirmed 5q SMA into 2 study cohorts: the risdiplam cohort and the DMT-naive cohort. The study will aim to include 300 patients treated with risdiplam during the eligibility period (risdiplam cohort) and up to 300 untreated patients (DMT-naive cohort) depending on availability of data, as defined by eligibility criteria in Section 8.1.3. The sample size is based on both practical and statistical considerations.

A study size of 300 patients is considered to be sufficient to provide a reasonable level of precision (e.g., width of confidence interval [CI]) for the effectiveness outcomes in the subgroups.

The following example is provided for illustrative purposes only: If at least 10% (30/300) of the risdiplam cohort are pre-symptomatic with 4 *SMN2* copies (Calucho et al. 2017), and 23% of these (7/30) experience SMA symptoms during the study, the 95% CI will be 10% to 42%. There will also be a 61% risk reduction in SMA symptoms compared with the DMT-naive cohort, if 60% (18/30) of the patients in the DMT-naive cohort who are pre-symptomatic with 4 *SMN2* copies experience symptoms (Wijngaarde et al. 2020) during the study.

**Data Analysis**

This study will comprise descriptive, time-to-event, regression, and comparative analyses with adjustment for confounding factors.

All primary effectiveness outcomes will be analysed by treatment cohort (withdrawal from treatment will be analysed in the risdiplam cohort only), as well as according to pre-symptomatic/symptomatic status (except onset of symptoms, which will be analysed in pre-symptomatic patients only) and number of *SMN2* copies.

The preferred approach for data analyses across data sources is to extract raw data from the different data sources and then to perform a pooled central analysis. In case this is not possible, alternative approaches will be considered, e.g., study-specific common data model or local analysis.

- **Descriptive Analysis**

All effectiveness outcomes will be summarised descriptively by cohort (risdiplam cohort and DMT-naive cohort) for the study population by time point (approximately 6-month intervals from index up to the end of the observation period).

Descriptive analysis will be used to summarise the following by cohort:

  - Patient disposition
  - Demographic and clinical characteristics at baseline
  - Effectiveness outcomes by time point (approximately 6-month intervals from the index date up to the end of the study observation period)
  - Exposure characteristics

Continuous variables will be described with summary statistics such as n, mean, standard deviation, median, minimum, and maximum values. For each categorical variable, the frequency and percentage in each category will be reported, alongside 95% confidence intervals (CIs) when relevant. Percentages will be calculated using the specified denominator in the table. The frequency and percentage of subjects with missing data for each data point will be presented.

- **Time-to-Event Analysis**

Time-to-event analysis will be used for outcomes that assess the length of time until the occurrence of a predefined endpoint. The following time-to-event outcomes will be analysed:

  - Survival (i.e., all-cause mortality at each time point)
  - Permanent/prolonged ventilation-free survival
  - Time to need for nutritional support/tube feeding
  - Time to onset of symptoms (only within the pre-symptomatic group)

The proportion of patients who experience each event by year after the index date will be summarised. In addition, the time to event for each outcome during the study period will be reported in months, summarised descriptively (minimum, median, quartiles, and maximum), and analysed using the Kaplan-Meier method and Cox proportional hazards regression model (Cox regression).

- **Regression Analyses**

Regression models (univariable and multivariable) will be used to evaluate the association between the outcomes of interest and relevant predictors, depending on sample size and if the number of events permits. Generalised linear models and mixed models for repeated measures may be used, considering the longitudinal nature of the data, the possibility for repeated measurements, and exposure varying over time. Binary outcomes will be analysed using logistic regression. For continuous outcomes, treatment differences and 95% CIs will be presented. For categorical outcomes, odds ratios or relative risks and 95% CIs will be presented.

- **Comparative Analyses: Adjustment for Covariates and Confounders**

To achieve the second study objective, effectiveness outcomes will be compared between the risdiplam cohort and the DMT-naive cohort. Because of the real-world nature of the study, a high potential for imbalance exists between the cohorts with regard to observed covariates. To address this imbalance, adjusted analyses may be employed using statistical techniques, including inverse probability weighting and multivariable regression analysis with propensity scores as an adjustment variable, using covariates and confounding factors. The method of adjustment will be finalised in the statistical analysis plan.

- **Subgroup Analyses**

In order to meet the first study objective, effectiveness outcomes will be summarised by the following subgroups:

  - Symptomatic status (pre-symptomatic and symptomatic)
  - *SMN2* copy number

- **Interim and Final Analyses**

It is anticipated that there will be 5 interim data extractions from existing patient registries (SDU) and 5 interim data extractions from the PDC. The first interim results will be produced after the eligibility period and annually thereafter. The final study results will be based on the sixth and final data extraction from the patient registries (SDU), as well as the final study database from the PDC (see Section 8.4 for additional details regarding data sources).

**Milestones**

An eligibility period (enrolment/cohort entry period) of up to 3 years is planned in order to reach the target sample size. If the target sample size is reached in less than three years, the eligibility period will end earlier. The study aims to collect 5 years of follow-up data per patient. Due to the rare disease context of this study, data collection will be maximised, i.e., if patients are enrolled at the start of the eligibility period, they could potentially have up to 8 years of follow-up data.

- **Start Date of Study**

The estimated study start date: Q2 2022.

- **End of Study**

The estimated end of the study: Q4 2030.

- **Length of Study**

This study is estimated to last for approximately 8 years.

## 4. PROTOCOL AMENDMENTS AND UPDATES

Any protocol amendments will be prepared by the Marketing Authorisation Holder (MAH) or its designee. The Scientific Responsible will seek Counsel / Consultancy for the Protocol and succeeding amendments with the competent institutional review board (IRB)/ethics committee(s) (EC).

Substantial protocol amendments / updates so far: none.

## 5. MILESTONES

Study milestones are given in the following table.

| Milestone | Planned Date |
|---|---|
| Start of data collection | Q2 2022 |
| End of data collection | Q1 2030 |
| Progress report 1 | Q2 2023 |
| Progress report 2 | Q2 2024 |
| Progress report 3 & Interim report 1 | Q3 2025 |
| Interim report 2 | Q3 2026 |
| Interim report 3 | Q3 2027 |
| Interim report 4 | Q3 2028 |
| Interim report 5 | Q3 2029 |
| Final report of study results | Q4 2030 |

# 6. RATIONALE AND BACKGROUND

Refer to Section 6.2**Error! Reference source not found.** for the study rationale. Refer to Section 8.1.1 for the study design rationale. Refer to Section 8.4.1 regarding the patient registry landscape for spinal muscular atrophy (SMA).

## 6.1 SPINAL MUSCULAR ATROPHY

### 6.1.1 SMA Overview

SMA is a monogenic neuromuscular disorder that results in severe weakness of the limbs, trunk, bulbar, and respiratory muscles (Finkel et al. 2015). SMA is characterized by the dysfunction of alpha motor neurons within the anterior horn of the spinal cord, leading to failure to gain and maintain functional motor nerve innervation of skeletal muscles (Crawford and Pardo 1996; Lunn and Wang 2008; Lorson et al. 2010).

SMA is an autosomal recessive disorder secondary to loss-of-function mutations in both alleles of the survival motor neuron 1 (*SMN1*) gene, with subsequent loss of SMN protein expression. In humans, there are 2 *SMN* genes, the *SMN1* gene and its paralog *SMN2*. The *SMN2* pre-messenger ribonucleic acid (mRNA) undergoes alternative splicing that excludes exon 7 from 85% to 90% of mature *SMN2* transcripts, which produces an unstable SMN$\Delta$7 protein that is rapidly degraded. Therefore, full-length *SMN2* mRNA is generated in only 10% to 15% of splicing events (Monani et al. 1999; Markowitz et al. 2012). Accordingly, patients with SMA lacking a functioning *SMN1* gene are dependent on their *SMN2* gene, and symptomatic SMA is the consequence of decreased, insufficient levels of functional SMN protein produced by the *SMN2* gene. Children born with multiple copies of the *SMN2* gene have milder phenotypes, further demonstrating that the pathophysiology of the disease is due to insufficient production of functional SMN protein (Feldkötter et al. 2002; Harada et al. 2002).

Clinically, muscle weakness and atrophy are symmetrical and most severe in the proximal limbs, often affecting the legs more than the arms, and, in the most severe infantile-onset form, results in failure to gain motor milestones, no meaningful motor function, and loss of respiratory and bulbar muscle function, which leads to early death. In patients with later-onset disease, the distribution of weakness is the same, leading to profound disability due to poor mobility and poor proximal upper limb function, with many patients requiring respiratory and feeding support (Arnold et al. 2015).

SMA subtypes are defined by age at onset of symptoms and most advanced motor milestone achieved during development and are classified as Types 0 through 4 (Finkel et al. 2015), where Types 1, 2, and 3 represent approximately 99% of the SMA population (Darras 2015). Type 0 (congenital SMA) is very rare, and most of these patients do not survive beyond 6 months of age. Type 4 SMA (adult onset) accounts for only approximately 1% of all SMA cases (Darras 2015). Although SMA is clinically classified into these different “Types,” it is considered as a disease spectrum or continuum of disease severity (Talbot and Tizzano 2017). Based on a large review,

mainly from European data, the estimated prevalence of SMA is approximately 1 to 2 per 100,000 persons, and the disease incidence is around 1 in 10,000 live births (Verhaart et al. 2017). SMA Types 1, 2, and 3 are estimated at approximately 60%, 27%, and 12% of all incident SMA cases, respectively (Ogino et al. 2004). With regards to correlation between *SMN2* copy number and expected SMA phenotype, the majority of patients with 1 to 2 *SMN2* copies present with Type 1 SMA. Among patients with 3 *SMN2* copies, 54% present with SMA Type 2, 31% with Type 3, and 15% with Type 1. Finally, when considering patients with 4 *SMN2* copies, 82% have Type 3 SMA and 11% have Type 2 (Calucho et al. 2018).

### 6.1.2 SMA Current Standard of Care

Complex and comprehensive multidisciplinary care is often required for the clinical care of SMA. Non-therapeutic management strategies for SMA are described in the international standard of care recommendations published in 2018 (Finkel et al. 2018; Mercuri et al. 2018b) and rely on prevention and treatment of comorbidities, such as swallowing and feeding difficulties, scoliosis and thoracic deformity, contractures, and respiratory insufficiency. Over time, palliative management for patients with the most severe Type 1 SMA has been introduced more frequently at home, with increased levels of technical supportive care such as enteral nutrition, oxygen therapy, and analgesic and sedative treatments (Hully et al. 2020).

In recent years, the standard of care has significantly evolved with the approval of 3 disease-modifying therapies (DMTs): risdiplam (Evrysdi®), onasemnogene abeparvovec (Zolgensma®), and nusinersen (Spinraza®), which in the European Union (EU) have the following indications at the time of writing this protocol:

- Spinraza (EU Marketing Authorisation: 30 May 2017) is indicated for the treatment of 5q SMA
- Zolgensma (EU Marketing Authorisation: 18 May 2020) is indicated for the treatment of:
    - Patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1, or
    - Patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene.
- Evrysdi (EU Marketing Authorisation: 26 March 2021) is indicated for the treatment of 5q SMA in patients 2 months of age and older, with a clinical diagnosis of SMA Type 1, Type 2, or Type 3 or with 1 to 4 *SMN2* copies.

Globally, Evrysdi (risdiplam) has also gained regulatory approval for treatment of SMA in more than 50 countries, including the US, Canada, Australia, the United Kingdom, China, Japan, and Brazil.

Risdiplam is an orally administered, *SMN2* mRNA splicing modifier that directly targets the underlying molecular deficiency of the disease. It promotes the inclusion of exon 7 to

generate full-length *SMN2* mRNA, thereby increasing the production of functional SMN protein from the *SMN2* gene, both in the central nervous system and throughout the body. For further information on approved SMA treatments, please refer to the relevant, currently approved local Product Information.

Clinical evidence indicates that optimal efficacy of DMTs is achieved when patients are treated early, even before the onset of symptoms (Dangouloff and Servais 2019). Based on this knowledge, treatment guidelines for SMA-positive infants identified through newborn screening and based upon *SMN2* copy number were published (Glascock et al. 2018; Glascock et al. 2020). According to these guidelines, all infants with 2, 3, or 4 copies of *SMN2* should receive immediate treatment, and infants with one copy should receive treatment based on the physician's decision regarding whether the infant and family would benefit from treatment given the infant's current disease state.

## 6.2 STUDY RATIONALE

On 26 February 2021, CHMP recommended granting a marketing authorisation in the EU for Evrysdi, the first oral treatment for 5q SMA. As a requirement of the marketing authorisation, the CHMP mandated that the MAH conduct a post-authorisation efficacy study (PAES): a long-term, prospective, observational study to further evaluate disease progression in patients with SMA (both pre-symptomatic and symptomatic) who have 1 to 4 *SMN2* copies and who are being treated with risdiplam, and to compare the data collected with natural history data collected from untreated patients.

The PAES will provide further data on maintenance of effectiveness in the long-term in risdiplam-treated patients.

# 7. RESEARCH QUESTION AND OBJECTIVES

## 7.1 RESEARCH QUESTION

This prospective, observational study aims to evaluate disease progression in patients with genetically confirmed 5q SMA (both pre-symptomatic and symptomatic) who have been treated with risdiplam and to compare disease progression with that observed in patients not receiving any DMT for SMA, i.e., DMT-naive patients. Symptomatic status and *SMN2* copy number are key subgroups for consideration in this study, as they represent potential effect modifiers for the level of effectiveness of risdiplam. All treatment decisions will be made during routine care and will be independent of the study.

## 7.2 OBJECTIVES

### 7.2.1 Primary Objectives

The primary objectives for this study are as follows:

- To describe the real-world, long-term effectiveness of risdiplam on disease progression and to compare the impact of potential effect modifiers (symptomatic status, *SMN2* copy number) on long-term effectiveness
- To compare the real-world, long-term effectiveness outcomes between a cohort of risdiplam-treated patients and a cohort of DMT-naive patients (untreated with any DMT approved for SMA)

# 8. RESEARCH METHODS

## 8.1 STUDY DESIGN

This study is a multi-country, non-interventional, prospective, longitudinal cohort study that will use a hybrid method of 2 sources of data collection:

- Secondary data use (SDU): Data will be extracted from existing SMA patient registries.
- Primary data collection (PDC): Data will be collected de novo from sites in countries not covered by the SDU.

Study countries will be primarily in Europe, although non-European countries (e.g., those in North America or Australasia) can be included in order to achieve the target sample size. The study design intends that SDU will be prioritized in terms of the selection of the countries to be included: in the first case, selection of countries for the study will be driven by the patient SMA registries that participate in this study. PDC will be included to complement the SDU, and in order to avoid overlap of patients in both SDU and PDC and to increase the coverage of patients with SMA, PDC sites will be selected from countries not covered by SDU for this study.
Refer to Section 8.4 for a description of the study data sources and to Section 8.9 for a description of study data analysis.

### 8.1.1 Rationale for Study Design

Refer to Section 6.2 for the study rationale. Refer to Section 8.1 for the study design.

The study design has been chosen so as to fulfil, most efficiently, the study objectives. As the therapeutic area of this study is a rare disease, and because there are already patient registries collecting data relevant for this study, data extracted from these patient registries will be leveraged.

Additionally, according to the European Medicines Agency (EMA) guidance on PAES studies (EMA 2016), comparisons between different exposure cohorts within observational studies are preferred, where possible, to be based on concurrent (contemporary, not historical) sets of patients, because the clinical background of the disease (standard of care) may have changed over time, as is the case with SMA. Hence, this will be a prospective study. Patient registries also allow for continued assessment of outcomes and comparisons using a similar methodology (EMA 2016).

To maximise the size of the study population, the study design will also include PDC from sites that do not participate in the patient registries (in countries not covered by the SDU).

### 8.1.2 Study Population and Cohort Definitions

The study population will include patients with genetically confirmed 5q SMA (both pre-symptomatic and symptomatic).

Study patients will be included in 2 study cohorts:

(1) Risdiplam cohort

(2) DMT-naive cohort

The risdiplam cohort will comprise patients who are new users of risdiplam. The DMT-naive cohort will be operationally defined as patients with no previous history of having received a DMT approved for SMA (in any setting) at the time of cohort entry. DMTs approved for SMA will be defined based on treatments approved for the treatment of SMA according to national labelling and local standard of care. See Section 6.1.2 for a specification of which DMTs are currently approved for SMA. This list is subject to change throughout the study eligibility period, according to any changes that are made in national labelling and local standard of care. All treatment decisions will be made during routine care and will be independent of the study.

In order to address the first study objective, the analysis will also be stratified by 2 main subgroups:

(1) Symptomatic status (symptomatic; pre-symptomatic)

(2) *SMN2* copy number

Imbalance in size across the subgroup strata is expected. For instance, based on previous research (Calucho et al. 2018), it is expected that fewer patients with an *SMN2* copy number of 1 or an *SMN2* copy number of 4 will be available for inclusion in the study population (compared to patients with an *SMN2* copy number of 2 or of 3, since they are more prevalent). It is also expected that fewer patients will be available for inclusion in the DMT-naive cohort of the study population, since patients contemporaneous to risdiplam new users are likely to receive some DMT for SMA, especially patients with *SMN2* copy number of 2.

**Table 1 Patient Study Cohorts and Key Subgroups**

| | Cohorts | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Key Subgroups** | Risdiplam Cohort | | | | | | | | DMT-naïve Cohort | | | | | | | |
| Symptomatic status subgroups | Pre-symptomatic | | | | Symptomatic | | | | Pre-symptomatic | | | | Symptomatic | | | |
| *SMN2* copy number subgroups* | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |

Abbreviation: DMT, disease-modifying therapy.
*See section 8.7.4 for information on analysis by *SMN2* copy number: the primary analysis of this study will not restrict the study population to only patients confirmed to have *SMN2* copy number 1-4.

### 8.1.3 Eligibility Criteria

The study population will include 2 cohorts of patients with genetically confirmed 5q SMA and who fulfil the study eligibility criteria for inclusion into either the risdiplam cohort or the DMT-naive cohort. See Table 1 and Section 8.1.2 for information regarding the study cohorts.

In this study, patient data will be present in only one of the two types of data collection: SDU or PDC. Figure 1 and Figure 2 provide schematics to demonstrate how patient eligibility criteria will be operationalized within this study design for SDU and PDU, respectively.

If patients are first enrolled in the DMT-naive cohort, then they will be subsequently eligible to enrol in the risdiplam cohort, provided that they initiate risdiplam treatment as part of routine care during the study eligibility period and that they fulfil the cohort-specific eligibility criteria at the time of entry into the relevant cohort. Of note, by definition, it will not be possible for patients who are first enrolled in the risdiplam cohort to subsequently be enrolled in the DMT-naive cohort.

**Figure 1 Scenarios to Demonstrate How Patient Eligibility Will Be Operationalized Within the Study Design – SDU**

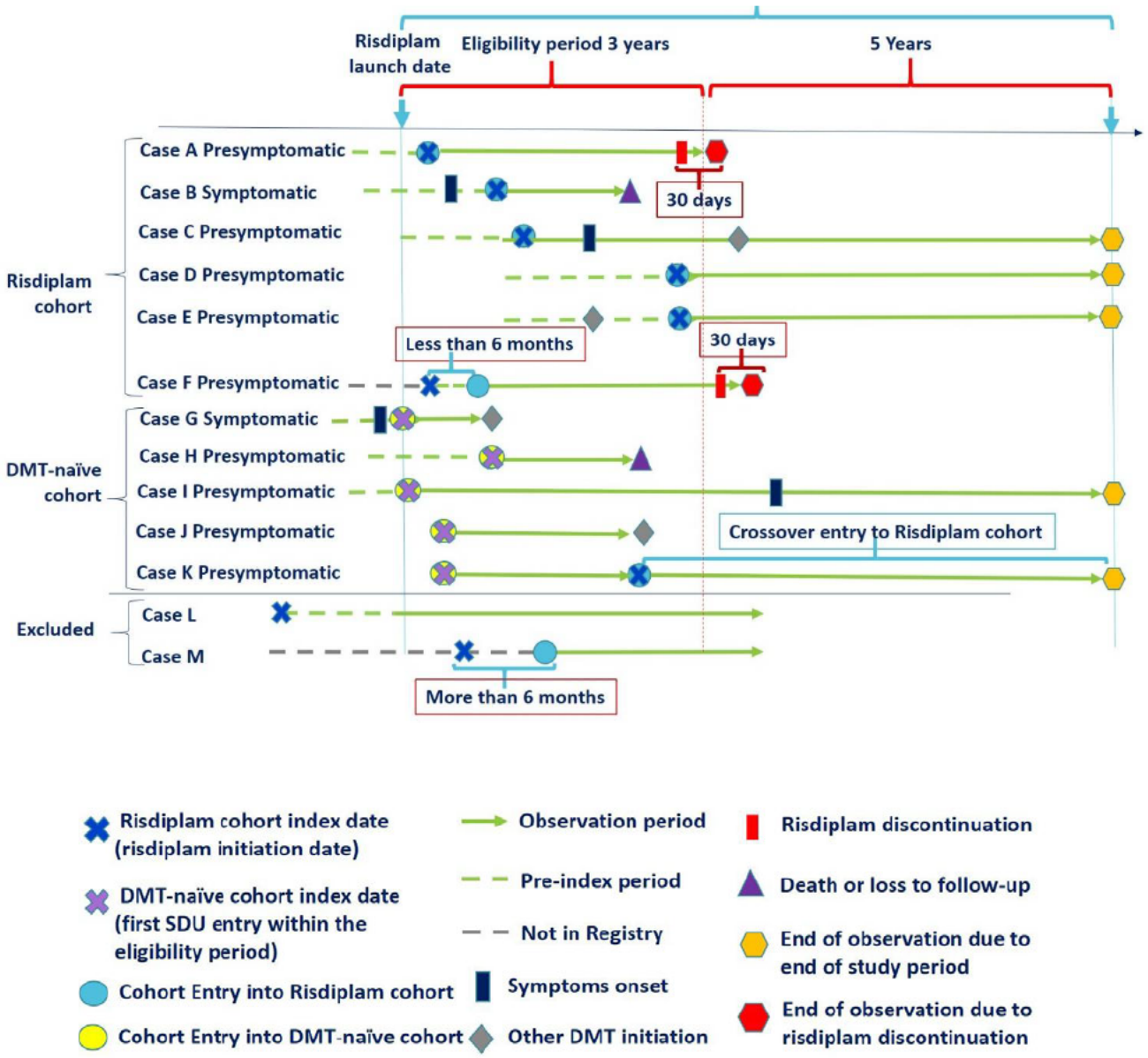
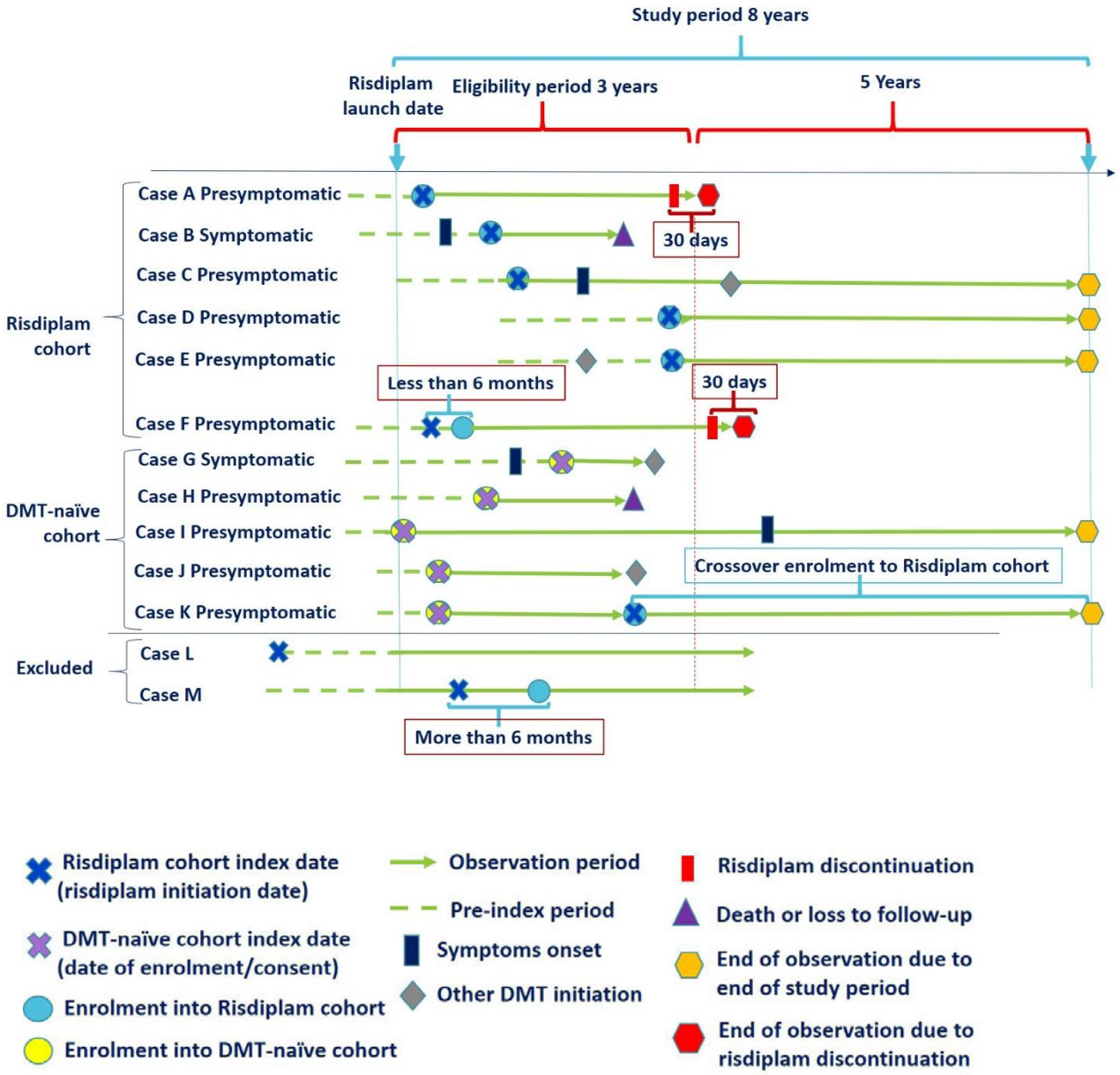


**Figure 2 Scenarios to Demonstrate How Patient Eligibility Will Be Operationalized Within the Study Design – PDC**




Abbreviations: DMT, disease-modifying therapy

#### 8.1.3.1 Risdiplam Cohort Eligibility Criteria

At the index date (see Section 8.2.2), patients must meet all of the following inclusion criteria and none of the exclusion criteria to be enrolled in the risdiplam cohort.

- **Risdiplam Cohort Inclusion Criteria**
  - **Risdiplam cohort from SDU**
    1. Patients are alive, with genetically confirmed 5q SMA (pre-symptomatic or symptomatic)
    2. New users of risdiplam: Patients have a start date for risdiplam treatment that is within the eligibility period (see Section 8.2.1)
    3. Patients are included in a registry at the index date (risdiplam start) or are included in a registry up to 6 months* after the index date and have retrospective study data available for the time period between the index date and cohort entry (*the rationale for this criterion is to maximize the size of the study population, due to the rare disease area)
  - **Risdiplam cohort from PDC**
    1. Patients are alive, with genetically confirmed 5q SMA (pre-symptomatic or symptomatic)
    2. New users of risdiplam: Patients have initiated risdiplam at cohort entry or have initiated risdiplam up to 6* months before cohort entry and have retrospective study data available for the time period between risdiplam initiation and cohort entry (*the rationale for this criterion is to maximize the size of the study population, due to the rare disease area.)
    3. Patients are being treated at participating study sites by physicians who are prescribing risdiplam as part of routine practice
    4. Patients have signed the informed consent (or assent), as required by local regulations, at cohort entry
- **Risdiplam Cohort Exclusion Criteria**
  - **For both SDU and PDC patients,** patients will be excluded if they meet the following criterion:
    1. Patients who previously received risdiplam outside of a commercial setting (routine care), for example as part of a clinical trial or an Early Access Program

Note: Patients who have received a DMT for SMA (other than risdiplam) either previously or concurrently to risdiplam are eligible for inclusion in the risdiplam cohort from SDU or PDC.

#### 8.1.3.2 DMT-Naive Cohort Eligibility Criteria

At the index date (see Section 8.2.2), patients must meet all of the following inclusion criteria and none of the exclusion criteria to be enrolled in the DMT-naive cohort.

- **DMT-naive Cohort Inclusion Criteria**
  - **DMT-naive cohort from SDU**
    1. Patients are alive, with genetically confirmed 5q SMA (pre-symptomatic or symptomatic)
  - **DMT-naive cohort from PDC**
    1. Patients are alive, with genetically confirmed 5q SMA (pre-symptomatic or symptomatic)
    2. Patients are being treated at participating study sites by physicians as part of routine practice
    3. Patients have signed the informed consent (or assent), as required by local regulations, at cohort entry
- **DMT-naive Cohort Exclusion Criteria**
  - **For both SDU and PDC**, patients will be excluded if they meet the following criteria:
    1. Patients have a record of any treatment with an approved DMT for SMA (see Section 6.1.2)

### 8.1.4 Rationale for Patient Population

The study population will include patients with genetically confirmed 5q SMA (both pre-symptomatic and symptomatic) as per the objectives of the study.

### 8.1.5 Recruitment Procedure

For SDU, database feasibility will guide selection of existing patient registries for participation (see Section 8.4.1).

For PDC, this study will be conducted by qualified investigators under the sponsorship of Roche (the sponsor). For PDC, the geography of the patient registries that agree to participate, as well as site feasibility, will guide the selection of sites invited for participation. The study design intends that SDU will be prioritized in terms of the selection of the countries to be included: in the first case, selection of countries for the study will be driven by the patient SMA registries that participate in this study. PDC will be included to complement the SDU, and in order to avoid overlap of patients in both SDU and PDC and to increase the coverage of patients with SMA, PDC sites will be selected from countries not covered by SDU for this study.

## 8.2 SETTING AND STUDY PERIOD

This study is a multi-country, non-interventional, prospective, longitudinal cohort study using SDU and PDC. Decisions regarding dosing and duration of treatment with the

studied medicinal product, risdiplam, will be made at the discretion of the treating physicians in accordance with local clinical practice and local labelling..

See Section 8.1 for additional information regarding the study design.

### 8.2.1 Study Periods

An eligibility period (enrolment/cohort entry period) of up to 3 years is planned in order to reach the target sample size. If the target sample size is reached in less than three years, the eligibility period will end earlier (see Section 0). The study aims to collect up to 5 years of follow-up data per patient.

#### Eligibility Period:

In each country, the eligibility period will start when risdiplam is commercially available within that country (i.e., this date will be based on the actual date of launch in the country, when reimbursement is available, in the time period when physicians can actually prescribe risdiplam to their patients). The end of the eligibility period is up to 3 years after its start (i.e., 3 years after when risdiplam is commercially available in the first participating country; note, countries in which risdiplam becomes commercially available later in the eligibility period will have less than 3 years in the eligibility period. In the case that the target sample size is reached in less than 3 years, the eligibility period will be ended earlier).

#### Start Date of Study Period:

The start date of the study period will be the date of the first data collection; that is, the date from which information on the first patient is recorded in the study database, the earliest of either SDU or PDC (refer also to the definition of the eligibility period, as well as the definition of index date). The start of the study period will depend on the start of the eligibility period.

#### End of Study Period:

The end of the study period will be the date from which the last data collected from the last patient is recorded in the study database, which should be 5 years after the last patient is included. This will be the latest of either SDU or PDC. A data collection overview is provided in Appendix 2.

#### Observation Period for the Patient:

Due to the rare disease context of this study, data collection will be maximised. If patients are enrolled at the start of the eligibility period, they could potentially have up to 8 years of follow-up data.

**Patients Enrolled from SDU**

The term “observation period” for patient data from SDU will be defined as the maximum duration of available data, starting from the index date (see Section 8.2.2) until the date of death, discontinuation of risdiplam treatment plus 30 days (for risdiplam cohort), start

of any DMT (for DMT-naive cohort), loss to follow-up, end of the study period, or study closure by the Sponsor, whichever occurs first.

**Patients Enrolled from PDC**

The term "observation period" for patients enrolled from PDC is defined as the period spanning from the index date (see Section 8.2.2) until the date of death, discontinuation of risdiplam treatment plus 30 days (for risdiplam cohort), start of any DMT (for DMT-naive cohort), loss to follow-up, withdrawal of consent, end of the study period, study closure by the Sponsor, or site withdrawal from the study, whichever occurs first.

**Pre-Index Period:**

The pre-index period will cover the available data extracted from the existing patient registries (SDU) or collected at the cohort entry visit (PDC) occurring before the index date (see Section 8.2.2).

### 8.2.2 Index Date

The definition of the index date (start of the observation period) will depend on whether the patient is in the risdiplam cohort or the DMT-naive cohort (see Section 8.1), as well as whether they are from the SDU or PDC (see Section 8.1). By definition, so that the patient can be included in the study, the index date has to occur within the eligibility period.

For patients in the risdiplam cohort (SDU or PDC), the index date will always be the date of risdiplam treatment initiation. For patients in the DMT-naive cohort, refer to Table 2 for the definition of the index date from SDU or PDC.

**Table 2 Definition of Index Date by Study Cohort and Type of Data Source**

| | Study Cohort | |
|---|---|---|
| **Type of Data Source** | **Risdiplam Cohort** | **DMT-naive Cohort** |
| **SDU** | Date of risdiplam treatment initiation | First SDU database entry within the eligibility period* |
| **PDC** | Date of risdiplam treatment initiation | Date of cohort entry/consent |

*Eligibility period: see Section 8.2.1.

## 8.3 VARIABLES

The table in Appendix 2 presents a non-exhaustive summary of the study variables that will be retrieved/collected at the index date and during the follow-up period. A final list of study variables will be documented in the statistical analysis plan (SAP). For SDU, only variables within the scope of the study objectives will be requested for extraction from the existing patient registries based on the available variables within the patient registries. For PDC, only variables obtained according to routine clinical practice and

collected according to the study objectives will be documented in this study. The same or similar variables will be collected from both PDC and SDU.

More details will be described in the SAP, including definitions of variables for exposures, outcomes, patient characteristics, and potential confounders.

### 8.3.1 Demographic and Clinical Characteristic Variables

Demographic and clinical characteristic variables will be used to provide a general description of the health and characteristics of patients in the study cohorts and in the analysis to control for potential confounding factors. Demographic and clinical characteristic variables will include, but are not limited to:

- Socio-demographic information
- Height and weight
- Medical history
- Level of respiratory support
- Comorbidities
- Prior and concomitant treatments (incl. SMA DMT)
- Symptomatic status, either:
    - Symptomatic (date of SMA symptoms onset and presenting symptom(s), or
    - Pre-symptomatic
- SMA genetic diagnosis and other information:
    - Genetic diagnosis date, *SMN1* pathogenic mutation
    - Number of *SMN2* gene copies, method for identification of *SMN2* copies
- Family history of SMA

Notably, variables regarding SMA disease characteristics, including prior and concomitant treatment with other DMTs, will enable understanding of patient disease context and treatment history. The level of detail and completeness may vary across data sources, and this will be assessed during data analysis.

### 8.3.2 Exposure Variables

Exposure variables will be collected in order to assess:

1) Risdiplam treatment characteristics (risdiplam cohort)
2) SMA DMT treatment characteristics after the index date (including any change in risdiplam treatment)

Exposure variables to assess the treatment characteristics will include, but are not limited to:

- Start and end dates
- Treatment duration, derived from index date and discontinuation date
- Initial dose in mg/kg/day
- Frequency of administration
- Any change in risdiplam dose or frequency of administration, including risdiplam treatment discontinuation
    - Date of change(s)
    - Reason for change(s)

The SAP will address the methods for exposure definition in case of multiple periods of exposure (e.g., sum of exposure days for all periods, definition of minimally acceptable interruption period).

The SAP will contain detailed information regarding how the analysis will account for patients who may be first enrolled in the DMT-naive cohort and later enrolled in the risdiplam cohort.

### 8.3.3 Effectiveness Outcomes

Effectiveness outcomes for this study are those that are likely to be available in the existing patient registries, based on information derived during database feasibility (see Section 8.4.1.1), as well as from the international consensus for SMA patient registries (TREAT-NMD).

Effectiveness outcomes to be collected during SDU will depend on what is collected and made available for this study by existing patient registries. Effectiveness outcomes to be collected during PDC will be designed to optimise consistency with those of SDU from existing patient registries. Definitions of variables collected via SDU and PDC will be documented in the SAP (and via the list of variables requested for extraction for SDU and via the eCRF for PDC). For a summary, see Appendix 2.

For PDC, data will be collected during routine patient visits. The timing and frequency of follow-up visits and assessments will depend on routine practice, but patients with SMA are usually seen once or twice a year in a specialized outpatient clinic for neuromuscular diseases (where the patients will be recruited; Pechmann et al. 2019).

This study aims to evaluate whether risdiplam treatment results in improvement or maintenance of motor function and the development of motor milestones that are clinically meaningful and that deviate from the natural history of the disease. The selected effectiveness outcomes are based on the experience gained in the risdiplam clinical development program and are based on the results of a review of the variables collected in SMA patient registries. These effectiveness outcomes are considered appropriate and clinically meaningful for patients with SMA.

The effectiveness outcomes for this study have been divided into primary, secondary, and tertiary effectiveness outcomes and are based on data recording in routine care and patient registries, likely accuracy of measurement, and relevance to the whole study population.

#### 8.3.3.1 Primary Effectiveness Outcomes

- **Survival**

The time to all-cause mortality (survival) by the end of study participation is defined as the time from the index date to the date of death due to any cause for deceased patients or to last clinical visit for patients alive at last contact. Causes of death will also be collected.

- **Prolonged/permanent ventilation-free survival**

Ventilation-free survival is defined as the time from the index date to the date the patient requires permanent or prolonged ventilation. Prolonged/permanent ventilation is defined as the need for ≥16 hours of non-invasive ventilation per day or the need for awake and sleep non-invasive ventilation or tracheostomy. The need for prolonged/permanent ventilation will need to be confirmed at 2 consecutive data collection dates to minimise cases where this need is only temporary; for example, during an acute illness. If confirmed, the date of start for need of prolonged/permanent ventilation will be the first date of collection of this data.

- **Developmental motor milestone achievement**

Data on the achievement of motor milestones (such as head control / sitting independently / standing independently / walking independently) may be derived from different variables collected within the patient registries, depending on availability, patient age, and phenotype and including but not limited to the assessment of the Hammersmith Infant Neurological Examination Module 2 (HINE-2), the World Health Organization (WHO) motor development milestones, and the Bayley Scales of Infant Development III (BSID-III). They may also be derived from specific items of motor function variables, e.g., specific items of the Hammersmith Functional Motor Scale Expanded (HFMSE) or derived from general “motor function” items within registry forms, e.g., maximum motor function achieved (e.g., sitting without support).

    - **Hammersmith Infant Neurological Examination−Module 2**

      The HINE-2 evaluates 8 developmental motor milestones (head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking) in infants and has been previously used to evaluate motor function in SMA natural history studies and in clinical trials of infantile-onset SMA (De Sanctis et al. 2016; Finkel et al. 2017; Baranello et al. 2021). It is scored on a 3- to 5-point scale per milestone. This tool was also used to assess motor milestone acquisition

following the implementation of the standards of care in SMA, confirming HINE-2 to be a reliable outcome measure in young patients with SMA (De Sanctis et al. 2016).

- **World Health Organization milestones**

  The WHO motor milestones evaluate gross motor development and comprise the time windows of achievement for 6 gross motor milestones based on data derived from the WHO Multicentre Growth Reference Study (MGRS 2006). The windows represent normal variation among healthy children and are recommended for descriptive comparisons among populations. The 6 gross motor milestones are sitting without support, hands-and-knees crawling, standing with assistance, walking with assistance, standing alone, and walking alone.

- **Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)**

  The gross motor scale of the BSID-III is a validated outcome measure in infants used to assess attainment of motor milestones, including static positioning (e.g., head control, sitting), dynamic movement including locomotion (e.g., crawling), quality of movement (e.g., kicking), balance, and motor planning. It has been widely used in children at risk of motor development delay (Connolly et al. 2013). Each of the 72 items is scored on a 2-point scale and measures whether patients are able to perform the assessed items.

- **Motor function assessed using CHOP-INTEND, HFMSE or RULM**

Change in motor function will be assessed by validated rating scales, including:

- Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) in patients up to 2 years of age
- Hammersmith Functional Motor Scale Expanded (HFMSE) in patients from 2 years of age
- Revised Upper Limb Module (RULM) in patients from 2 years of age

- **CHOP-INTEND**

  The CHOP-INTEND is a reliable, easily administered and well-tolerated motor function measure for Type 1 SMA and similarly weak infants with neuromuscular diseases. It provides a useful assessment of motor skills in this population, both for clinical monitoring and research trials (Glanzman et al. 2010).

  The CHOP-INTEND scale consists of 16 items, with a total score that ranges from 0 to 64. Items assess both active and elicited reflexive movement (16 items in total, each scored from 0 to 4), such as spontaneous movement of upper and lower extremity, hand grasping, rolling, head control and others.

Although the CHOP-INTEND scale usually assesses children up to 2 years of age, it may continue to be used in children greater than 2 years of age for whom the test is appropriate (e.g., patients with Type 1 SMA who have low motor function). In this latter case, data will continue to be collected until the last date of data availability.

- **HFMSE**

The HFMSE was developed to assess gross motor function in individuals aged 2 years or older who have Type 2 or 3 SMA (O'Hagen et al. 2007). The HFMSE has well-established psychometric properties in children with SMA (O'Hagen et al. 2007; Glanzman et al. 2011). The scale was modified, and 13 items were added to the original version of the measure (HFMS) in order to also capture changes in stronger patients; those extra items were aimed specifically at ambulant individuals (Cano et al. 2014). The HFMSE contains 33 items designed to assess important functional abilities, including standing, transfers, ambulation and proximal and axial function. Each item is scored on a 0- to 2-point scale by a clinical evaluator. A total score from 0 to 66 is calculated, with higher scores indicating greater functioning.

- **RULM**

The RULM assesses upper limb motor performance in patients with SMA. It is a validated scale in SMA, which has demonstrated good reliability and validity (Mazzone et al. 2017). The RULM has typically been used in conjunction with the HFMSE (which does not assess fine motor function of the hand, wrist or elbow) to understand changes in upper limb ability and to capture changes in weaker patients with SMA. The RULM is particularly important for non-ambulant patients who rely on preservation of upper limb ability to complete daily activities. The RULM consists of 19 items (scored on a 0- to 2-point scale for 18 items and a 0- to 1-point scale for one item) assessing the performance of shoulder, elbow, wrist, and hand function. A total score from 0 to 37 is calculated, with higher scores indicating greater upper limb functioning.

#### 8.3.3.2 Secondary Effectiveness Outcomes

- **Onset of symptoms (within the pre-symptomatic group)**

The time to onset of symptoms (only within the pre-symptomatic group) is defined as the time from index date to the date of onset of symptoms (e.g., muscle weakness, hypotonia, breathing difficulties, swallowing difficulties). The symptoms will be described if available.

- **Need for nutritional support/tube feeding**

The time to need for nutritional support/tube feeding is defined as the time from index date to the date of initiation of feeding using a tube.

- **Hospitalisations and reasons for hospitalisations**

Variables on start and end dates of hospitalisation will be used to generate length of stay in hospitalisation. Reasons for hospitalisations will be described.

- **Withdrawal of risdiplam treatment and reasons for withdrawal of treatment (risdiplam cohort only)**

The dates of risdiplam treatment discontinuation and reason for treatment withdrawal will be described.

#### 8.3.3.3 Tertiary Effectiveness Outcomes

- **Motor function measure 32**

Motor function measure 32 (MFM32) is a valid and reliable assessment of motor function ability in neuromuscular diseases, including SMA, with demonstrated validity and reliability for patients of at least 2 years of age (Berard et al. 2005; Trundell et al. 2020).The MFM32 contains 32 items, all of which patients have confirmed are related to everyday activities of daily living (Duong et al. 2021). The MFM32 is assessed in 3 domains of motor function: D1 (standing and transfers), D2 (axial and proximal motor function), and D3 (distal motor function). The 32 items scored on a 0- to 3-point scale are summed and then transformed onto a 0- to 100-point scale (i.e., sum of scores for 32 items divided by 96 and multiplied by 100) to yield the MFM32 total score expressed as a percentage of the maximum score possible for the scale (the one obtained with no physical impairment). The lower the total score, the more severe the functional impairment.

- **Revised Hammersmith Scale**

The Revised Hammersmith Scale (RHS) is an assessment of motor function in patients with SMA, ranging from weak SMA Type 2 through to very strong patients with SMA Type 3. The scale consists of 36 items; 33 items are graded on an ordinal scale of 0, 1, and 2, where 0 denotes the lowest level of ability/function progressing to the highest level of ability to achieve a score of 2, and the remaining 3 items are scored 0 and 1, where 0 is unable and 1 is able to achieve the item. The maximum achievable RHS total score is 69.

- **Timed function tests**

Timed function tests (TFTs) measure motor function during a specific time; such tests include the 6-Minute Walk Test (6MWT), 10-Metre Walk Test (10MWT), and Timed Up and Go (TUG) Test.

  - **6-Minute Walk Test**

    The 6MWT is an objective evaluation of functional exercise capacity that measures the maximum distance a person can walk in 6 minutes over a 25-metre linear course. It provides a measure for integrated global response of multiple cardiopulmonary and musculoskeletal systems involved in exercise. The distance covered over a time of 6 minutes is used as the outcome by which to benchmark changes in performance capacity. The 6MWT has been widely used as an outcome measure in clinical trials in neuromuscular diseases, including Duchenne muscular dystrophy, Becker muscular dystrophy and SMA.

  - **10-Metre Walk Test**

    This test records the time taken to safely walk 10 metres on a marked 10-metre course.

  - **Timed Up and Go Test**

    The TUG Test is an objective measure of balance, gait speed, and functional mobility. It measures the time it takes a patient to stand up from an armchair, walk a distance of 3 metres, turn, walk back to the chair, and sit down (Podsiadlo et al. 1991). In SMA, the TUG Test is easily administered, reliable, and correlates with established effectiveness outcomes (Dunaway et al. 2014).

- **SMA Independence Scale**

The SMA Independence Scale (SMAIS) was developed to assess the degree of assistance required to perform typical daily activities. The SMAIS upper limb module can be used with non-sitters and sitters. The SMAIS ambulatory module can be used with walkers. There is a caregiver-reported version for individuals aged 2 years and older and a self-report version for individuals aged 12 years and older. The SMAIS (upper limb and ambulant module) asks individuals to rate the amount of assistance that they need to perform daily activities over the past 7 days. Item scores are summed to create the total score. Lower scores indicate greater dependence on another individual or aid.

### 8.3.4 Other Variables

Other variables will be collected as needed to meet study objectives and to meet routine pharmacovigilance requirements. For instance, adverse events (AE) and serious adverse events (SAEs) will be collected only for PDC patients within the risdiplam cohort and for routine pharmacovigilance; not for analysis.

## 8.4 DATA SOURCES: SDU AND PDC

Two data sources will be used in this study: SDU and PDC. Refer to Section 8.1 for a description of the study design and to Section 8.7 for a description of study data analysis.

### 8.4.1 SDU: Existing SMA Patient Registries

Globally, there are a number of established and active SMA patient registries. These patient registries and networks of registries represent an important source of information regarding patients, treatments, standard of care, and outcomes over time, and represent a potential source of quality data.

Within Europe, the patient registries included in database feasibility include, but are not limited to, the following:

- Translational Research in Europe for the Assessment and Treatment of Neuromuscular Disorders (TREAT-NMD): An EU–funded network of excellence for genetic neuromuscular diseases that has an SMA-specific dataset that collects data from multiple national/regional registries (Bladen et al. 2014; Lusakowska et al. 2021). The countries in Europe included in the network are Austria, Bulgaria, Czech Republic, Denmark, Finland, Germany, Hungary, Ireland, Italy, Lithuania, Norway, the Netherlands, Poland, Russian Federation, Serbia, Slovakia, Spain, Switzerland, Ukraine, and the United Kingdom. TREAT-NMD was launched in January 2011, but not all countries included in the network launched at the same time. Since 2018, all member registries collect data as per the standardized TREAT-NMD SMA Registries Core Dataset (version 2.0 was launched in 2020 with improved functionality).
- SMArtCARE: A prospective, multi-centre non-randomized registration and outcome study, created in 2017 to collect real-world longitudinal data in Germany, Switzerland and Austria on all available patients with SMA independent of their actual treatment regimen. For this purpose, SMArtCARE also provides an online platform for data entry and processing for patients with SMA (Pechmann et al. 2019).
- SMA Research and Clinical Hub (REACH UK): A new initiative in collaboration with existing SMA patient registries in the United Kingdom such as the UK SMA Patient Registry and SMArtNet Clinical Network UK. The registry of the SMA REACH UK started recruitment in 2014 (Ramsey et al. 2014).

- French Register of Patients with Spinal Muscular Atrophy (R-SMA France): A prospective observational study that aims to obtain clinically meaningful data on treatment, survival and outcomes of all the patients with 5q SMA, being followed in the reference centers of the disease in France between 1 Sept 2016 and 31 Aug 2024. Recruitment target of the R-SMA France is ~1,000 SMA 5q patients.
- Neuromuscular Diseases in Sweden – Neuromuskulära Sjukdomar i Sverige (NMiS): A Swedish national registry set up in 2012 to collect data on how to better understand long-term outcomes in people with hereditary neuromuscular diseases (including SMA) and patients' perception and experience with the disease and its treatment, as well as to foster and improve communication and cooperation between different professional categories to provide opportunities for patients in Sweden to be included in international treatment studies. Data collection efforts had been limited until a restructuring in 2017-2018. Since then, the NMiS registry became part of the Swedish Neuro-Registry (Svenska Neuroregister) and has significantly increased recruitment and data collection, which can be augmented via linkage with the national registries. Several research initiatives have been launched, and the publications are expected by the end of this year.

Outside of Europe, patient registries included in database feasibility include, but are not limited to, the following:

- The Australian Neuromuscular Disease Registry is a nationwide registry of people diagnosed with neuromuscular diseases, including SMA.
- The Canadian Neuromuscular Disease Registry is a nationwide registry of people diagnosed with neuromuscular diseases, including SMA (Wei et al. 2018). It was launched in 2011.
- CureSMA: There are 3 databases: CureSMA Membership Database, Pediatric Neuromuscular Clinical Research (PNCR), and the Clinical Care Network. The CureSMA membership database is worldwide, patient-reported data provided through personal communications and surveys. Data collection started in 2009. The PNCR dataset in the United States covers SMA and includes 5 sites: Columbia University Medical Center, Boston Children's Hospital, Children's Hospital of Philadelphia (CHOP), Stanford Health Care, and Nemours Children's Health System. The current database began data collection in May 2018. The Clinical Care network has national coverage and is composed of electronic medical record (EMR) data and survey data that represents patient clinical data from primary care (CureSMA 2019). Data collection began in October 2018.

#### 8.4.1.1 SDU: Technical Approach for Database Feasibility of Existing SMA Patient Registries

A database feasibility assessment is being conducted in parallel with the development of this protocol to provide an in-depth evaluation of existing patient registries. The final list of patient registries to be used as part of the SDU will depend on the availability and

accessibility of data and their potential to provide enough patients to reach the target sample size.

The data required to answer the study objectives will need to maximise relevancy and reliability while providing sufficient sample size and representativeness. Data relevancy will include an assessment of whether and how key study variables (baseline characteristics and primary outcomes) are included in the existing SMA patient registries, in view of what will be required to answer the study objectives. The assessment of data reliability will entail an in-depth investigation of the routines and processes for data capture, consolidation, quality assurance, curation, security, and compliance. Selection of the most appropriate data source(s) will result in data that are as follows:

- Accurate: Valid, consistent, and conforming.
- Complete: Assessment of missing data patterns and description of non-respondents, as well as the possibility of linkage, queries, and/or additional data curation (e.g., from unstructured fields).
- Accessible and traceable: For transparency and reproducibility of results (as well as submission to regulatory authorities when applicable).

The database feasibility assessment of these existing SMA patient registries will include the following aspects:

- Patient population: Ability to identify both cohorts and subgroups, patient counts, and representativeness.
- Data content: Availability of the necessary data elements, completeness and quality, data gaps, and potential mitigation strategies.
- Willingness to participate: Willingness, preconditions, and expectations (publication rights, authorship, intellectual property rights, etc.).
- Data transfer/hosting: Permission to transfer data for pooled analyses versus federated model, information technology environment, etc.
- Compliance/permissions: Need for additional institutional review board (IRB)/ethics committee (EC) approvals.
- Study conduct: Timelines and data recency.

### 8.4.2 PDC: Prospective Site-Based Data Collection

PDC will be performed at sites in countries not covered by the SDU. Including additional patients will supplement and increase the size of the study population so as to reach the target sample size, given that SMA is a rare disease.

For PDC, the data from enrolled patients will be recorded via eCRF using a web-based electronic data capture (EDC) system. The eCRF will be designed to optimise

consistency of data collection with those of existing patient registries. The degree of detail and completeness of data collected are dependent on local clinical practice. Data from patient notes should be entered into the eCRF as soon as they become available.

The web-based EDC system aims to serve as an integrated, transparent tool to collect and manage data and track study progress at the site and patient level. Data in the EDC system is kept in a central location.

Each study investigator has ultimate responsibility for collecting and reporting all data entered in the eCRFs and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The eCRFs must be electronically signed prior to database lock by the study investigator or by an authorised staff member to attest that the data contained in the eCRFs are correctly recorded. The contract research organisation (CRO) will inform sites when it is time for eCRF sign-off to occur.

In the present case, the source documents are the patient medical charts (see details in Section 8.6.3) and, therefore, data collected in the eCRFs should match the data in the charts.

The final list of countries for PDC will depend on the availability and accessibility of patient registries and their potential to reach the target sample size.

#### 8.4.2.1 PDC: Sites

The number of potential sites in each country will be determined through a feasibility assessment as part of the site qualification process. Sites will be selected in countries not covered by the SDU in order to cover a greater geographic area and to avoid any risk of overlap of patients between SDU and PDC in study data. The country/site mix and the planned number of enrolled sites (overall and by country) will depend on the study's effective start-up date, risdiplam market uptake, number of patients with SMA who are initiating treatment with risdiplam at each site, and overall site interest in participation. Additional countries and sites may be added or substituted if those selected do not perform as expected.

Every effort will be made to maximise use of SDU via collaboration with existing patient registries and networks in order to optimise patient recruitment, leverage any existing data collection, and minimise the burden to reporting sites.

## 8.5 STUDY SIZE

The study aims to enrol patients with genetically confirmed 5q SMA into 2 study cohorts: the risdiplam cohort and the DMT-naive cohort. The study will aim to include 300 patients treated with risdiplam during the eligibility period (risdiplam cohort) and up to 300 untreated patients (DMT-naive cohort) depending on availability of data, as defined by eligibility criteria in Section 8.1.3. The sample size is based on both practical and statistical considerations.

A study size of 300 patients in the risdiplam cohort is considered to be sufficient to provide a reasonable level of precision (e.g., width of confidence interval [CI]) for the effectiveness outcomes in the subgroups.

The following example is provided for illustrative purposes only: If at least 10% (30/300) of the risdiplam cohort are pre-symptomatic with 4 *SMN2* copies (Calucho et al. 2017), and 23% of these (7/30) experience SMA symptoms during the study, the 95% CI will be 10% to 42%. There will also be a 61% risk reduction in SMA symptoms compared with the DMT-naive cohort, if 60% (18/30) of the patients in the DMT-naive cohort who are pre-symptomatic with 4 *SMN2* copies experience SMA symptoms (Wijngaarde et al. 2020) during the study. CIs are calculated with the Clopper-Pearson “exact” method.

## 8.6 DATA MANAGEMENT

### 8.6.1 Data Quality Assurance

For PDC, the CRO will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via EDC. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, and the sites will resolve the discrepancies electronically in the EDC system.

The Sponsor will perform oversight of the data management of this study. The CRO will produce the eCRF specifications for the study based on the Sponsor’s templates, including quality checking to be performed on the data.

The eCRFs and correction documentation will be maintained in the EDC system audit trail. System backups for data stored at the CRO and records retention for the registry data will be consistent with the CRO’s standard procedures. The CRO will comply with the Sponsor’s procedures regarding archiving and record management, as is reported in Section 8.8.4.

### 8.6.2 Electronic Case Report Forms

For PDC, eCRF are to be completed using a web-based EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. The eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the CRO.

All eCRFs should be completed by designated and trained site staff. The eCRFs should be reviewed and electronically signed and dated by the treating physician or a designee.

At the end of the study, the treating physician will receive the data related to participants from his or her site in an electronically readable format (e.g., on a compact disc). Data must be kept with the study records. Acknowledgement of receipt of the data is required.

### 8.6.3 Source Data Documentation

Source documents (paper or electronic) are those in which participant data are recorded and documented for the first time and constitute the patient medical charts. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, and participant files and records kept at pharmacies, laboratories, and medico-technical departments involved in the study.

For PDC and before initiation of the study, the types of source documents that contain study-relevant information will be clearly defined in a clinical monitoring plan (CMP). The CMP defines which kind of source data (if available from clinical routine) can be used for documentation in the study. No additional creation of source data beyond that which is routine is allowed.

Source documents that are required to verify the validity and completeness of data entered in the study must not be obliterated or destroyed and must be retained per the policy for retention of records, which is described in Section 8.8.4.

### 8.6.4 Data Management for SDU

When possible, the data will be transferred electronically to the Sponsor or its designee, and the Sponsor or designee's standard procedures will be used to handle and process the electronic transfer of these data.

## 8.7 DATA ANALYSIS

### 8.7.1 General Aspects

An overview of planned statistical analyses is provided in Sections 8.7.2 to 8.7.9.

Planned statistical analyses will be described in detail in a stand-alone SAP. A detailed methodology for analyses of data collected in this study (including analysis for interim reports and the final report) will be documented in the SAP, which will be dated, filed, and maintained by the sponsor. The SAP will define planned analytic populations, subpopulations, and definitions for variables and outcomes. The SAP will also contain details of how the analysis accounts for patients who may initiate the study in the DMT-naive cohort but then initiate risdiplam during the study period and become enrolled in the risdiplam cohort.

The SAP will include tables, listings, and figure shells to be populated during the final data analysis and details of changes in the planned analysis after protocol finalisation, if applicable. It will also provide a description of the methods used to deal with missing

data, censoring, and procedures to control potential sources of bias and their influence on the results.

All analyses will be conducted in accordance with the study objectives, SAP, and applicable guidelines. Statistical methods will be driven, in part, by the final sample size and the number of events.

Adverse events (AE) will be captured as part of the study EDC but not analysed as part of the study objectives in the clinical study report. They will be transferred from the EDC to the Roche safety database in accordance with routine pharmacovigilance practices and will be described and reviewed in an ongoing process (EMA GVP M6, 2017) and reported in the Periodic Risk Benefit Evaluation Report.

### 8.7.2 Analysis Across Data Sources

For SDU, data will initially be analysed as pooled analysis if feasible. Per registry analysis is not anticipated, due to expected small sample size per registry. For PDC, data will be analysed as pooled analysis with PDC data only, and then as pooled analysis with SDU data if feasible.

The preferred approach for data analyses across data sources is to extract raw data from the different data sources and then to perform a pooled, central analysis (data sharing approach as mentioned in the ENCePP Methodological Guidance, Revision 9, Section 4.6.2.3) (ENCePP 2021). Consequently, every effort will be made to maximise homogeneity in data collection across data sources to allow for a pooled data analysis.

In case this is not possible, alternative approaches are as follows:

- Local data extraction and transformation to a common data model (CDM); local analysis with common statistical programs (as defined in the ENCePP Methodological Guidance, Revision 9, Section 4.6.2.4).
- Local data extraction and analysis, without a CDM but with common variable definitions (as defined in the ENCePP Methodological Guidance, Revision 9, Section 4.6.2.2).

### 8.7.3 Descriptive Statistics

All effectiveness outcomes will be summarised descriptively by cohort (risdiplam cohort and DMT-naive cohort) for the study population by time point (approximately 6-month intervals from the index date up to the end of the observation period).

Continuous variables will be described with summary statistics such as n, mean, standard deviation, median, minimum, and maximum values. For each categorical variable, the frequency and percentage in each category will be reported. Percentages will be calculated using the specified denominator in the table. The frequency and

percentage of subjects with missing data for each data point will be presented. Ninety-five percent CIs will be calculated when relevant.

#### 8.7.3.1 Patient Disposition

The number of patients included in each data source (PDC and SDU) will be summarised by data source and overall. The number of patients who completed the study and discontinued early will be summarised. The reasons for study discontinuation (e.g., lost to follow-up) will also be summarised.

#### 8.7.3.2 Demographic and Clinical Characteristics

Baseline characteristics, including demographics (such as age at cohort entry, sex, race/ethnicity, if permitted by local regulations), SMA genetic confirmation, *SMN2* copy number, symptomatic status, level of respiratory support, comorbidities, anthropometric data, medical history, prior and concomitant treatments (including SMA DMT), and family history of SMA, will be summarised descriptively. Please see detailed information in Appendix 2.

#### 8.7.3.3 Exposure Characteristics

The observation period in person-years will be summarised for both cohorts.

### 8.7.4 Study Population

The study population will be defined as all patients who meet the eligibility criteria. The patients will be grouped by cohort at the start of the study (i.e., risdiplam cohort and DMT-naive cohort).

The primary analysis of this study will include all patients with SMA, regardless of *SMN2* copy number, i.e. the study population will not be restricted to patients confirmed to have *SMN2* copy number 1-4, since information collected during database feasibility has so far indicated that many of the existing SMA patient registries collect information on *SMN2* copy number in the following format: 1; 2; 3; 4+; unknown. It may therefore not be possible to know how many patients have an *SMN2* copy number of 4 versus >4.

The SAP will contain detailed information on how the analysis will account for patients who may be first enrolled in the DMT-naive cohort and later enrolled in the risdiplam cohort.

### 8.7.5 Overview of Primary Analysis

The primary effectiveness outcomes and summary of the analysis methods and metrics are presented in Table 3.

The primary effectiveness estimand is based on a hypothetical treatment strategy that assumes patients will continue in their originally assigned cohort (treated with risdiplam

or DMT-naive) until the end of the study. Only data collected during the observation period will be included, as follows:

1) Risdiplam cohort: Until patients stop taking risdiplam
2) DMT-naive cohort: Until patients take any DMT for the treatment of SMA (e.g., risdiplam, nusinersen)

All effectiveness outcomes will be summarised separately by treatment cohort (risdiplam cohort or DMT-naive cohort). A comparison between the risdiplam and DMT-naive cohorts will be presented for each outcome measure, as described in subsequent sections.

Subgroup analyses and multivariate regression models will be run if the sample size allows. Any approach to account for multiple testing will be described in the SAP as relevant.

**Table 3 Summary of Effectiveness Outcomes and Analysis Methods**

| Effectiveness Outcomes | Variable Type | Analysis Methods |
|---|---|---|
| **Primary Effectiveness Outcomes** | | |
| Survival | Time-to-event | • KM (median survival time with 95% CI)<br>• Cox regression (HR, 95% CI)<br>• KM and Cox regression curves and cumulative incidence curves |
| Prolonged/permanent ventilation-free survival | Time-to-event | • KM (median survival time with 95% CI)<br>• Cox regression (HR, 95% CI)<br>• KM and Cox regression curves and cumulative incidence curves |
| Developmental motor milestone achievement | Binary | • Logistic regression (OR, 95% CI) |
| Motor function assessed using CHOP-INTEND, HFMSE, RULM(scores) | Continuous | • GLMM<br>• MRM |
| **Secondary Effectiveness Outcomes** | | |
| Onset of symptoms (for pre-symptomatic group) | Time-to-event | • KM (median survival time with 95% CI)<br>• Cox regression (HR, 95% CI)<br>• KM and Cox regression curves and cumulative incidence curves |
| Need for nutritional support/tube feeding | Time-to-event | • KM (median survival time with 95% CI)<br>• Cox regression (HR, 95% CI)<br>• KM and Cox regression curves and cumulative incidence curves |
| Hospitalisations and reasons for hospitalisations | • Discrete<br>• Categorical | • Hospitalisation rates<br>• GLM (Poisson distribution) |
| Withdrawal of risdiplam treatment and reasons for withdrawal of treatment (risdiplam cohort only) | • Binary<br>• Categorical | • Treatment withdrawal rates<br>• GLM (Poisson distribution) |
| **Tertiary Effectiveness Outcomes** | | |
| Motor function measure 32 (MFM32) (scores) | Continuous | • GLM<br>• MMRM |
| Revised Hammersmith Scale (RHS) | Continuous | • GLM<br>• MMRM |
| Timed function tests (e.g., 6MWT, 10MWT, TUG Test) (scores) | Continuous | • GLM<br>• MMRM |
| SMAIS (scores) | Continuous | • GLM<br>• MMRM |

Abbreviations: 6MWT, 6-Minute Walk Test; 10MWT, 10-Metre Walk Test; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI, confidence interval; DMT, disease-modifying therapy; GLM, generalised linear model; HFMSE, Hammersmith Functional Motor Scale Expanded; HR, hazard ratio; KM, Kaplan Meier; MFM32, motor function measure 32; MMRM, mixed model for repeated measures; OR, odds ratio; RHS, Revised Hammersmith Scale; RULM, Revised Upper Limb Module; SMAIS, SMA Independence Scale; *SMN2*, survival of motor neuron 2; TUG, Timed Up and Go.

#### 8.7.5.1 Time-to-Event Analysis

Time-to-event analysis will be used for outcomes that assess the length of time until the occurrence of a predefined endpoint. The following time-to-event outcomes defined in Section 8.3.3 will be analysed:

- Survival (i.e., all-cause mortality at each time point)
- Permanent/prolonged ventilation-free survival
- Time to onset of symptoms (only within the pre-symptomatic group)
- Time to need for nutritional support/tube feeding

The proportion of patients who experience each event by year after their index date will be summarised. In addition, the time to event for each outcome during the study period will be reported in months, summarised descriptively (minimum, median, quartiles, and maximum), and analysed using the Kaplan-Meier (KM) method and Cox proportional hazards regression model (Cox regression).

**Kaplan-Meier method**

KM curves and cumulative incidence (1-KM estimators) curves will be used to illustrate the survival probability estimates and the number of patients at risk over time. Median survival time estimates and survival probabilities (with two-sided 95% CIs) at each study period time point will be provided.

**Cox regression model**

Cox curves illustrating the cumulative hazard at a time t of the risk of an event between time 0 and time t will be provided. If the data fail to satisfy the proportionality assumption required for a Cox proportional hazards regression model, then several alternatives will be pursued.

For patients who are event free, the censoring time will be calculated as the time interval between the index date and the patient's final contact with available data concerning the event (or the end of the observation period, whichever is earliest).

#### 8.7.5.2 Regression Analyses

Regression models (univariable and multivariable) will be used to evaluate the association between outcomes of interest and relevant predictors, depending on sample size and if the number of events permits. Generalised linear models (GLMs) and mixed models for repeated measures may be used, considering the longitudinal nature of the data, the possibility for repeated measurements, and exposure varying over time. Binary outcomes will be analysed using logistic regression. For continuous outcomes, treatment

differences and 95% CIs will be presented. For categorical outcomes, odds ratios or relative risks and 95% CIs will be presented.

#### 8.7.5.3 Analysis of Hospitalisation and Reasons for Hospitalisations

Hospitalisation rates defined as the number of hospitalisations divided by the person-years of follow-up (observation period) will be summarised for each cohort. These rates will be compared by calculating the relative risk.

Hospitalisation rates and length of stay will be analysed using GLMs.

Reason for hospitalisation will be described as a categorical variable, and the number and proportion and associated 95% CI of patients hospitalised will be reported.

#### 8.7.5.4 Analysis of Treatment Withdrawal and Reasons for Withdrawal of Treatment

Treatment withdrawal rates, defined as the number of patients who withdraw from treatment divided by the person-years of follow-up, will be measured in risdiplam-treated patients.

Regression models for count data will be used to estimate trends in treatment withdrawal rates in the treated cohort.

The reason for withdrawal will be generated as a categorical variable, and the number and proportion and associated 95% CI of patients who withdraw from treatment will be reported.

#### 8.7.5.5 Comparative Analyses: Adjustment for Covariates and Confounders

To achieve the second study objective, effectiveness outcomes will be compared between the risdiplam cohort and the DMT-naive cohort. Because of the real-world nature of the study, a high potential for imbalance exists between the cohorts with regard to observed covariates. To address this imbalance, adjusted analyses may be employed using statistical techniques, including inverse probability weighting (IPW) and multivariable regression analysis. Final analysis details will be fully described in the SAP.

**Inverse probability weighting**

The IPW method (Austin and Stuart 2015) will be used to improve balance between cohorts. For the comparison between the risdiplam cohort and the DMT-naive cohort, weights will be based on propensity scores that are calculated using a logistic regression model, with cohort assignment as the outcome and adjusted for key prognostic factors (e.g., SMA type, *SMN2* copy number, age at enrolment/cohort entry), which will be confirmed in the SAP). If balance can be achieved, then weights will be incorporated into

the regression models used to calculate the adjusted relative risk or hazard ratio for each outcome. The assessment of balance will be described in the SAP.

#### 8.7.5.6 Subgroup Analyses

In order to meet the first study objective, effectiveness outcomes will be summarised by the following subgroups:

- Symptomatic status (pre-symptomatic and symptomatic)
- *SMN2* copy number

Additional subgroups may be defined in the SAP (e.g., age, time since diagnosis).

#### 8.7.5.7 Sensitivity Analyses

Sensitivity analyses may also be conducted to examine the extent to which changes in certain methods or assumptions affect the results. For example:

- Using the treatment policy estimand, including all data until the end of the study, regardless of treatment received
- Excluding patients confirmed to have greater than 4 *SMN2* copies or with unknown *SMN2* copy number.
- Excluding patients who are treated with any other approved DMT apart from risdiplam
- Excluding patients who start risdiplam before the start of study enrolment(This sensitivity analysis is intended to exclude patients who are in the primary analysis population but whose cohort entry occurred after their risdiplam initiation and who were eligible because they had retrospective data for the up to 6 months between risdiplam index and cohort entry.)
- Excluding patients who were previously or during follow-up enrolled in an investigational drug trial for SMA (This sensitivity analysis is intended to exclude patients who are in the primary analysis population but who at index had previously been in a trial for SMA treatment other than risdiplam, or for patients during the observation period were involved in any trial for SMA treatment.)
- Extending the observation period for patients who discontinue risdiplam to up to 1 year after discontinuation, using SDU data only (PDC will not collect data for this sensitivity analysis)

### 8.7.6 Handling of Missing Data

There will be no imputation for missing data in this study; however, the count and percentages of patients with missing values will be reported for both continuous and categorical variables. In some cases, missing data will be included as a separate category depending on the nature of the variable. Additional details on the handling of missing data will be described in the SAP.

### 8.7.7 Free Text Data

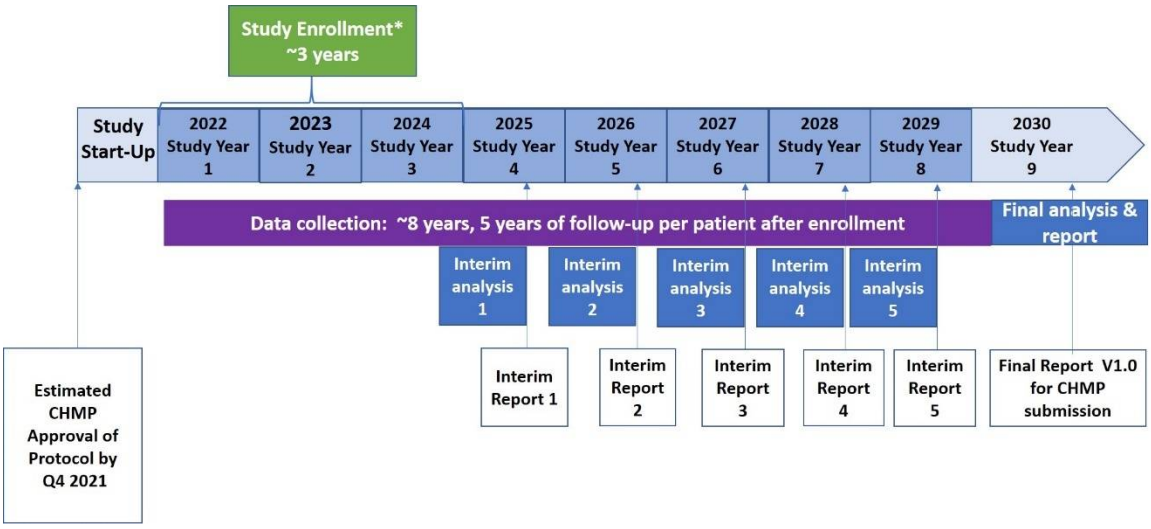
Free text entries of medical conditions, including AE, and medicinal exposures will be coded twice per year using the Medical Dictionary for Regulatory Activities (MedDRA) and WHODrug, respectively. All free text data will be reported in listings. In addition, free text data will also be classified into categories, as appropriate, for analysis and reporting.

### 8.7.8 Interim/Final Analysis and Timing of Analyses

It is anticipated that there will be 5 interim data extractions from existing patient registries (SDU) and 5 interim data extractions from the PDC. The first interim results will be produced after the eligibility period and annually thereafter. The final study results will be based on the sixth and final data extraction from the patient registries (SDU), as well as the final study database from the PDC (see Section 8.4 for additional details regarding data sources).

Interim analyses will be descriptive only. Estimated timelines related to data collection during the study period are provided inFigure 3.

**Figure 3 Estimated Study Timelines**




*These estimated timelines are based on the assumption that the study protocol will be approved by CHMP in Q4 2021. Timelines are also subject to change pending: 1) patient registries' agreement to provide data extractions for use in this study; 2) sites' agreement to provide prospective data collection via electronic data capture; 3) local ethics committee/regulatory authorities' approval of the study protocol (where required); 4) if planned access/reimbursement dates for risdiplam change.

### 8.7.9 Statistical Software

The analyses will be performed using SAS® statistical software, Version 9.4 or higher. Further details will be provided in the SAP.

## 8.8 QUALITY CONTROL

This section applies only to the PDC.

### 8.8.1 Study Documentation

The physician 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, informed consent forms, and documentation of IRB/EC and governmental approval/notification. In addition, at the end of the study, the physician will receive the patient data, which will include an audit trail containing a complete record of all changes to data.

The MAH shall ensure that the dataset 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.

### 8.8.2 Site Audits and Inspections

The physician will permit the MAH or its designee to audit facilities and records relevant to this study.

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs.

The physician will also permit national and local health authorities, Sponsor Monitors, representatives and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

### 8.8.3 Use of Site Computerized Systems

When clinical observations are entered directly into a participating site's computerized medical record system (i.e., in lieu of original hard copy records), the electronic record can serve as the source document if the system has been validated in accordance with Health Authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

### 8.8.4 Retention of Records

Archiving at the study site of records and documents pertaining to the conduct of this study, including eCRFs, informed consent forms, and laboratory test results, has to be for at least 5 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 the MAH or its designee 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 MAH or its designee. Written notification should be provided to the MAH or its designee prior to transferring any records to another party or moving them to another location.

All supporting functional parties will comply with the procedures of the MAH or its designee regarding archiving and record management.

### 8.8.5 Administrative Structure

The Sponsor of the study is F. Hoffmann-La Roche Ltd.

A CRO will be responsible for study management, monitoring, data management, statistical analysis, medical writing for the clinical study report, and, in some cases, vendor oversight.

A Data Review Committee will be implemented to ensure successful implementation of the PDC, to guarantee that the data quality and relevance of the data collected meet predefined criteria, and to prioritise research that will most benefit patients. It will be composed of Roche experts who will assess the data quality and relevancy at the interim analysis time point. This committee may be advised by external consultants as needed.

## 8.9 LIMITATIONS OF THE RESEARCH METHOD

This study aims to evaluate the long-term effectiveness of risdiplam in patients with SMA in a real-world setting. This study's limitations are inherent to the design of non-interventional studies and rare disease studies; potential limitations and proposed strategies to address them are described in the following sections.

### 8.9.1 Sample Size and Selection Bias

A key limitation of this study is the availability of patients in both study cohorts, especially in the DMT-naive cohort.

In the risdiplam cohort, given that there are already 2 other DMTs approved for SMA, three scenarios are anticipated for patients at index: 1) patients would be prescribed risdiplam as a first-ever and only DMT for SMA; 2) patients would be prescribed risdiplam as a substitution for a previous DMT; 3) patients would be prescribed risdiplam as a concurrent/concomitant treatment with another DMT (including gene therapy given prior or during risdiplam treatment). In addition, these patients may be different in terms of clinical characteristics, which would induce a selection bias, i.e., eligibility for other DMTs, severity of SMA, being non-respondent to other DMTs, or treatment preferences. Therefore, some types of patients may be underrepresented in the study population.

In the DMT-naive cohort, given the availability of DMTs, the number of untreated patients will be more limited. Furthermore, experts recommend immediate treatment of patients with 2 to 4 *SMN2* copies identified via newborn screening, as not treating these

patients and waiting for symptoms to emerge may result in motor neuron loss and irreversible disability that could be avoided through the use of DMTs approved for SMA. Therefore, recruiting treatment-naive patients as part of this study may be particularly challenging.

To achieve a sample size large enough to provide clinically meaningful data, cohort entry will be optimised through use of 2 different sources of the data: the use of data collected from existing SMA patient registries where available (SDU), and the use of data collected via PDC at specialised sites in countries not covered by the SDU. In addition, continuous monitoring of patient recruitment at site and country levels will allow the rapid deployment of mitigation strategies in response to any challenges.

Despite expected difficulties in observing DMT-naive patients in the DMT-era, the prospective data collection design has several advantages. These advantages include that comparisons between different exposure cohorts will be based on concurrent (contemporary, not historical) data, and therefore biases due to marked changes in SMA standard of care in recent years will be mitigated. In addition, data from both cohorts will be generated using a similar methodology from the same data sources, thus minimising other sources of bias (EMA 2016).

### 8.9.2 Data Source and Data Collection

The data collected via SDU will come from different existing patient registries where there might be differences in the variables collected, their standards and their format. Early feasibility assessment and collaboration with registry owners aims at understanding these differences and trying to increase standardisation. In the same way, the PDC eCRF will be designed to increase consistency with SDU data.

Collaborations with existing patient registries and networks for patient recruitment across various European countries will ensure diversity among prescribers and patients. The eCRF will be designed to minimise the level of missing data collected at baseline and at follow-up visits. In addition, standardised training and documentation for completing the eCRFs, particularly regarding the importance of accurately collecting exposure and outcome information, will be provided to all participating PDC sites.

Patient visits and outcome assessments in real-world studies are not planned at fixed times, and they strongly depend on the medical needs of the patient and the treatment or care they receive as part of standard practice. Inconsistent frequency, timing and type of assessments are thus expected in this study. The eCRF will be developed with flexibility to allow the collection of diverse data across usual care patterns and outcomes.

### 8.9.3 Observational Study Design Limitations

Due to the observational nature of this study and the inherent characteristics of such a design, this study may be subject to bias, including selection bias, variability in local

treatment practices, guidelines and information bias (data quality). These differences may be present either 1) between SDU and PDC and/or 2) across different patient registries and sites.

Data collected de novo as part of the PDC are fit for the study purpose, and investigators and sites will be aware of the study objectives. In contrast, data in existing patient registries are not collected for the purpose of this study and, thus, might be of variable quality across the different patient registries and have a higher proportion of missing data. Sensitivity analyses by data source will help explore the impact of this potential information bias.

Due to the limitations described in Section 8.9.1 regarding collecting adequate sample size in the study cohorts and subgroups, patient characteristics will likely not be well balanced between the risdiplam and DMT-naive cohorts. This may cause confounding in the effectiveness comparison. Analysis approaches to reduce the impact of this bias, such as regression adjustment and IPW based on propensity scores, will be applied, if possible. If sample sizes are too small or the imbalance is too severe, the cohorts will be analysed separately.

Selection bias due to non-consent will be mitigated by providing clear information to patients and their legal representative(s) regarding the importance of the study and the absence of burden for them. The extent of the selection bias will be monitored via the maintenance of an enrolment log at the site, which will anonymously list all eligible patients, their consenting status, and characteristics and will inform the implementation of mitigation strategies.

In addition, time-related selection biases are also possible given the operational aspects of finding or enrolling patients. For example, this study may not capture non-treated patients with the most severe disease, because their lifespan may not sufficiently overlap with the eligibility period such that the patients can physically enter the study cohort (through SDU or PDC). This selection may artificially inflate survival time in the DMT-naive cohort but is mainly an issue for patients with the most severe (Type 1) disease.

Importantly, we have chosen to maximise the study population to evaluate real-world effectiveness by not limiting the study to patients treated exclusively with risdiplam (e.g., allowing prior and concomitant use of DMTs while in the risdiplam cohort). By allowing this, the isolated treatment effect of risdiplam may not be clearly estimated. Planned sensitivity analyses will help alleviate this limitation.

The impact that potential biases will have on the study results is currently unknown. Still, each potential source of bias will be evaluated descriptively, assessed by sensitivity analyses, and discussed in the reports.

# 9. PROTECTION OF HUMAN SUBJECTS

## 9.1 PATIENT DISCONTINUATION

### 9.1.1 Discontinuation from Treatment with Studied Medicinal Product

Participants and physicians have the right at any time and for any reason to discontinue treatment with risdiplam. Every effort should be made to obtain information on the reasons for treatment discontinuation and start/end date of treatment.

### 9.1.2 Withdrawal from Primary Data Collection

Participants have the right at any time and for any reason to withdraw their consent from their data being collected in the study. Reasons for withdrawal of participants from the PDC may include, but are not limited to, the following:

- Participant's wish to withdraw consent at any time
- Participant is lost to follow-up
- Participant's death

Every effort should be made to obtain information on participants who withdraw consent to participate in the study. The primary reason for discontinuation from the study should be documented whenever possible on the appropriate page of the eCRF; however, it is not mandatory for the participant to disclose the reason for withdrawal of consent. If the participant has revoked his/her consent to participate in the PDC, in order to comply with regulatory requirements to protect the scientific integrity of the registry, all data that have already been collected during the registry will be retained, shared, and further used in accordance with this protocol and the ICF. Participants will not be followed for any reason after consent has been withdrawn.

A participant will be considered lost to follow-up if he/she does not report for the routine follow-up visit (as per standard of care) and if the participant/participant's legally authorised representative cannot be contacted even after 3 attempts, over a period of at least 6 months following the last planned visit.

In cases of participant death, all possible attempts should be made by site staff to collect information on death, date, and cause of death.

### 9.1.3 Site Discontinuation (PDC)

The Sponsor will notify the treating physicians if enrolment is halted/paused, or if the Sponsor decides to discontinue the PDC. The Sponsor has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Slow recruitment

- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) and Good Pharmacovigilance Practices (GVP) or any other pertinent local law or guideline
- Non-compliance with the safety collection process

## 9.2 COMPLIANCE WITH LAWS AND REGULATIONS

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

The study will comply with national and EU requirements for ensuring the well-being and rights of participants in non-interventional post-authorisation studies.

## 9.3 INFORMED CONSENT

### 9.3.1 Primary Data Collection

The MAH or its designee's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The MAH or its designee must review and approve any proposed deviations from the MAH or its designee's sample Informed Consent Forms or any alternate Consent Forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final Consent Forms approved by the IRB/EC must be provided to the MAH or its designee for archiving and for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before start of documentation of his or her data in the eCRF. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to first documentation of this patient's data in the eCRF.

By signing the form, the patient confirms that he/she has been informed about the study and agrees to pseudonymous data collection, pooling of data with similar scientific data (if applicable), and the possibility of monitoring activities. It is the accountability of the physician for ascertaining that the subject has comprehended the information and to obtain written informed consent from each patient participating in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by Site Operations Representatives at any time.

### 9.3.2 Secondary Use of Data

It is expected that, in most of the existing patient registries, the patients have explicitly agreed to any secondary use of their data.If this is not the case, and as it is not possible/practical to obtain informed consent for use of secondary data, certain precautions will be taken, including:

- Ensuring that data are anonymised / pseudonymised
- Ensuring that final analysis data are anonymised / pseudonymised
- Ensuring that the possibility of linkage back to individual identified patients is impossible or tightly controlled

## 9.4 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Site Operations Representative in consultation with the Scientific Responsible and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

In addition to the requirements for collecting and reporting SAEs and AEs as per Section 10 to the MAH or its designee, physicians must comply with requirements for AE reporting to the local health authority and IRB/EC.

## 9.5 CONFIDENTIALITY

The MAH or its designee 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 MAH or its designee's location.

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

The MAH or its designee, including affiliates, collaborators, and licensees, may use study data labelled with the patient ID numbers. Study data may also be shared with independent researchers or government agencies, but only after personal information that can identify the patient has been removed. Patients' study data may be combined with other patient's data and/or linked to other data collected from the patients. Patients' study data may be used to help better understand why people get diseases, how to best prevent, diagnose, and treat diseases, and to develop and deliver access to new medicines, medical devices, and healthcare solutions to advance patient care.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, the MAH or its designee's monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

## 9.6 FINANCIAL DISCLOSURE

Physicians will provide the MAH or its designee with sufficient, accurate financial information in accordance with local regulations to allow the MAH or its designee to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Physicians are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last data collection).

# 10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

## 10.1 SAFETY REPORTING REQUIREMENTS FOR STUDIED MEDICINAL PRODUCTS

For non-interventional studies based on secondary use of data, reporting of AE/adverse drug reactions (ADR) is not required. Based on current guidelines from the ISPE (ISPE, 2015) and the EMA GVP Module VI – Management and Reporting of Adverse Reactions to Medicinal Products (EMA GVP M6, 2017), non-interventional studies such as the one described in this protocol that use aggregated patient data from established patient registries do not require expedited reporting of suspected AEs. Therefore, for the SDU part of this study, no suspected AE/ADR are expected.

The remainder of Section 10 relates only to the PDC part of this study.

### 10.1.1 Safety Parameters and Definitions

For the PDC part of this study, all AEs that are observed and recorded in the process of routine care (standard medical practice) by site investigators will be collected. Exemptions to this are events that are clearly consistent with the expected pattern of progression of the underlying disease, which should not be recorded as AEs, and include deaths and hospitalisations attributed solely to progression of SMA. These data will be captured as effectiveness assessment data only. Further details are in the protocol section Exemption of Specific Adverse Events from Collection (Section 10.1.1.3).

Additionally, the reporting requirements in this section apply only to studied medicinal products (observational products of interest, i.e., risdiplam only, as specifically stated in the study objectives). For safety reporting requirements for non-studied medicinal products, see Section 10.2.

#### 10.1.1.1 Adverse Events

According to the International Conference of Harmonisation, an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Appendix 3
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.

#### 10.1.1.2 Assessment of Serious Adverse Events (Immediately Reportable to the Marketing Authorisation Holder), Non-Serious Adverse Events of Special Interest and Other Non-Serious Adverse Events

**Serious Adverse Events**

An SAE is any AE that meets any of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life-threatening (NOTE: The term “life-threatening” refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires or prolongs inpatient hospitalization (see Appendix 3)
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient’s ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study medicine
- Is a significant medical event in the physician’s judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Appendix 3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF (for detailed instructions, see Appendix 3).

### Non-Serious Adverse Events of Special Interest

AEs of special interest for this study include the following:

- Cases of potential medicine-induced liver injury that include an elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Appendix 3).
- Suspected transmission of an infectious agent by the study medicine, as defined below:
    - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term only applies when a contamination of the study medicine is suspected.

### Non-Serious Adverse Events Other Than Adverse Events of Special Interest

All non-serious AEs in addition to AEs of special interest must be collected for this study according to the appropriate level of MedDRA Classification.

#### 10.1.1.3 Exemption of Specific Adverse Events from Collection (AEs Including Deaths and Hospitalizations Attributed Solely to Progression of SMA)

Mortality and hospitalizations: For this protocol, mortality and hospitalizations (i.e., inpatient admission to a hospital) are effectiveness endpoints. Deaths and hospitalizations that occur during the protocol-specified AE reporting period (see Section 10.1.2.1) that are attributed by the investigator solely to progression of SMA should be recorded on the relevant effectiveness eCRFs only. All other deaths or hospitalizations that occur during the AE reporting period, regardless of relationship to study treatment, must also be recorded on the SAE eCRF and immediately reported to the Sponsor (see Section 10.1.3.1).

Additionally, an event that leads to hospitalization under the following circumstances should not be reported as an AE or a SAE:

- Hospitalization for respite care
- Hospitalization for a pre-existing condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not experienced an AE
- An event that leads to hospitalization under the following circumstances is not considered to be a SAE, but should be reported as an AE instead:
  - Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

Events consistent with expected progression of SMA: Medical occurrences or symptoms of deterioration that are anticipated as part of SMA should only be recorded as an AE if judged by the Investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the protocol-specified AE reporting period. When recording an unanticipated worsening of SMA on the AE eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., “accelerated SMA”).

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

### 10.1.2 Methods and Timing for Capturing and Assessing Safety Parameters

AEs that are observed and recorded in the process of routine care (standard medical practice) by site investigators will be collected. The physician is accountable for ensuring that all AEs collected as per protocol (see Section 10.1.1.1 for definition) are recorded in the AE section of the eCRF and reported to the MAH or its designee in accordance with instructions provided in this section and in Section 10.1.3.

For each AE recorded in the AE section of the eCRF, the physician will make an assessment of seriousness (see Section 10.1.1.2), severity (see Appendix 3), and causality (see Appendix 3).

#### 10.1.2.1 Adverse Event Reporting Period

All AEs subject to the collecting and reporting requirements outlined in this protocol, whether reported by the patient or noted by study personnel, will be recorded in the

patient's medical record and in the AE section of the eCRF. Once the patient is enrolled in the study, AEs will be collected during exposure to risdiplam (i.e., from initiation to 30 days after last dose). After this period, if the treating health care professional (HCP) becomes aware of any related AEs to any medicinal product, they should be notified to the competent authority in the Member State where the reactions occurred or to the MAH or its designee of the suspected medicinal product, but not to both (to avoid duplicate reporting).

#### 10.1.2.2 Procedures for Recording Adverse Events

HCPs should use correct medical terminology/concepts and MedDRA coding when recording AEs in the AE section of the eCRF. Colloquialisms and abbreviations should be avoided.

Only one AE term should be recorded in the event field of the eCRF.

See Appendix 3 for further specific instruction regarding:

- Diagnosis versus signs and symptoms
- AEs occurring secondary to other AEs
- Persistent or recurrent AEs
- Abnormal Laboratory Values
- Abnormal Vital Sign Values
- Abnormal Liver Function Tests
- Deaths
    - All events with an outcome or consequence of death should be classified as serious adverse events (SAEs) and reported to the MAH or its designee immediately. Refer to Section 10.1.1.3 and Appendix 3.3.7 for exemptions.
- Pre-existing Medical Conditions
- Lack of Therapeutic Efficacy or Worsening of SMA (also refer to Section 10.1.1.3 for exemptions)
- Hospitalization or Prolonged Hospitalization (also refer to Section 10.1.1.3 for exemptions)
- Overdoses, Misuses, Abuses, Off-Label Use, Occupational Exposure, or Medication Error
- Quality Defects, Falsified Medicinal Products, and Product Complaints
- Drug Interactions

### 10.1.3 Reporting Requirements from Healthcare Professional to Marketing Authorisation Holder

#### 10.1.3.1 Immediate Reporting Requirements from Healthcare Professional to Marketing Authorisation Holder

Certain events require immediate reporting to allow the MAH or its designee and the regulatory authorities to take appropriate measures to address potential new risks associated with the use of the medicine. The HCP must report such events to the MAH or its designee immediately; under no circumstances should reporting take place more than 24 hours after the HCP learns of the event. The following is a list of events that the HCP must report to the MAH or its designee within 24 hours after learning of the event, regardless of relationship to study medicine:

- SAEs
- Non-serious AEs of special interest
- Pregnancies

The HCP must report new significant follow-up information for these events to the MAH or its designee immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

For reports of SAEs and non-serious AEs of special interest, including follow-up, HCPs should record all case details that can be gathered immediately (i.e., within 24 hours) in the AE page of the eCRF and submit the report via the EDC system. A report will be generated and sent to Roche Drug Safety by the EDC system.

In the event that the EDC system is temporarily unavailable, please refer to Section 10.1.3.3.

HCPs must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

#### 10.1.3.2 Reporting Requirements for Non-Serious Adverse Events

For all non-serious AEs, including follow-up reports, HCPs must record all case details that can be gathered within 30 calendar days of learning of the event on the AE section of the eCRF and submit the report via the EDC system. A report will be generated and sent to Roche Drug Safety or the relevant MAH or its designee (for non-Roche studied

products, depending on local regulation) to allow appropriate reporting to relevant competent authorities.

In the event that the EDC system is temporarily unavailable, please refer to Section 10.1.3.3.

#### 10.1.3.3 If EDC System Is Temporarily Unavailable or Not Used

In the event that the EDC system is temporarily unavailable, a completed paper reporting form and fax coversheet should be faxed/scanned to Roche Drug Safety or its designee immediately (i.e., no more than 24 hours after learning of the event) or within 30 days for non-serious AEs if not AEs of special interest, using the fax number or email address provided to physicians.

Once the system is available again, all information should additionally be entered and submitted via the EDC system.

#### 10.1.3.4 Reporting Requirements for Pregnancies/Breastfeeding

##### Pregnancies/Breastfeeding in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the physician if they become pregnant during the study or within 28 days after the last dose of risdiplam. A Pregnancy Report should be completed by the physician immediately (i.e., no more than 24 hours after learning of the pregnancy) and sent to Roche Drug Safety. Pregnancy should not be recorded on the AE section of the eCRF. The physician should counsel the patient, discussing the risks of the pregnancy and the possible effects on the foetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the foetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the AE section of the eCRF.

Suspected adverse reactions that occur in infants following exposure to a medicinal product from breast milk should be reported to Roche Drug Safety.

##### Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the physician if their partner becomes pregnant during the study or within 4 months after the last dose of study medicinal product. A Pregnancy Report should be completed by the physician immediately (i.e., no more than 24 hours after learning of the pregnancy) and sent to Roche Drug Safety. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study medicine. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the physician will update the Pregnancy Report with additional information on the course and outcome of the pregnancy. A physician who is contacted by the male patient or his pregnant partner

may provide information on the risks of the pregnancy and the possible effects on the foetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

### Abortions

Any abortion should be classified as an SAE (as the MAH or its designee considers abortions to be medically significant), recorded in the AE section of the eCRF, and reported to the MAH or its designee immediately (i.e., no more than 24 hours after learning of the event; see Section 10.1.3.1).

### Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to risdiplam or the female partner of a male patient exposed to risdiplam should be classified as an SAE, recorded in the AE section of the eCRF, and reported to the MAH or its designee immediately (i.e., no more than 24 hours after learning of the event; see Section 10.1.3.1).

## 10.1.4 Follow-up of Patients After Adverse Events

### 10.1.4.1 HCP Follow-up

The HCP should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the HCP, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to risdiplam until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented in the AE section of the eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed by the treating physician until pregnancy outcome.

### 10.1.4.2 Marketing Authorisation Holder Follow-up

For all AEs, the MAH or its designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case. AE follow-up should be documented in the AE section of the eCRF.

## 10.2 SAFETY REPORTING REQUIREMENTS FOR NON-STUDIED PRODUCTS

Although AE information is not being actively solicited for non-studied products, the physician/consumers are reminded to report any adverse reactions (for which they suspect a causal role of a product) that come to their attention to the MAH or its

designee of the suspected product, or to the concerned competent authorities via the national spontaneous reporting system.

In addition, the following should also be reported if occurring during exposure to a marketed product, even in the absence of AEs:

- Pregnancy
- Breastfeeding
- Abnormal laboratory findings
- Overdose, abuse, misuse, off-label use, medication error, or occupational exposure
- Reports of lack of efficacy
- Product quality defects and falsified medicinal products
- Data related to a suspected transmission of an infectious agent via a medicinal product
- Drug interactions (including drug/drug, drug/food, drug/device, and drug/alcohol)

When a patient is not exposed to a marketed medicinal product, but the HCP/consumer becomes aware of the potential for a medication error, or an intercepted medication error, this should also be reported.

## 10.3 REPORTING OF PRODUCT COMPLAINTS WITHOUT ADVERSE EVENTS

Report Roche product complaints without AEs, where Product Complaint is any written or oral information received from a complainant that alleges deficiencies related to Identity, Quality, Safety, Strength, Purity, Reliability, Durability, Effectiveness, or Performance of a product after it has been released and distributed to the commercial market, to . Report non-Roche-product complaints as per local regulation.

# 11. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the MAH or its designee is dedicated to openly providing information on the study to HCPs and to the public, both at scientific congresses and in peer-reviewed journals. The MAH or its designee will comply with all requirements for publication of study results.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the physician must agree to submit all manuscripts or abstracts to the MAH or its designee prior to submission for publication or presentation. This allows the MAH or its designee to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the physician.

In accordance with standard editorial and ethical practice, the MAH or its designee will generally support publication of multicentre studies only in their entirety and not as individual centre data. In this case, a coordinating physician will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors' authorship requirements. Any formal publication of the study in which contribution of the MAH or its designee's personnel exceeded that of conventional monitoring will be considered as a joint publication by the physician and the appropriate MAH or its designee personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the MAH or its designee, except where agreed otherwise.

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

Not applicable.

# Appendix 2
# Summary of the Variables Collected During the Study

| Study Variable Category[1] | Index/Closest to Index Date[2] | Follow-up Visits[3,4] |
|---|---|---|
| **Demographic and Clinical Characteristic Variables** | | |
| Socio-demographic information[5] | X | |
| Height and weight | X | X |
| Medical history | X | |
| Level of respiratory support | X | X |
| Comorbidities[6] | X | X |
| Prior and concomitant treatments (incl. SMA DMT) | X | X |
| Symptomatic status, either:<br>- Symptomatic (date of SMA symptoms onset and presenting symptom(s), or<br>- Pre-symptomatic | X | X |
| SMA genetic diagnosis and other information:<br>- Genetic diagnosis date, *SMN1* pathogenic mutation<br>- Number of *SMN2* gene copies, method for identification of *SMN2* copies | X | |
| Family history of SMA | X | |
| **Exposure Variables** | | |
| Risdiplam treatment characteristics (risdiplam cohort)[7] | X | X |
| SMA DMT after the index date (including any change in risdiplam treatment) | | X |
| **Effectiveness Outcomes** | | |
| **Primary Effectiveness Outcomes** | | |
| Survival[8] | X | X |
| Prolonged/permanent ventilation-free survival[9] | X | X |
| Developmental motor milestone achievement[10] | X | X |
| Motor function assessed using CHOP-INTEND, HFMSE or RULM | X | X |

[1] Signed informed consent will be obtained before any primary data collection.
[2] Index: refer to Table 2 Definition of Index Date by Study Cohort and Hybrid Study Database Category.
[3] As per routine practice. The study aims to collect 5 years of follow-up data per patient (if available). If patients are enrolled at the start of the eligibility period, they could potentially have up to 8 years of follow-up data.
[4] Last follow-up visit: risdiplam discontinuation, withdrawal, lost to follow-up, end of study period, or death.
[5] e.g., age at cohort entry, sex, race/ethnicity, if permitted by local regulations.
[6] e.g., scoliosis.
[7] e.g., start and end dates, dosing, frequency.
[8] e.g., date and cause of death.
[9] e.g., start and end dates, duration, level of respiratory support.
[10] e.g., head control/sitting independently/standing independently/walking independently.

| Study Variable Category[1] | Index/Closest to Index Date[2] | Follow-up Visits[3,4] |
|---|---|---|
| **Secondary Effectiveness Outcomes** | | |
| Onset of symptoms (for pre-symptomatic group) | X | X |
| Need for nutritional support/tube feeding | X | X |
| Hospitalisations and reasons for hospitalisations | X | X |
| Withdrawal of risdiplam treatment and reasons for withdrawal of treatment (risdiplam cohort only) | | X |
| **Tertiary Effectiveness Outcomes** | | |
| Motor function measure 32 (MFM32) | X | X |
| Revised Hammersmith Scale (RHS) | X | X |
| Timed function tests[11] | X | X |
| SMA Independence Scale (SMAIS) | X | X |
| **Other Variables** | | |
| AE and SAEs (only for PDC patients within the risdiplam cohort and for routine pharmacovigilance; not for analysis) | X | X |

[11] Timed function tests include 6-Minute Walk Test (6MWT), 10-Metre Walk Test (10MWT), and Timed Up and Go (TUG) Test.

# Appendix 3
# Methods for Assessing and Recording Adverse Events

| Organization of Appendix 3 | |
|---|---|
| **Appendix 3.1** | **Assessment of Severity of Adverse Events** |
| **Appendix 3.2** | **Assessment of Causality of Adverse Events** |
| **Appendix 3.3** | **Procedures for recording Adverse Events** |

## Appendix 3.1 Assessment of Severity of Adverse Events

The AE severity grading scale for the NCI CTCAE (v5.0) will be used for assessing AE severity. The table below will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

### Adverse Event Severity Grading Scale

| Grade | Severity |
|---|---|
| 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated |
| 2 | Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a] |
| 3 | Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c] |
| 4 | Life-threatening consequences or urgent intervention indicated [d] |
| 5 | Death related to AE [d] |

Note: Based on the NCI CTCAE (v5.0), which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as an SAE (see Section 10.1.3.1 for reporting instructions), per the definition of SAE in Section 10.1.1.2.

[d] Grade 4 and 5 events must be reported as SAEs (see Section 10.1.3.1 for reporting instructions), per the definition of SAE in Section 10.1.1.2.

### Appendix 3.2 Assessment of Causality of Adverse Events

Physicians should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study medicine, indicating “yes” or “no” accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study medicine
- Course of the event, considering especially the effects of dose reduction, discontinuation of study medicine, or reintroduction of study medicine (when applicable)
- Known association of the event with the study medicine or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each of the medicinal product.

## Appendix 3.3 Procedures for Recording Adverse Events

### Appendix 3.3.1 Diagnosis versus Signs and Symptoms

For AEs, a diagnosis (if known) should be recorded in the AE section of the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded in the AE section of the eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

### Appendix 3.3.2 Adverse Events Occurring Secondary to Other Events

In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be recorded as an independent event in the AE section of the eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal haemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately in the AE section of the eCRF if it is unclear as to whether the events are associated.

### Appendix 3.3.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once in the AE section of the eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent AE becomes more severe, the most extreme severity should also be recorded in the AE section of the eCRF. If the event becomes serious, it should be reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 10.1.3.1 for reporting instructions). The AE section of the eCRF should be updated by changing

the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.

A recurrent AE is one that resolves between patient's evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded separately in the AE section of the eCRF.

### Appendix 3.3.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalaemia) or a change in concomitant therapy
- Is clinically significant in the physician's judgment

It is the physician's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × the upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded in the AE section of the eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded in the AE section of the eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalaemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once in the AE section of the eCRF (see Appendix 3.3.4 for details on recording persistent AEs).

### Appendix 3.3.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms

- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the physician's judgment

It is the physician's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded in the AE section of the eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once in the AE section of the eCRF (see Appendix 3.3.4 for details on recording persistent AEs).

**Appendix 3.3.6 Abnormal Liver Function Tests**

The finding of an elevated ALT or AST ($> 3 \times$ the ULN) in combination with either an elevated total bilirubin ($> 2 \times$ the ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, physicians must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ the ULN
- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded in the AE section of the eCRF (see Appendix 3.3.5) and reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event) either as an SAE or a non-serious AE of special interest (see Section 10.1.3.1).

**Appendix 3.3.7 Deaths**

For this protocol, mortality is an effectiveness endpoint. Deaths that occur during the protocol-specified AE reporting period (see Section 10.1.2.1) that are attributed by the investigator solely to progression of SMA should be recorded on the relevant effectiveness eCRFs only. All other deaths that occur during the AE reporting period, regardless of relationship to study treatment, must also be recorded on the SAE eCRF and immediately reported to the Sponsor (see Section 10.1.3.1).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the AE section of the eCRF. Generally, only one such event should be reported. The term **"sudden death"** should only be used for the occurrence of an abrupt

and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the AE section of the eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

### Appendix 3.3.8 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the first observational visit for this study. Such conditions should be recorded on the medical history section of the eCRF.

A pre-existing medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events in the AE section of the eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

### Appendix 3.3.9 Lack of Therapeutic Efficacy or Worsening of SMA

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as effectiveness assessment data only. Medical occurrences or symptoms of deterioration that are anticipated as part of SMA should only be recorded as an AE if judged by the Investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the protocol-specified AE reporting period. When recording an unanticipated worsening of SMA on the AE eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated SMA"). If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE. This exception from reporting includes events of disease progression with a fatal outcome which are clearly attributable to disease progression.

### Appendix 3.3.10 Hospitalisation or Prolonged Hospitalisation

For this protocol, hospitalisations (i.e., inpatient admission to a hospital) are effectiveness endpoints. Hospitalisations that occur during the protocol-specified AE reporting period (see Section 10.1.2.1) that are attributed by the investigator solely to progression of SMA should be recorded on the relevant effectiveness eCRFs only. All other hospitalisations that occur during the AE reporting period, regardless of relationship to study treatment, must also be recorded on the Serious AE eCRF and immediately reported to the Sponsor (see Section 10.1.3.1).

- Hospitalisation for respite care
- Hospitalisation for a pre-existing condition, provided that all of the following criteria are met:

- The hospitalisation was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
- The patient has not experienced an AE

- An event that leads to hospitalisation under the following circumstances is not considered to be a SAE, but should be reported as an AE instead:
  - Hospitalisation that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

### Appendix 3.3.11 Overdoses, Misuses, Abuses, Off-Label Use, Occupational Exposure, or Medication Error

Any overdose, misuse, abuse, off-label use, occupational exposure, medication error (including intercepted or potential), or any other incorrect administration of medicine under observation should be noted in the Drug Administration section of the eCRF. Any overdose, abuse, misuse, inadvertent/erroneous administration, medication error (including intercepted or potential), or occupational exposure reports must be forwarded to the marketing authorization holder with or without an AE.

Reports with or without an AE should be forwarded to the MAH or its designee as per non-serious timelines. If the associated AE fulfils the seriousness criteria, the event should be reported to the MAH or its designee immediately (i.e., no more than 24 hours after learning of the event, see Section 10.1.3.1).

For the purpose of reporting cases of suspected adverse reactions, an occupational exposure to a medicine means an exposure to a medicine as a result of one's professional or non-professional occupation.

### Appendix 3.3.12 Quality Defects, Falsified Products and Product Complaints, Including Co-packed Devices

Reports of suspected or confirmed falsified product or quality defect of a product, with or without an associated AE, should be forwarded to the MAH or its designee as per non-serious timelines. This includes quality defects of the co-packed devices (press in-bottle adapter and dispenser/syringe). If the associated AE fulfils the seriousness criteria, the event should be reported to the MAH or its designee immediately (i.e., no more than 24 hours after learning of the event, see Section 10.1.3.1).

### Appendix 3.3.13 Drug Interactions

Reports of suspected or confirmed drug interactions, including drug/drug, drug/food, drug/device and drug/alcohol, should be forwarded to the MAH or its designee as per non-serious timelines. If the associated AE fulfils the seriousness criteria, the event should be reported to the MAH or its designee immediately (i.e., no more than 24 hours after learning of the event, see Section 10.1.3.1).