NOVARTIS

Clinical Development

LMI070/Branaplam

LMI070X2201 / NCT02268552

# An open-label multi-part first-in-human study of oral LMI070 in infants with Type 1 spinal muscular atrophy

# Statistical Analysis Plan (SAP)


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| 26-Aug-20 | Prior to IA4 DB lock | Further update of Parts 1 & 2 | Alignment with TFL | |
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| 8-Dec-22 | Prior to Final DB | Add Part 3 | Incorporate Part 3 into analyses for Parts 1 & 2; adapt to reflect pruning of some analyses, add some neurophysiological spaghetti plots | |

## Table of contents

## List of tables



## List of figures

## List of abbreviations

| | |
|---|---|
| AE | Adverse event |
| ATC | Anatomical Therapeutic Chemical class |
| AUC | Area Under the Curve |
| BSA | Body Surface Area |
| CMAP | Compound Motor Action Potential |
| CSR | Clinical Study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DDS | Dose Determining Set |
| DLT | Dose Limiting Toxicity |
| DMC | Data Monitoring Committee |
| eCRF | Electronic Case Report Form |
| FAS | Full Analysis Set |
| IA3 | Interim Analysis 3 |
| IA4 | Interim Analysis 4 |
| MAR | Missing at Random |
| MedDRA | Medical Dictionary for Drug Regulatory Affairs |
| Mos. | Months |
| MTD | Maximum Tolerated Dose |
| NCV | Nerve Conduction velocity |
| PD | Pharmacodynamics |
| PK | Pharmacokinetics |
| PT | Preferred Term |
| RAP | Report and Analysis Process |
| SAE | Serious Adverse Event |
| SAF | Safety Set |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SMA | Spinal muscular Atrophy |
| SMN2 | Survival motor neuron 2 |
| TEAE | Treatment Emergent Adverse Event |
| TFLs | Tables, Figures, Listings |
| WHO | World Health Organization |

# 1 Introduction

The Report Analysis Plan (RAP) documents contain detail information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for study "***LMI070X2201***".

The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis planned in the protocol, including planned interim analysis (see Section 2.13) and the full analysis for Parts 1, 2, and 3 after the final database lock.

This document is consistent with the current study protocol amendment version 11, 19-Jul-2021.
Study design

This is an open-label, multi-part, first-in-human proof of concept study in infants with Type 1 spinal muscular atrophy (SMA), to evaluate safety, tolerability, PK, PD and efficacy of oral branaplam. Parts 1, 2, and 3 are intended to be non-confirmatory.

All subjects must have confirmed SMA type 1 and 2 copies of the survival motor neuron 2 (SMN2) gene.

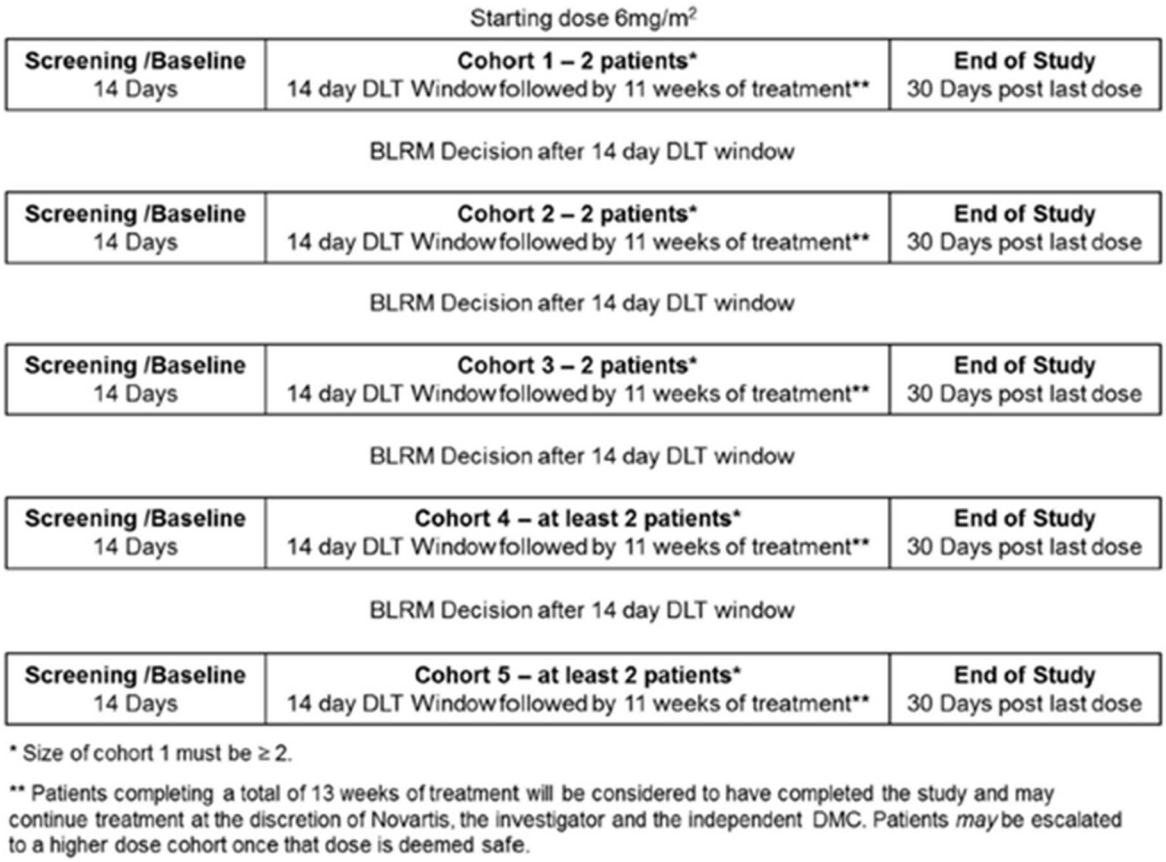
## Part 1

In Part 1 of the study, subjects will be dosed once weekly with branaplam. The branaplam dose will be escalated in subsequent cohorts until maximum tolerated dose (MTD) was determined or when sufficient pharmacokinetics (PK) results would not confirm that the MTD could not be reached due to a potential pharmacokinetic exposure plateau at higher doses. Subjects will be dosed at least 24 hours apart for the first dose of each dose level to ensure subject safety.

A decision to dose-escalate the next cohort will be made after safety data have been collected for 14 days following the first dose (14-day DLT window). PK will be used to confirm that there is no accumulation of the compound. If PK data show the potential for accumulation, the dosing frequency may be decreased. For Part 1, subjects completing 13 weeks of treatment will be considered to have completed the study. Subject who are continuing to receive study drug follow the Assessment schedule-part1- Extended treatment period. The assessment schedule repeats until the subject discontinues the study or transfers to Part 3 if the investigator agree that this is in the best interest of the subject.

Figure 1-1 depicts the study design for Part 1, where 13 subjects have been enrolled (at least 2 subjects planned in each of 5 cohorts). No new subjects will be enrolled in Part 1.

**Figure 1-1 Study design for Part 1**




* Size of cohort 1 must be ≥ 2.

** Patients completing a total of 13 weeks of treatment will be considered to have completed the study and may continue treatment at the discretion of Novartis, the investigator and the independent DMC. Patients *may* be escalated to a higher dose cohort once that dose is deemed safe.

**Table 1-1 Provisional dose levels for Part 1 dose escalation**

| Dose level | Provisional weekly dose | Increment from previous dose[b] |
|---|---|---|
| -2[a] | 1 mg/m$^2$ | 67% reduction |
| -1[a] | 3 mg/m$^2$ | 50% reduction |
| **1** | **6 mg/m$^2$** | **Starting dose** |
| 2 | 12 mg/m$^2$ | 100% increase |
| 3 | 24 mg/m$^2$ | 100% increase |
| 4 | 48 mg/m$^2$ | 100% increase |
| 5* | 60 mg/m$^2$ | 25% increase |

[a] Dose level -1 and -2 may be used if appropriate (e.g. if the **starting dose** level is not well tolerated)

[b] The dose increase will be guided by BLRM. Up to 100% dose increase is permitted per dose level if the recommended dose increment is higher than 100%

* This weekly dose level 5 would convert into a 2.95 mg/kg dose of branaplam for a 6.5 kg, 62 cm subject with BSA of approximately 0.32m$^2$

Table 1-1 is intended as an example for guidance for the dose escalation part only. Intermediate dose levels may be used, and some dose levels may be skipped if the dose-escalation rules presented in this protocol are followed. Actual dose levels will be confirmed in writing by Novartis and provided to all participating study sites before treatment of subjects in a new cohort.

In Part 1, the dose unit changed from a body surface-normalized unit ($mg/m^2$) to a body weight-normalized unit (mg/kg). The body weight-normalized doses will be used in all study reports. These will be labelled "nominal dose".

### Part 2

Part 2 of the study enrolled new subjects into one of 2 different dose cohorts; cohort 1 at 0.625 mg/kg and cohort 2 at 2.5 mg/kg with once weekly dosing for 52 weeks, as shown in Figure 1-2 below. The branaplam dose was escalated in subsequent cohorts after 6 subjects have been enrolled or at least 3 subjects from the initial cohort have completed 13 weeks of treatment.

A total of 25 subjects have been enrolled into Part 2 and assigned to either of the two doses, previously tested in Part 1. It is designed to evaluate whether a change over time in infant and growth parameters can be detected and interpreted as an effect in branaplam treatment.

Subjects will be receiving the same dose of branaplam once weekly, as allocated at enrollment throughout the initial 52 weeks, no intra-cohort escalation is planned. Exceptionally in case of lack of efficacy/progressive disease, as assessed by investigator, subject(s) from cohort 1 (0.625 mg/kg) may receive next level dose (2.5 mg/kg).

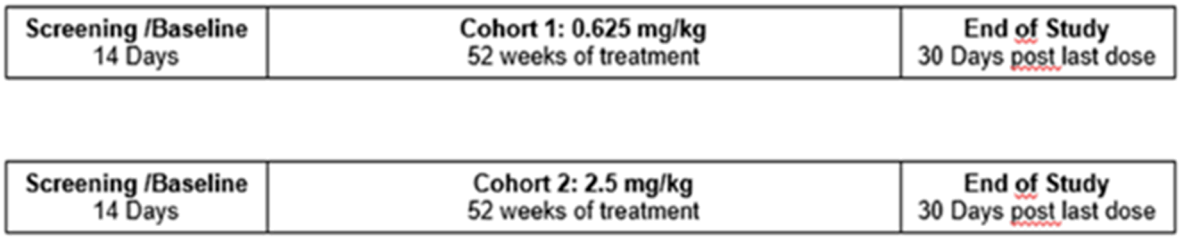
In general, the loss of positive benefit of the cohort 1 dose of branaplam will be assessed on a subject by subject level. If positive benefit cannot be confirmed for majority of the subjects, the cohort 1 might be closed and ongoing subject will be escalated to 2.5 mg/kg.

After completing 52 weeks of treatment, subjects will have the possibility to continue receiving further branaplam treatment under Part 3 (see below).

However, in order to ensure subject safety, a dose escalation within cohort 1 will be allowed in case there is no benefit at the 0.625 mg/kg dose or if there is evidence of loss of benefit (nondurable effect). Efficacy and safety data will be reviewed after three subjects have completed at least 13 weeks of treatment. In the event of no positive effect, or a loss of positive effect of 0.625 mg/kg will allow subjects to receive the next higher dose.

Part 2 subjects who have completed at least 52 weeks of branaplam treatment will be eligible to continue receiving branaplam treatment, as long as this is in the best interest of the subject, as assessed by the investigator and will be enrolled to Part 3. For subjects who will not be eligible to enter Part 3 or decide to discontinue, End of Study of Part 2 will be performed.

**Figure 1-2 Study design for Part 2**




In Part 2, dosing will be changed from dosing per $m^2$ of body surface to per weight based dosing (mg/kg) in order to simplify study conduct, by following a more common out subject care practice while achieving *in vivo* exposures to branaplam that are similar to those associated with clinical response in Part 1. The doses administered in Part 1 were originally normalized to body surface area (BSA). The equivalent mg/kg doses were calculated for a selection of dosing events (all events with PK sampling, 119 in total) and the results are shown in Table 1-2. The calculations were based on 13 subjects who ranged in age from 2 to 17 months, in weight from 5 to 11 kg, and in length from 60 to 88 cm. As can be seen from Table 1-2, the calculated mg/kg doses were strongly correlated and increased linearly with the BSA normalized doses. Plasma exposure measured by AUC was approximately dose-proportional up to 60 mg/$m^2$ with an exposure overlap at the two highest doses (48 and 60 mg/$m^2$). The 48 mg/$m^2$ dose was chosen as the dose to anchor all dose calculations for Part 2. The planned weight-based doses for Part 2 were calculated as factors of 2.5 mg/kg (corresponding to 48 mg/$m^2$ in Part 1) as shown in Table 1-3.

**Table 1-2 Dose conversion between BSA and weight for subjects in Part 1**

| Dose level | Weekly dose by BSA | N | Calculated weekly dose by weight | CV (%) | Planned weekly dose by weight |
|---|---|---|---|---|---|
| 1 | 6 mg/$m^2$ | 28 | 0.302 mg/kg | 8.7 | 0.3125 mg/kg |
| 2 | 12 mg/$m^2$ | 12 | 0.640 mg/kg | 5.0 | 0.625 mg/kg |
| 3 | 24 mg/$m^2$ | 22 | 1.27 mg/kg | 7.6 | 1.25 mg/kg |
| 4 | 48 mg/$m^2$ | 27 | 2.51 mg/kg | 8.3 | 2.5 mg/kg |
| 5 | 60 mg/$m^2$ | 30 | 2.89 mg/kg | 5.3 | 3.125 mg/kg |

N= number of data points used for dose conversion

**Table 1-3 Planned doses for Part 2**

| Dose level | Planned weekly dose by weight | Approximate equivalent weekly dose by BSA |
|---|---|---|
| 1 | 0.625 mg/kg | 12 mg/$m^2$ |
| 2 | 2.5 mg/kg | 48 mg/$m^2$ |

## Part 3

Part 3 of the study is long term safety and efficacy follow up of extended oral/enteral, once a week branaplam treatment, as shown in Figure 1-3. All subjects who participated in Part 1 and Part 2 of the study and have completed at least 52 weeks of treatment or more, can continue receiving treatment with branaplam in Part 3 of the study, as long as this is in the best interest of the subject, as assessed by the investigator.

Continuation of the treatment will be done at the dose assigned while in Part 1 or Part 2 of the study. However, if at any later time an interim analysis of Part 1 or Part 2 study data suggest one optimal dose considering existing safety as well as efficacy data, the dose subjects are receiving might be switched to the selected optimal dose. Details of the planned doses for Part 3, are shown in Table 1-4.

Here is the rationale for selecting the higher dose in Part 3:

**Figure 1-3 Study design for Part 3**

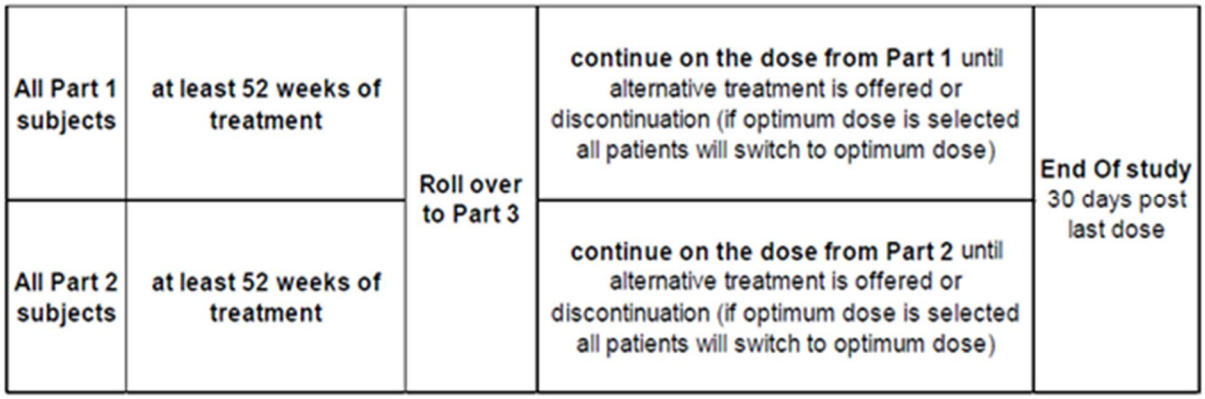



**Table 1-4 Planned doses for Part 3**

| Dose level | Planned weekly dose by weight | Approximate equivalent weekly dose by BSA |
|---|---|---|
| 1 | 0.3125 mg/kg | 6 mg/m$^2$ |
| 2 | 0.625 mg/kg | 12 mg/m$^2$ |
| 3 | 1.25 mg/kg | 24 mg/m$^2$ |
| 4 | 2.5 mg/kg | 48 mg/m$^2$ |
| 5 | 3.125 mg/kg | 60 mg/m$^2$ |

Here is the rationale for selecting the higher dose in Part 3:

There was a consensus [redacted], that the higher dose should be selected for future studies

a. No apparent safety concerns, so maximize potential long-term benefit

b. Anecdotal evidence that some kids on lower dose did better after switching to higher dose (part 2) and some kids did worse after switching to a lower dose (part 1)

c. Evidence of more target engagement with higher dose

## 1.1 Study objectives and endpoints

The purpose of Part 1 of the study was to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy; and to estimate the Maximum Tolerated Dose (MTD) of branaplam.

The purpose of Part 2 of the study is to characterize dose-exposure-response to inform dose selection of orally administered branaplam in subjects with Type 1 SMA.

The purpose of Part 3 of the study is to provide continuous treatment with branaplam to patients who have participated in Part 1 or 2 of the study and have completed at least 52 weeks of treatment. In addition, Part 3 provides long-term safety and efficacy follow-up for patients treated with branaplam for more than 52 weeks.

### 1.1.1 Primary objective(s)

| Objective | Endpoint |
|---|---|
| **Part 1:** Determine the safety and tolerability of ascending weekly doses and estimate the MTD of branaplam in infants with Type 1 SMA.<br>**Part 2:** Evaluate the safety and tolerability of 2 doses of branaplam administered for 52 weeks in subjects with Type 1 SMA.<br>**Part 3:** Assess long-term safety and tolerability of extended oral/enteral, once a week branaplam treatment in patients with type 1 SMA who have had at least 52 weeks of treatment in either Part 1 or 2 study of this protocol. | **For all parts:**<br>• Physical exam<br>• Vital signs<br>• ECG and echocardiographic evaluation<br>• Safety laboratory parameters<br>• Ophthalmologic examination<br>• Neurologic examination<br>• Nerve conduction study: sensory nerve action potential (SNAP), nerve conduction velocity (NCV) for sensory and motor nerves and ulnar nerve compound motor action potential (CMAP)<br>• Adverse events |

### 1.1.2 Secondary objective(s)

| Objective | Endpoint |
|---|---|
| **Part 1, Part 2, Part 3:** | **Part 1, Part 2, Part 3:** |
| • To evaluate branaplam pharmacokinetics in plasma after single and repeated doses of branaplam | • AUC and Cmax of branaplam |
| • To evaluate the effect of branaplam on growth parameters | • Growth measurements (body weight, head circumference, length and chest circumference) |
| • To evaluate the effect of branaplam on respiratory function | • Pulse oximetry*, respiratory rate, paradoxical breathing assessment, chest circumference during quiet breathing*.<br>• |
| • To evaluate the effect of branaplam on infant motor development. | • CHOP-INTEND infant motor scale up to the age of 36 months.<br>• Hammersmith Infant Neurologic Examination |
| **In addition to the above for Part 2:** | **In addition to the above for Part 2:** |

| | |
|---|---|
| • To evaluate the efficacy of branaplam on motor and developmental milestones | • Preservation of oral feeding |
| • To evaluate the efficacy of branaplam on the ability to sit without support. | • Ability to sit without support over time as assessed by HINE-2 |
| **In addition to the above for Part 3:** | **In addition to the above for Part 3:** |
| • To evaluate the efficacy of branaplam on motor and developmental milestones | • Preservation of oral feeding |
| • To evaluate the efficacy of branaplam on the ability to sit without support. | • Ability to sit without support, stand or walk over time as assessed by HINE-2 |
| • To assess the proportion of infants who are alive and are without permanent ventilation over time | • Adverse Events and deaths over time |
| • To assess the impact of treatment with branaplam on time-to-event (death, permanent ventilation) | • Adverse Events and deaths over time |
| Note: * these secondary endpoints will not be analysed in this analysis (see Section 4 for a rationale) | |

[redacted]

# 2 Statistical methods

## 2.1 Data analysis general information

A statistical vendor (CRO), [redacted] to which the statistical analysis is outsourced, will perform all planned analyses, i.e. IAs (Section 2.13) as well as the final analysis after the final database lock. Details of the analyses for Parts 1, 2, and 3 at the upcoming final database lock are outlined in this document.

Data will be analyzed using SAS® version 9.4 (or higher).

Descriptive summary statistics, unless otherwise specified, for continuous variables include number of non-missing observations (n), mean, median, standard deviation (SD), Q1 (25$^{th}$ percentile), Q3 (75$^{th}$ percentile), minimum and maximum, while for categorical variables frequencies and relative percentages will be reported.

Descriptive analyses will be stratified by part as follows:

- For disposition, demographics, baseline characteristics, and medical history, and protocol deviations, by parts (Part 1, Part 2, Part 1 & 2, Part 3)
- For all other summaries and figures: Part 1 & 3, Part 2 & 3, and Total (where applicable)

For analysis summaries, Part 1 will not be stratified by titration dose, while Part 2 will be stratified by the two treatment doses. For patients in Part 3 from Part 2, the fixed dose in Part 2 will be used as a strata; thus transitions from a low dose to a higher dose in Part 3 will not be analysed separately.

Individual graphs, such as spaghetti plots by study part and treatment and panel plots by study part and subject (with actual dose displayed as background shading) relative to time from first dose (in months) will be provided for selected endpoints, as applicable. Individual graphs relative to calendar age (in months) such as growth curve plots of vital signs, etc. will also be presented.

Listings will be provided by study part, cohort and subject.

The following treatment labels will be used for all tables, listings and figures in the order provided here:

- **Part 1:**
  LMI070 0.3125 mg/kg, LMI070 0.625 mg/kg, LMI070 1.25 mg/kg, LMI070 2.5 mg/kg, LMI070 3.125 mg/kg
- **Part 2:**
  LMI070 0.625 mg/kg, LMI070 2.5 mg/kg
- **Part 3 (from Part 1):**
  LMI070 0.625 mg/kg, LMI070 2.5 mg/kg, LMI070 3.125 mg/kg
- **Part 3 (from Part 2):**
  LMI070 0.625 mg/kg, LMI070 2.5 mg/kg

### 2.1.1 General definitions

***'Actual dose'*** will be derived as the current dose for each subject on a daily basis across the entire study; in the case of the day of a dose change, the new dose will used.

***'Treatment group'*** in Parts 2 & 3 will refer to the treatment group combination (as mentioned above) for efficacy analyses, and to the actual treatment for safety analyses (see definition below). In Parts 1 & 3, this will be Overall.

***'Cohort'*** will refer to the initial dose for baseline or demographic characteristics.

The term ***'Study Day'*** in this document relates to the Analysis Relative Day, Relative Start Day or Relative End Day as applicable. ***'Study Day'*** is defined relative to the analysis reference date, which is the date of treatment assignment; it is the number of days from the reference date to the analysis date. For all dates on or after the analysis reference date, the study day is the difference to the analysis reference date plus one day (i.e. for date ≥ reference date, study day = date - reference date + 1); for any dates prior to the analysis reference date, the study day is

simply the difference to the reference date (i.e. for date < reference date, study day = date - reference date). Thus, the Subject Reference Start Date is designated as Study Day 1, while the date directly prior to the reference date is defined as Study Day -1 (there is no Study Day 0).

***'Baseline'*** is the last non-missing assessment obtained prior to the first administration of study drug. That means that if the measurement at the baseline visit is missing, then the previous measurement preceding baseline will be used as the baseline measurement. For pulse and blood pressure vital sign values, the baseline is the last non-missing value taken prior to the first administration of study drug.

***'Treatment phase'*** includes the time interval on treatment and post-treatment follow-up. Any measurements taken after baseline will be considered as post-baseline measurements.

***'Actual treatment'*** is defined as the treatment group the patient has most exposure to in each Part (for Parts 2 & 3), leading to a treatment group combination; in the case of two treatments having identical exposure, the higher dose will be used. This will be used for safety analyses.

***'Calendar age'*** is defined as the age at the date of evaluation.

In this study, ***'last contact with the subject'*** will be the end of study visit, unless an SAE occurs. However, to ensure subject safety, every SAE must be reported to Novartis:

- occurring until 30 days after the last study visit, regardless of causality
- occurring after the 30 days period, if a causal relationship to study treatment is suspected

***'Nominal visits'*** Nominal visits are defined as all scheduled visits as per the clinical study protocol including the EOS visits. The definition of nominal visit excludes unscheduled visits.

***'Safety cutoff'*** Unless explicitly otherwise stated (e.g. SAEs and deaths), data up to and including the safety cutoff will be included in the analysis and data beyond this time point for a given subject will be excluded from the safety analysis. The safety cutoff is defined as the minimum of

- the study day the patient leaves study Parts 1, 2*, or 3
- the database cutoff date (the Final Database Lock date)
- 30 days after permanent study drug discontinuation.
- day of first dose of alternate treatment for SMA

***'Efficacy cutoff'*** Unless explicitly otherwise stated, data up to and including the efficacy cutoff will be included in the analysis and data beyond this time point for a given subject will be excluded from the efficacy analysis. The efficacy cutoff is defined as the minimum of

- the study day the patient leaves study Parts 1, 2*, or 3
- the database cutoff date (the Final Database Lock date)
- day of first dose of alternate treatment for SMA

The following rules will be applied to assign data to part 3:

a. For datasets/endpoints that have planned visit numbers populated (e.g. HINE, CHOP-INTEND, etc.), the visit number included in the IFC dataset under 'Consent for

additional follow-up study phase' which is the first visit of Part 3 (as confirmed by Cmed) will be used:

i.e. assessments with visit numbers that are >= that IFC visit number will be assigned to Part 3.

b. For datasets/endpoints that do not have planned visit numbers populated (e.g. AEs, Feeding status, etc.), the visit date that corresponds to the above IFC visit number will be used:

i.e. assessment dates that are >= that IFC visit date will be assigned to Part 3. In particular, AEs or concomitant medication with start date time >= that IFC visit date will be assigned to Part 3.

In general, data collected at a visit during the Part 3 will be analysed together with the part the subject came from (i.e. 'Parts 1 & 3', 'Parts 2 & 3').

The safety cutoff applies to safety analyses only. The only exception to this are serious adverse events and deaths. Any SAEs occurring after the 30 days period, where a causal relationship to study treatment is suspected, will be reported. All deaths will be reported irrespective of safety cutoff.

In general, treatment emergent AEs are defined as events starting after the first dose of study drug that were absent pre-treatment, or events present prior to the first dose but increased in severity after the first dose. This assumes the same AE with increased severity is properly entered as a separate record in the database with start date being the date when severity increases and that a second AE with same severity won't be entered before the same AE is resolved.

For any other safety analyses based on post-baseline abnormalities compared to baseline (i.e. ECGs, vital signs, etc.), where either of the results is not available, the ***'missing'*** category will be included to avoid any abnormalities being overlooked.

When showing values over time, for subjects who prematurely discontinued the study, study completion visit assessments will be displayed as if they had occurred at the next scheduled visit.

The eGFR is calculated using the MDRD formula. eGFR [mL/min/1.73 m2]=175 × (serum

Creatinine [umol/L]/88.4)-1.154 × (age [years])-0.203 × (0.742 if female) × (1.212 if African American) (Levey et al. 2007).

### 2.1.2 Visit windows

Visit-windows will be used for both efficacy and safety data summaries by visit. Visit windows define a time period "around" the targeted visit date as defined in the evaluation schedule of the clinical study protocol. Visit-windows are non-overlapping and defined without gaps between consecutive visit windows. The width of visit windows may vary over the course of the study period.

The purpo-se of visit windows is to analyze data based on the actual study days (rather than "nominal" visits). E.g., if a subject's Week 3 visit is delayed; it is possible that the Week 3 data be re-aligned to visit-window Week 5 and be summarized under Week 5.

- For **efficacy analyses** all nominal visits (i.e. excluding unscheduled visits) will be mapped into one of the defined visit-windows.
- For **safety analyses** all nominal visits (i.e. excluding unscheduled visits) will be mapped into one of the defined visit-windows. Data from unplanned visits and unscheduled visits will not be re-mapped to other visits for the purpose of displaying variables over time except for laboratory data. For laboratory data, a time window will be used to identify the assessment closest to the target day within the window over time. The unplanned and unscheduled visits will be used in the analysis of event endpoints, and will be counted towards shift tables or other analyses regarding the worst observed values for patients.

It is possible that more than one assessment of a subject fall into a particular visit-window. Section 2.1.3, deals with the statistical approaches to handle multiple visits in a given visit-window.

Tables displaying summary statistics "by visit" will also use the term *visit-window* as column header; this is to remind the reviewer that multiple assessments of a subject might be summarized. Table 2-1 up to Table 2-12, provide visit-windows definitions for applicable parameters in Part 1 and Part 2.

In all scenarios, later visits in Part 1, Part 1 & 3 and/or visits in Parts 2 & 3, will be treated in a similar fashion to those displayed, so that days between visits are divided evenly, without any gaps. The target day is number of weeks * 7 – 6. For Part 1, after week 26 visit, the extended treatment period (as per protocol Table 7-2) is repeated. For example, for CHOP-INTEND, after week 26 visit, there are week 32 (+6 weeks) and week 39 (+7 weeks) visits.

Note: When deriving week 52 visit-window for Part 2 data, the upper bound of the week 52 visit-window will be ignored in order to make sure we do not miss any week 52 Part 2 data. Indeed, data collected by visit are assumed to be Part 3 assessments if visit numbers are >= IFC ('Consent for additional follow-up study phase') visit number.

For the visit windows for monthly assessments in Part 3, Table 2-13 uses the following logic: planned day -13 days for the start of visit window and +14 days for the end of the visit windows.

Day 0 in Tables 2-13 and 2-14 corresponds to the date of informed consent 'Consent for additional follow-up study phase', which is the first visit of Part 3.

Note: some assessments were collected only every 3 months in Part 3 (e.g. CHOP-INTEND, HINE-2). For those endpoints, please display in summary statistics tables only planned visits for Part 3 (as per protocol).

Part 3 visits will be appended to whichever part the subject came from (i.e. Parts 1 & 3 and Parts 2 & 3).

**Table 2-1 Visit windows for CHOP INTEND**

| | Part 1 Day | | | Part 2 Day | | |
|---|---|---|---|---|---|---|
| **Visit-window** | **Start** | **Target** | **End** | **Start** | **Target** | **End** |
| Week 6 | 1 | 36 | 60 | 1 | 36 | 60 |
| Week 13 | 61 | 85 | 106 | 61 | 85 | 106 |
| Week 19 | 107 | 127 | 151 | 107 | 127 | 151 |
| Week 26 | 152 | 176 | 200 | 152 | 176 | 197 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Week 32 | 201 | 218 | 242 | 198 | 218 | 242 |
| Week 39 | 243 | 267 | 291 | 243 | 267 | 287 |
| Week 45 | 292 | 309 | 333 | 288 | 309 | 333 |
| Week 52 | 334 | 358 | 382 | 334 | 358 | 382 |

**Table 2-2 Visit windows for HINE**

| | Part 1 Day | | | Part 2 Day | | |
|---|---|---|---|---|---|---|
| **Visit-window** | **Start** | **Target** | **End** | **Start** | **Target** | **End** |
| Week 6 | | | | 1 | 36 | 60 |
| Week 13 | | | | 61 | 85 | 106 |
| Week 19 | 107 | 127 | 151 | 107 | 127 | 151 |
| Week 26 | 152 | 176 | 200 | 152 | 176 | 197 |
| Week 32 | 201 | 218 | 242 | 198 | 218 | 242 |
| Week 39 | 243 | 267 | 291 | 243 | 267 | 287 |
| Week 45 | 292 | 309 | 333 | 288 | 309 | 333 |
| Week 52 | 334 | 358 | 382 | 334 | 358 | 382 |

**Table 2-3 Visit windows Acceptability and Palatability Questionnaire**

| | Part 1 Day | | | Part 2 Day | | |
|---|---|---|---|---|---|---|
| **Visit-window** | **Start** | **Target** | **End** | **Start** | **Target** | **End** |
| Week 2 | | | | 1 | 8 | 11 |
| Week 3 | | | | 12 | 15 | 18 |
| Week 4 | | | | 19 | 22 | 57 |
| Week 14 | 89 | 92 | 95 | 58 | 92 | 95 |
| Week 15 | 96 | 99 | 102 | 96 | 99 | 102 |
| Week 16 | 103 | 106 | 109 | 103 | 106 | 144 |
| Week 27 | 110 | 183 | 186 | 145 | 183 | 186 |
| Week 28 | 187 | 190 | 193 | 187 | 190 | 193 |
| Week 29 | 194 | 197 | 200 | 194 | 197 | 235 |
| Week 40 | 201 | 274 | 277 | 236 | 274 | 277 |
| Week 41 | 278 | 281 | 284 | 278 | 281 | 284 |
| Week 42 | 285 | 288 | 291 | 285 | 288 | 291 |

**Table 2-4 Visit windows for Motor and Speech milestones**

| | Part 1 Day | | | Part 2 Day | | |
|---|---|---|---|---|---|---|
| **Visit-window** | **Start** | **Target** | **End** | **Start** | **Target** | **End** |
| Week 13 | | | | 61 | 85 | 106 |
| Week 19 | 103 | 127 | 151 | 107 | 127 | 151 |
| Week 26 | 152 | 176 | 200 | 152 | 176 | 197 |
| Week 32 | 201 | 218 | 242 | 198 | 218 | 242 |
| Week 39 | 243 | 267 | 291 | 243 | 267 | 287 |
| Week 45 | 292 | 309 | 333 | 288 | 309 | 333 |
| Week 52 | 334 | 358 | 382 | 334 | 358 | 382 |

**Table 2-5 Visit windows for ECG evaluations**

| | Part 1 Day | | | Part 2 Day | | |
|---|---|---|---|---|---|---|
| **Visit-window** | **Start** | **Target** | **End** | **Start** | **Target** | **End** |
| Day 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Week 2 | 2 | 8 | 46 | 2 | 8 | 46 |
| Week 13 | 47 | 85 | 130 | 47 | 85 | 99 |
| Week 17 | | | | 100 | 113 | 145 |
| Week 26 | 131 | 176 | 221 | 146 | 176 | 190 |
| Week 30 | | | | 191 | 204 | 236 |
| Week 39 | 222 | 267 | 312 | 237 | 267 | 281 |
| Week 43 | | | | 282 | 295 | 326 |
| Week 52 | 313 | 358 | 403 | 327 | 358 | 389 |

**Table 2-6 Visit windows for body temperature and blood pressure/pulse rate/respiratory rate**

| | Part 1 Day | | | Part 2 Day | | |
|---|---|---|---|---|---|---|
| **Visit-window** | **Start** | **Target** | **End** | **Start** | **Target** | **End** |
| Day 2 | 1 | 2 | 2 | 1 | 2 | 2 |
| Day 3 | 3 | 3 | 3 | 3 | 3 | 5 |
| Day 5 | 4 | 5 | 6 | | | |
| Week 2 | 7 | 8 | 11 | 6 | 8 | 18 |
| Week 3 | 12 | 15 | 18 | | | |
| Week 4 | 19 | 22 | 25 | | | |
| Week 5 | 26 | 29 | 32 | 19 | 29 | 43 |
| Week 6 | 33 | 36 | 39 | | | |
| Week 7 | 40 | 43 | 46 | | | |
| Week 8 | 47 | 50 | 53 | | | |
| Week 9 | 54 | 57 | 60 | 44 | 57 | 71 |
| Week 10 | 61 | 64 | 67 | | | |
| Week 11 | 68 | 71 | 74 | | | |
| Week 12 | 75 | 78 | 81 | | | |
| Week 13 | 82 | 85 | 102 | 72 | 85 | 102 |
| Week 18 | 103 | 120 | 134 | 103 | 120 | 134 |
| Week 22 | 135 | 148 | 162 | 135 | 148 | 162 |
| Week 26 | 163 | 176 | 190 | 163 | 176 | 193 |
| Week 31 | 191 | 211 | 225 | 194 | 211 | 225 |
| Week 35 | 226 | 239 | 253 | 226 | 239 | 253 |
| Week 39 | 254 | 267 | 281 | 254 | 267 | 284 |
| Week 44 | 282 | 302 | 316 | 285 | 302 | 316 |
| Week 48 | 317 | 330 | 344 | 317 | 330 | 344 |
| Week 52 | 345 | 358 | 372 | 345 | 358 | 372 |

[redacted]

**Table 2-8 Visit windows for physical examination, respiratory function, body weight/body length/BSA, head and chest circumference**

| | Part 1 Day | | | Part 2 Day | | |
|---|---|---|---|---|---|---|
| **Visit-window** | **Start** | **Target** | **End** | **Start** | **Target** | **End** |
| Week 2 | 1 | 8 | 11 | 1 | 8 | 18 |
| Week 3 | 12 | 15 | 18 | | | |
| Week 4 | 19 | 22 | 25 | | | |
| Week 5 | 26 | 29 | 32 | 19 | 29 | 43 |
| Week 6 | 33 | 36 | 39 | | | |
| Week 7 | 40 | 43 | 46 | | | |
| Week 8 | 47 | 50 | 53 | | | |
| Week 9 | 54 | 57 | 60 | 44 | 57 | 71 |
| Week 10 | 61 | 64 | 67 | | | |
| Week 11 | 68 | 71 | 74 | | | |
| Week 12 | 75 | 78 | 81 | | | |
| Week 13 | 82 | 85 | 102 | 72 | 85 | 102 |
| Week 18 | 103 | 120 | 134 | 103 | 120 | 134 |
| Week 22 | 135 | 148 | 162 | 135 | 148 | 162 |
| Week 26 | 163 | 176 | 190 | 163 | 176 | 193 |
| Week 31 | 191 | 211 | 225 | 194 | 211 | 225 |
| Week 35 | 226 | 239 | 253 | 226 | 239 | 253 |
| Week 39 | 254 | 267 | 281 | 254 | 267 | 284 |
| Week 44 | 282 | 302 | 316 | 285 | 302 | 316 |
| Week 48 | 317 | 330 | 344 | 317 | 330 | 344 |
| Week 52 | 345 | 358 | 372 | 345 | 358 | 372 |

**Table 2-9 Visit-windows for Ulnar CMAP and mRNA blood collection**

| | Part 1 Day | | | Part 2 Day | | |
|---|---|---|---|---|---|---|
| **Visit-window** | **Start** | **Target** | **End** | **Start** | **Target** | **End** |
| Week 13 | 1 | 85 | 130 | 1 | 85 | 130 |
| Week 26 | 131 | 176 | 221 | 131 | 176 | 221 |
| Week 39 | 222 | 267 | 312 | 222 | 267 | 312 |
| Week 52 | 313 | 358 | 403 | 313 | 358 | 403 |

**Table 2-10 Visit-windows for ophthalmological evaluations**

| | Part 1 Day | | | Part 2 Day | | |
|---|---|---|---|---|---|---|
| **Visit-window** | **Start** | **Target** | **End** | **Start** | **Target** | **End** |
| Week 12 | 1 | 78 | 123 | 1 | 78 | 123 |
| Week 25 | 124 | 169 | 214 | 124 | 169 | 214 |
| Week 38 | 215 | 260 | 305 | 215 | 260 | 305 |
| Week 51 | 306 | 351 | 396 | 306 | 351 | 396 |

**Table 2-11 Visits windows for Hematology, Blood chemistry, and Urine analysis**

| | Part 1 Day | | | Part 2 Day | | |
|---|---|---|---|---|---|---|
| **Visit-window** | **Start** | **Target** | **End** | **Start** | **Target** | **End** |
| Day 3 | 1 | 3 | 5 | 1 | 3 | 5 |
| Week 2 | 6 | 8 | 11 | 6 | 8 | 18 |
| Week 3 | 12 | 15 | 22 | | | |
| Week 5 | 23 | 29 | 36 | **19** | 29 | 43 |
| Week 7 | 37 | 43 | 50 | | | |
| Week 9 | 51 | 57 | 64 | 44 | 57 | 71 |
| Week 11 | 65 | 71 | 78 | | | |
| Week 13 | 79 | 85 | 102 | 72 | 85 | 102 |
| Week 18 | 103 | 120 | 134 | 103 | 120 | 134 |
| Week 22 | 135 | 148 | 162 | 135 | 148 | 162 |
| Week 26 | 163 | 176 | 190 | 163 | 176 | 193 |
| Week 31 | 191 | 211 | 225 | 194 | 211 | 225 |
| Week 35 | 226 | 239 | 253 | 226 | 239 | 253 |
| Week 39 | 254 | 267 | 281 | 254 | 267 | 284 |
| Week 44 | 282 | 302 | 316 | 285 | 302 | 316 |
| Week 48 | 317 | 330 | 344 | 317 | 330 | 344 |
| Week 52 | 345 | 358 | 372 | 345 | 358 | 372 |

**Table 2-13 Monthly visit windows in Part 3**

| | Part 3 Day | | |
|---|---|---|---|
| **Visit-window** | **Start** | **Target** | **End** |
| P3 Month 0 | 0 | 0 | 14 |
| P3 Month 1 | 15 | 28 | 42 |
| P3 Month 2 | 43 | 56 | 70 |
| P3 Month 3 | 71 | 84 | 98 |
| P3 Month 4 | 99 | 112 | 126 |
| P3 Month 5 | 127 | 140 | 154 |
| P3 Month 6 | 155 | 168 | 182 |
| P3 Month 7 | 183 | 196 | 210 |
| P3 Month 8 | 211 | 224 | 238 |
| P3 Month 9 | 239 | 252 | 266 |
| P3 Month 10 | 267 | 280 | 294 |
| P3 Month 11 | 295 | 308 | 322 |
| P3 Month 12 | 323 | 336 | 350 |
| P3 Month x | 28*x-13 | 28*x | 28*x+14 |

**Table 2-14 Three-monthly visit windows in Part 3**

| | Part 3 Day | | |
|---|---|---|---|
| **Visit-window** | **Start** | **Target** | **End** |
| P3 Month 0 | 0 | 0 | 42 |
| P3 Month 3 | 43 | 84 | 126 |
| P3 Month 6 | 127 | 168 | 210 |
| P3 Month 9 | 211 | 252 | 294 |
| P3 Month 12 | 295 | 336 | 378 |
| P3 Month x | 28*x-41 | 28*x | 28*x+42 |

* post-baseline values

**Table 2-15 Bin widths for HINE subscale stacked bar charts**

| | Study Day | |
|---|---|---|
| **Visit-window** | **Start** | **End** |
| >0-3 months | 1* | 91 |
| >3-6 months | 92 | 182 |

| | | |
|---|---|---|
| >6-9 months | 183 | 273 |
| >9-12 months | 274 | 364 |
| >x-x+3 months | (x/3)*91+1 | ((x+3)/3)*91 |

* post-baseline values

### 2.1.3 Multiple assessments within visit windows

It is possible that multiple assessments of a subject fall into the same visit-window (e.g. due to unscheduled visits). All results (scheduled and unscheduled) will be displayed in listings, but only one value (observed or derived) will be selected for summary statistics by visit-window.

For **quantitative variables**, the assessment closest to the target day will be selected. If more than one assessment is at the same distance to the target day, the worst case will be selected. For tables displaying the worst-case scenario, all assessments within a visit window will be used to identify the worst (e.g. the maximum or the minimum depending on parameter).
For qualitative variables, the worst record is selected; it is noted that in the relevant data subsection, worst case is always well defined.

**Table 2-13 Worst case direction for each parameter**

| Assessment | Worst case |
|---|---|
| CHOP INTEND | The lower the value |
| HINE | The lower the value |
| ECGs | The higher the value |
| Vital Signs | The higher the value |
| Labs | Usually the higher the value; however for some labs, such as hemoglobin and platelets, both higher and lower values can be worst case direction |
| Neurophysiological evaluations (NCV, CMAP, etc.) | The lower the value |
| Growth measurements | The lower the value |
| Respiratory measurements | The lower the value |
| [redacted] | |

### 2.1.4 Issues resolved in the analysis datasets

#### 2.1.4.1 ECG/ECHO data

For some patients, ECG/ECHO data was entered mistakenly as unscheduled visits instead of scheduled visits. The algorithms for multiple assessments for quantitative variables will be applied (see Section 2.1.3). For descriptive analyses for these patients, all data within each scheduled visit window will be taken into account, and the value on the closest day followed

by the worst case will be used. For worst case analyses, the worst case within a time window will be used.

## 2.2 Analysis sets

The following populations will be used for the statistical analyses:

**Enrolled Set (ENR)** will consist of all subjects giving study informed consent and are assigned a treatment.

**Full Analysis Set (FAS)** will consist of all subjects in the Enrolled Set who received at least one dose of study drug. Patients will be analyzed according to the treatment group (as defined in Section 2.1.1).

**Safety Set (SAF)** will consist of all subjects in the Enrolled Set who received at least one dose of study drug. Patients will be analyzed according to the actual treatment received (as defined in Section 2.1.1). The Safety Set will be used for the analyses of safety variables.

**Dose Determining Set (DDS)** (Part 1 only) will consist of all subjects from the safety set who have sufficient safety evaluations to provide DLT information 2 weeks after the first dosing or discontinue earlier due to DLT. Subjects who do not experience DLT during the first 2 weeks after the first dose are considered to have sufficient safety evaluations if they are considered by both the Sponsor and Investigators to have sufficient safety data to conclude that a DLT did not occur.

**PK Analysis Set** will include all subjects that received at least one dose of branaplam with available PK data and no protocol deviations with relevant impact on PK data. The PK Analysis Set will be used for the analyses of PK variables.

### 2.2.1 Subgroups of interest

Subgroup analyses will be performed using descriptive statistics.

The following subgroups will be used for selected efficacy and safety analyses:

- Sex (M/F)
- Baseline Age Group (<= 4 months/> 4 months)

## 2.3 Subject disposition, demographics and other baseline characteristics

Analyses for subject disposition, demographic characteristics, other baseline characteristics, and medical history, will be summarized by study part for the FAS (and additionally by cohort for Parts 2 & 3) using frequency distributions (for categorical variables) and descriptive

statistics of mean, standard deviation, minimum, median and maximum (for continuous variables). They will also be listed by study part, treatment, and subject. The numbers in each population with be tabulated. Frequencies of protocol deviations will be displayed stratified by deviation category and part.

### 2.3.1 Subject disposition

The number and percentage of subjects who completed each study part, who prematurely discontinued and the reason for discontinuation will be presented by study part.

### 2.3.2 Background and demographic characteristics

Summary of baseline demographic characteristics will include:

- Age
- Sex
- Predominant race
- Ethnicity
- Weight
- Length
- Body surface area
- Chest circumference
- Head circumference

Summary of other baseline characteristics will include:

- Mean supine SBP
- Mean supine SBP categories
  - < 130 mmHg
  - >= 130 mmHg
- Mean supine DBP
- Mean supine DBP categories
  - < 80 mmHg
  - >= 80 mmHg
- Mean supine pulse
- Paradoxical breathing assessment,
- eGFR per MDRD formula categories
  - < 30 mL/min/SA
  - >= 30 to < 60 mL/min/SA
  - >= 60 to < 90 mL/min/SA
  - > 90 mL/min/SA
- QTcF
- [redacted]

### 2.3.3 Medical history

Medical history will be summarized by study part for the FAS (and additionally by cohort for Parts 2 & 3). Any condition entered on the Medical History (MH) CRF will be coded using the MedDRA dictionary. The medical history will be summarized by primary system organ class (SOC), preferred term (PT) and cohort.

## 2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

The SAF set will be used for the analyses below.

### 2.4.1 Exposure to study treatment / compliance / time at risk for AE

Duration of treatment exposure in months = (minimum(study day of last non-missing dose (>0) + 6, end of study date, Database cutoff date) - study day of first dose + 1)/30.4375.

Duration of exposure to study drug will be summarized descriptively on the safety set by parts, treatment group and duration category (≥ 1 mos., ≥ 3 mos., ≥ 6 mos., ≥ 9 mos., ≥ 12 mos., ≥ 18 mos., ≥ 24 mos., ≥ 30 mos., ≥ 36 mos., ≥ 42 mos., etc. till no longer any patients).

For each treatment group, the number of patient-years is calculated as (the sum of the number of days of exposure for all patients in the group)/365.25 and will be summarized by baseline age group and gender.

**Time at risk for AE** is defined as (in months)

- (minimum(study day of permanent study drug discontinuation + 30, study day of end of study part, Database cutoff date, study day of first dose of alternate treatment for SMA) - study day of first dose + 1)/30.4375 (as defined in Section 2.1.1).

Time at risk for AEs will be summarized in a similar way to duration of exposure to study drug.

**Compliance to the study drug administration schedule** will be calculated as

- (Number of doses received / number of expected doses up to treatment discontinuation)*100
- Number of doses received = Doses with non-missing dates and a non-missing dose >0
- Number of expected doses = round((study day of last treatment day-1)/7) + 1
- The last treatment date/day is taken from the CMP dataset.
- If number of received doses exceeds the number of planned doses, then compliance = 100% Premature discontinuation from study drug will not be considered non-compliance.

Last treatment day corresponds to the last record of the administration page for parts 1, 2 or 3 with non-missing date for the patient. A dose is received if dose is non-missing and >0.

This rule means that compliance will be measured during the time interval the patient took study drug: premature discontinuation from study drug will not be considered non-compliance. Compliance to study drug administration will be summarized descriptively on SAF by treatment group. In addition, compliance will be summarized with cumulative number and percentage of patients in each compliance category (*i.e., ≥ 20%, ≥ 30%, ≥ 40%, ≥50%, ≥60%, ≥70%, ≥80%, ≥90%, ≥95%, ≥98%, =100%*).

### 2.4.2 Prior, concomitant and post therapies

Data for study drug administration will be listed by study part, cohort and subject.

Concomitant medications will be summarized for the safety set in separate tabulations based on the coding dictionary used. Concomitant medications used during the treatment phase will be summarized by anatomical therapeutic chemical (ATC) class, and preferred term.

Concomitant medications and significant non-drug therapies will be summarized by study part, therapeutic class and preferred term for the SAF. Any medication given at least once between the day of first dose of actual study drug received and the last day of the study will be a concomitant medication, including those which were started pre-baseline and continued into the treatment period. Concomitant medication will be identified based on recorded or imputed start and end dates of medication taking.

Concomitant medication will be assigned to Part 3 if the start date of the medication is after/on the date of first visit for Part 3 (see section 2.1.1).

## 2.5 Analysis of the primary objective

The primary objective of Part 1 was analyzed in the Interim 3 CSR. This analysis will not be repeated here. Details of the planned analysis can be found in Appendices 5.4.

The primary objective of Part 2 is to evaluate the safety and tolerability of multiple doses of branaplam for 52 weeks in subjects with Type 1 SMA. The primary objective for Part 3 is to assess long-term safety and tolerability of extended oral/enteral, once a week branaplam treatment in patients with type 1 SMA who have had at least 52 weeks of treatment in either Part 1 or 2 study of this protocol. The analyses are described below in the safety section. All information obtained on adverse events will be displayed by initial and administered dose and subject.

## 2.6 Analysis of the key secondary objective

There is no key secondary objective for this study.

## 2.7 Analysis of secondary objectives

All efficacy analyses will be conducted using the full analysis set (FAS).

### 2.7.1 Secondary endpoint

The following efficacy endpoints will be summarized with appropriate descriptive tables over time by study part and in Parts 2 & 3, additionally by treatment group:

- CHOP INTEND infant motor total score
- Respiratory function assessments (respiratory rate, pulse oximetry, paradoxical breathing, breathing pattern [chest circumference measured during quiet breathing (sleep)])
- Growth measurements (body weight, head circumference, length and chest circumference)
- Ventilation status
- Preservation of oral feeding
- HINE motor total score

- Ability to sit without support at 12-months of treatment: This is part of the HINE, if a subject has the ITEM=”Sitting” with Score 3 or 4 then they are considered as able to sit without support. See Table 2-14 below.

For all continuous secondary endpoints, summary statistics for raw and change from baseline (when baseline is available), will be provided.

For the categorical secondary endpoints, frequencies and relative percentages will be reported.

Other secondary endpoints

- AUC and Cmax of branaplam

For PK analysis please refer to section 2.9.

A summary of the number of patients and relative frequencies of patients with and without tracheostomy at baseline, installed or removed during the study will be provided by part and cohort (for parts 2 & 3).

The number of patients who had a tracheostomy or permanent ventilation during the study and discontinued the study drug on/after the start of the event will be provided by part and cohort (for parts 2 & 3).

### HINE-2 and the Motor and Speech Domains

The domains for the HINE-2 motor score are provided in Table 2-14 below. If all subscores are “Did Not Test” (DNT) then the HINE Motor Total Score is missing. If at least one subscore is available, then any other DNT will be imputed as 0 in the sum for the HINE Motor Total Score derivation.

Note: HINE motor score information is available in two source datasets, MOT and QUE. Data from both datasets will be combined and used in the HINE data analysis.

**Table 2-14 HINE-2 and the Motor and Speech Domains**

| | | Functional definitions and score | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Item** | **Score** | **0** | **1** | **2** | **3** | **4** | **5** | **6** |
| Head Control | Did Not Test | Unable to maintain upright | Wobbles | All the time upright | | | | |
| Sitting | DNT | Cannot sit | Sits with support at hips | Sits with support (props) | Stable independent sit | Pivots (rotates) | | |
| Ability to Kick (in supine) | DNT | Does not kick | Kicks horizontal, leg(s) do not lift | Upward (vertical) | Touches leg | Touches toes | | |
| Rolling | DNT | Does not roll | Rolls to side (supine) | Rolls to side (prone) | Rolls prone to supine | Rolls supine to prone | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Crawling (from supine) | DNT | Does not lift head | Props on elbow | Supports weight on hand | Crawls flat on abdomen (commando crawl) | Crawls on hands and knees | | |
| Standing | DNT | Does not support weight | Supports weight | Stands with support | Stands unaided | | | |
| Walking | DNT | Makes no attempt at walking | Bounces | Cruises (holding on) | Takes a few steps | Walks independently (>10 steps) | | |
| Hip strength | DNT | Unable to flex hips | Briefly flexes hip against gravity | Maintains hip flexion against gravity | | | | |
| Speech | DNT/ Can-not assess | Weak cry (cannot be heard outside of room with closed door) | Loud cry (can be heard outside of room with closed door) | Coos | Babbles in a speech-like way and uses many different sounds, including sounds that begin with p, b, and m | Babbles using long and short groups of sounds (tata, upup, bibibi) | Imitates differ-ent speech sounds | Says one word |
| Voluntary grasp | DNT | No grasp | Uses whole hand (rake) | Index finger and thumb but immature grasp | Pincer grasp | | | |
| Upper extremity function | DNT | Spontaneous movement of arm(s) | Hand(s) to midline on chest | Arm(s) held above head | Hand(s) to mouth | Arm(s) reach over body (supine) | Arm(s) reach over head (held upright) | |

## Feeding Status

Feeding status over the course of each part will be categorized as follows:

- Only exclusively tube fed
- Only orally fed
- Started on tube fed, switched to orally fed
- Started on orally fed, switched to tube fed
- Other (mixture of both tube and oral feeding)

### Ventilation status

Permanent ventilation is included in a composite endpoint with death, permanent ventilation or tracheostomy (see Sections 2.7.2 and 2.8.3). A timeline of ventilation status is described below.

A patient's ventilation information might be recorded in several records (for e.g if the number of hours/day changes). Information should be combined. If two records are available for the same day with different number of hours per day, the maximum will be assumed.

### Further Analyses

Additionally, the following analyses will be carried out:

- CHOP INTEND
  - Spaghetti plots of Total Score and Total Score Change from Baseline (Parts 1 & 3)
  - Spaghetti plots of Total Score and Total Score Change from Baseline stratified by treatment group (Parts 2 & 3)
  - Panel plots of individual CHOP INTEND Total Score and Total Score Change from Baseline – in each panel a spaghetti plot of all subjects (Parts 1 & 3, and 2 & 3)
  - Panel plots of individual Total Score Change from Baseline by time with dose as background shading – one panel per subject (Parts 1 & 3)
  - Stratified bar chart of subjects showing >= 4 improvement from baseline in Total Score by Baseline Age Group, and Time (Parts 1 & 3, and 2 & 3)
  - Table of Median Change in Total Score from Baseline by Visit and Baseline Age Group (Parts 1 & 3, and 2 & 3)
  - Table of subjects reaching Total Score >= 40 by Visit (Parts 1 & 3, and 2 & 3)
- Growth measurements
  - Spaghetti plots (growth curves) of length and weight versus age at evaluation by sex with CDC percentiles (Parts 1 & 3, and 2 & 3)
  - Summaries of chest circumference measured at the end of both inspiration and expiration during quiet breathing (sleep) by treatment group and part
- Feeding and Ventilation Status
  - Time lines of feeding and ventilation status with dose as background shading (Parts 1 & 3, and 2 & 3)
- HINE Motor Score and Items
  - HINE sub-scales Crawling, Head Control, Kicking, Rolling, Sitting, Standing, and Walking
    - Stacked bar chart by visit and part (Parts 1 & 3, and 2 & 3)
    - Table of milestones reached

| **HINE sub-scale** | **Milestone** |
|---|---|
| Head control | Wobbles or all the time upright |
| Kicking | Any kick |
| Rolling | Any roll |

| | |
|---|---|
| Sitting | Stable independent sit or Pivots (rotates) |
| Crawling | Lifts head in any way (Props on elbow) |
| Standing | Supports weight |
| Walking | Makes any attempt (ie Bounces) |

- HINE Motor Total Score
  - Table of frequencies of the following change from baseline categories by visit (Parts 2 & 3):
    - 1 = Worsening (<0)
    - 2 = No change (=0)
    - 3 = Improvement of 1 point
    - 4 = Improvement of 2 points
    - 5 = Improvement of > 2 points
  - Table of frequencies of subjects reaching a post-baseline score of >=3 by visit (Parts 1 & 3, and 2 & 3)
  - Panel plot of individual values by time with dose as background shading (Parts 1 & 3 and 2 & 3)
  - Panel plot of individual values – in each panel a spaghetti plot of all subjects (Parts 2 & 3)
- Motor and Speech Performance
  - Hip Strength, Speech, Upper Extremity Function, and Voluntary Grasp
    - Stacked bar chart by visit (Parts 1 & 3, and 2 & 3)

### 2.7.2 Statistical hypothesis, model, and method of analysis

A Kaplan Meier (KM) analysis by part will be carried out on time to death, permanent ventilation or tracheostomy; results will be displayed in a life table with respective KM estimates and 95% confidence intervals, along with appropriate plots. Permanent ventilation is defined as more than 21 consecutive days for more than 16 hours/day of non-invasive ventilation (BiPAP or CiPAP).

## 2.8 Safety Analyses

In general, data assigned to Part 3 (section 2.1.1) will be analysed together with the part the subject came from (i.e. ‘Parts 1 & 3’, ‘Parts 2 & 3’).

Safety analyses will be conducted using the safety set (SAF). In Parts 1 & 3, subjects will be analyzed overall, with some graphical methods including the current dose; in Parts 2 & 3, the analyses will be summarized by actual treatment group. Unless explicitly stated otherwise, only data up to the safety cutoff (as defined in Section 2.1.1) will be included in the analysis and data beyond this time point for a given subject will be excluded from the safety analysis.

The assessment of safety will be primarily based on the frequency of adverse events (including death and non-fatal serious adverse events), and adverse events of special interest. Additional safety assessments include laboratory tests, ECG evaluations, echocardiograms, vital signs, ophthalmology, physical and neurophysiological examinations. Clinically significant findings

in these additional safety assessments will be reported as adverse events and analyzed as such. In addition, all safety assessments will be summarized or listed as appropriate.

### 2.8.1 Treatment exposure

Treatment dosing will be investigated both descriptively and graphically:

- Table of treatment duration in total (in months) and frequencies of each separate dose
- Time line of each subject's dosing (Parts 1 & 3 and Parts 2 & 3)

For the plots only: Doses collected in the CRF will be remapped to two variables, one for each unit (mg/m2 and mg/kg). Indeed, doses were first collected in mg/m2 and unit was changed during Part 1 (see section 1.1). If dose as per CRF is not among the planned doses or dose is missing, the remapped dose variables will be missing. If a visit was missed or (remapped) dose was missing then the last non-missing dose will be displayed. The same is applied for plots with dose as background shading.

### 2.8.2 Adverse events (AEs)

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation of a subject after providing written informed consent for participation in the study. That means that a subject can report AEs before having started study drug. For reporting purposes, the main focus will be on treatment emergent adverse events (TEAEs). Treatment emergent AEs are defined as events starting on or after the first dose of study drug that were absent pre-treatment, or events present prior to the first dose but increased in severity after the first dose (based on the MedDRA lower level term (LLT). TEAEs are included up to the safety cutoff (as defined in Section 2.1.1). Except for serious TEAEs and death, only TEAEs up to and including safety cutoff (as defined in Section 2.1.1) will be included in the analyses. For serious TEAEs a modified safety cutoff is used (as defined in Section 2.1.1). TEAEs will be assigned to Part 3 if the start date is on/after the first visit date of Part 3 (see section 2.1.1). All deaths will be included, regardless of safety cutoff.

AEs will be reported by primary system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA version used for reporting the study will be described in a footnote.

The number and percentage of subjects reporting any TEAEs will be summarized by primary SOC, preferred term, maximum CTCAE grade (individual, as well as Grade 3 and above combined) and treatment group (Parts 2 & 3). Missing CTCAE grade will not be imputed. Separate summaries will be provided for serious TEAEs, drug related TEAEs, TEAEs leading to permanent discontinuation of study drug and most common TEAEs (10% in any group). Furthermore, exposure-adjusted incidences will be reported in an AE overview table, for all AEs in a table by system organ class and preferred term by part, and similarly for serious AEs.

If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the maximum CTCAE grade at the system organ class level, where applicable.

All AEs will be presented in listings.

The following graphs will be displayed:

- Bar charts of MedDRA system organ classes - crude incidences
- Bar charts of MedDRA preferred terms - crude incidences
- Similar bar charts for serious TEAEs

#### 2.8.2.1 Adverse events of special interest / grouping of AEs

Selected tables will be produced for Adverse Events of Special Interest (AESI) (i.e., risks) defined in the latest version of case retrieval sheet (eCRS) at the time of analysis implementation (i.e., study database lock).

The LMI070X2201 eCRS is available at **http://go/ecrs** by selecting either

- CRS NAME: (LMI070 Spinal muscular atrophy) or
- CRS ID: 3689
- Within the document, select SP="Y"

Specifically, incidence of TEAEs that fulfill the risk search terms as defined in eCRS will be summarized by risk name, level, study part and treatment group (for Parts 2 & 3 only) with crude incidences and 95% confidence intervals presented.

Similarly, separate summaries will be provided for serious TEAEs that fulfill the risk search terms as defined in eCRS. Additionally, incidence of any TEAEs that fulfill the search terms as defined in eCRS will also be summarized by risk name, level, and maximum CTCAE grade.

Bar charts of MedDRA preferred terms that fulfill the search terms as defined in eCRS will be produced for crude incidences by part.

### 2.8.3 Deaths

Deaths will be summarized by providing the number and percentage of subjects by study part. All deaths as recorded in the final database (i.e., up to database lock) will be included.

Additionally, time to death, permanent ventilation or tracheostomy will be displayed in a Kaplan-Meier plot along with the respective table (see Section 2.7.2).

### 2.8.4 Laboratory data

Data summaries will be provided in SI units. The summary of laboratory evaluations will be presented for three groups of laboratory tests: Hematology, Chemistry and Urinalysis. On presenting summary statistics, laboratory data will be grouped and displayed in an alphabetical order within each of the three groups.

Descriptive summary statistics (mean, median, standard deviation, Min and Max) of the change from baseline in the laboratory result to each study visit-window by treatment group will be presented for continuous variables. Change from baseline will only be summarized for subjects with both baseline and post baseline values and will be calculated as:

change from baseline = post baseline value – baseline value

In addition, shift tables will be provided for all parameters to compare a subject's baseline laboratory evaluation relative to the post-baseline values. For the shift tables, the normal local

laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high relative to whether or not the baseline value was normal, low, or high. These summaries will be presented by laboratory test overall in Parts 1 & 3, additionally by actual treatment group in Parts 2 & 3. Shift table will also be provided for urinalysis results to compare baseline to post-baseline extreme values (negative, +, 2+, 3+, or 4+).

Number of subjects with newly occurring liver enzymes abnormalities will be summarized using the respective criteria. Newly occurring liver enzymes abnormalities are defined in Section 5.3.2.

For both shift tables and newly occurring liver enzymes abnormalities, all applicable post-baseline values (including unscheduled or unplanned visits) will be checked against the respective criteria and the rules for handling multiple laboratory assessments within visit windows will not be applied.

For continuous variables databased as <lower limit, these will be imputed as being half of the lower limit.

The following graphs will be generated for liver enzymes:

- Panel plot of individual subjects for alkaline phosphotase, total bilirubin, ALT and AST with dose as background shading – one panel per subject (Parts 1 &3 and Parts 2 & 3)
- eDISH scatterplot of Total Biliburin and ALT on log-log axes (Parts 1 & 3); additionally stratified by treatment group (Parts 2 & 3)
- Matrix plot of each of the parameters (ALT, AST, Total Bilirubin and Alkaline Phosphotase) maximum post-baseline/ULN normalized (Parts 1 & 3, and Parts 2 & 3)

All above summaries include only data up to and including safety cut off. If there is any value for a parameter outside of the normal range for a subject, then all data of this parameter for that subject will be listed.

### 2.8.5 ECG and echocardiographic data

Clinically significant findings from ECG evaluations will be reported as AEs and included in the analysis of AEs. ECG parameters include max heart rate, mean PR duration, mean QT duration, mean QRS duration, $QT_f$ (QT corrected using Fridericia's correction formula), and $QT_b$ (corrected using Bazett's correction formula) - all as collected on the ECG CRF. Descriptive statistics of each ECG parameter will be provided overall (Parts 1 & 3) and by treatment group (Parts 2 & 3) for baseline and all relevant post-baseline visits.

The number and percentage of subjects meeting the criteria defined in Table 2-15 will be provided for each criterion by treatment group for baseline and the relevant post-baseline assessments.

**Table 2-15 Criteria for relevant ECG absolute values**

| Absolute values criteria: |
|---|
| QT > 450 msec |
| QTc > 450 msec |

The number and percentage of subjects with echocardiography abnormality will be provided by treatment group for baseline and any time post-baseline.

All ECG data will be listed, and abnormalities will be flagged. For echocardiographic data, all patients with at least one abnormality will be listed.

### 2.8.6 Vital signs

Vital sign measurements include sitting systolic and diastolic blood pressures, sitting pulse, body temperature, height and body weight.

Derivation of baselines for blood pressure and pulse are provided in Section 2.1.1.

Height will be collected at screening visit only and will be summarized in the baseline characteristic summary only.

Analyses of vital sign measurements using descriptive summary statistics (mean, median, standard deviation, min, max) for the change from baseline for each post-baseline visit-window will be performed. These descriptive summaries will be presented by vital sign parameter and treatment group (Parts 2 & 3). Change from baseline will only be summarized for subjects with both baseline and post-baseline values and will be calculated as:

change from baseline = post-baseline value – baseline value

In addition, shift tables will be provided for all vital sign parameters to compare a subject's baseline value relative to the post-baseline values. For the shift tables, the reference ranges in Table 2-16 will be used to evaluate whether a particular value was normal, low, or high relative to whether or not the baseline value was normal, low, or high.

**Table 2-16 Reference ranges for vital sign parameters**

| Age window | Pulse rate | Systolic blood pressure | Diastolic blood pressure |
|---|---|---|---|
| 0–<3 months | 100-150 | 65-85 | 45-55 |
| 3-<6 months | 90-120 | 70-90 | 50-65 |
| 6-<12 months | 80-120 | 80-100 | 55-65 |
| 1-<3 years | 70-110 | 90-105 | 55-70 |
| 3-<6 years | 65-110 | 95-110 | 60-75 |
| 6-<12 years | 60-95 | 100-120 | 60-75 |

Source: Nelsons textbook of Pediatrics 18th Edition

Apart from the growth measurement graphs mentioned in Section 2.7.1, the following graph will be generated for vital signs data:

- Panel plot of individual vital signs over time – systolic and diastolic BP, and pulse

All above summaries include only data up to and including safety cut off. All vital signs data will be listed, and age-dependent abnormalities will be flagged

### 2.8.7 Ophthalmology Examination

All ophthalmological abnormalities will be descriptively summarized and for patients with at least one abnormality, data will be listed.

### 2.8.8 Neurophysiological Examination

All neurophysiological evaluations [Ulnar compound motor action potential (CMAP), Ulnar nerve conduction velocity (NCV), Sural SNAP, Sural sensory NCV] will be descriptively summarized and listed.

Furthermore the following analyses will be carried out:

- Spaghetti plot of raw neurophysiological parameters vs months from first dose over time with all raw data (Parts 2 & 3)
- Spaghetti plot of raw neurophysiological parameters vs months from first dose over time excluding implausible post-baseline zero values (Parts 2 & 3)
- Spaghetti plot on a log scale of raw neurophysiological parameters vs months from first dose over time excluding implausible post-baseline zero values (Parts 2 & 3)
- Spaghetti plot on a log scale of normalised neurophysiological parameters vs months from first dose over time with all normalised data (Parts 2 & 3)
- Spaghetti plot on a log scale of normalised neurophysiological parameters vs months from first dose over time excluding implausible post-baseline zero values (Parts 2 & 3)

### 2.8.9 Neurologic examination questionnaire

All data will summarized with appropriate descriptive statistics, and all data will belisted.

### 2.8.10 Acceptability and palatability questionnaire

All data will summarized with appropriate descriptive statistics.

## 2.9 Pharmacokinetic endpoints

### Parts 1 & 3 and Parts 2 & 3

The following pharmacokinetic parameters will be analyzed: Cmax, Tmax, AUCtau or AUC0-168h, AUClast, AUCinf, T1/2, Vz/F and CL/F from the plasma concentration-time data.

### Descriptive analyses

Branaplam plasma concentration data will be listed by study part, administered dose, subject, and sampling time point. Descriptive summary statistics will be provided by dose level (see Table 1-2) and sampling time point. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, maximum, and the frequency (n, %) of concentrations below the LLOQ. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values. For all doses, the unit is transferred from "mg/m$^2$" to "mg/kg" for summary statistics calculation. The summary statistics table also include columns with treatment group in Parts 2 & 3. A geometric mean will not be reported if

the dataset includes zero values. Graphical methods will be employed to show mean and individual concentration-time profiles. Pharmacokinetic parameters will be listed by study part, administered dose and subject and summarized by dose with descriptive summary statistics as described above. An exception to this is Tmax where median, minimum and maximum will be presented.

### 2.9.2 Accumulation ratio

#### Part 1

In subjects, who received the same dose in the first two treatment cycles of 3 months each, the parameters AUC0-168h for both observations and Cmax will be log transformed and used in an ANCOVA model with day as a factor, log dose as a covariate and day by dose interaction and subject as random effect. The LSMeans and their mean difference between treatment cycle 2 and Day 1 for each dose level, together with 90% confidence limit will be calculated from this model. These will be back-transformed to provide an estimate of the accumulation ratio with corresponding 90% CI.

#### Part 2

Accumulation ratio can be estimated as described for Part 1. Since no intra-individual dose escalation is planned, the accumulation will be estimated for each observation period versus first administration.

### 2.9.3 Age and weight dependency

PK parameters will be generated for all subjects over the whole duration of the study. Since the physiological changes in Type 1 SMA subjects is very dynamic, the PK parameters AUC (AUCinf after first administration, AUCtau or AUC0-168h after all other administrations), Cmax, CL/F, Vz/F, and T1/2 will be correlated with both age and weight. For Parts 1 & 3, AUC and Cmax will be dose-normalized using unit mg/kg. For Parts 2 & 3, the age and weight dependency will be executed for each dose independently. Scatter plots of PK parameters versus both age and weight at the time of the dose when PK parameter was calculated, including a regression analysis, will be provided on the individual level.

The analysis will be carried for each study part separately.

### 2.9.4 Comparison of dosing methods

Branaplam can be administered either *via* tube administration or orally. To test the impact of the dosing method on the systemic exposure, the exposure parameters AUC (AUCtau or AUC0-168h) and Cmax will be compared between both dosing methods. The comparison will be executed for each subject individually, who was treated with both methods. Since the number of oral administrations per subject is considered to be low, especially when compared to tube administration, proposed assessments might be not feasible for all subjects treated with both methods.

Two assessments will be executed (if feasible) for Parts 1 & 3:

- Exposure parameters across the complete study duration will be dose-normalized using unit mg/kg and summary statistics for each method executed. Box plot comparing the two dosing methods will be prepared for each PK parameter.
- Exposure parameters of two subsequent profiles, of which one was derived after tube administration and the other after oral administration, will be dose-normalized using unit mg/kg. The ratio will be calculated between tube administration and oral administration.

For Parts 2 & 3, the same will be executed (if feasible) but without dose-normalizing. Results will be computed and displayed for each dose individually.

## 2.10 PD and PK/PD analyses

Not applicable.

## 2.11 Subject-reported outcomes

Not applicable.

[redacted]

## 2.13 Interim analysis

In the third interim analysis, no DLT's in Part 1 were identified; this analysis will not be repeated in the upcoming fourth interim analysis of Parts 1 and 2 – details can be found in Appendix 5.4.3.

# 3 Sample size calculation

### Part 1

The sample size for Part 1 is driven by feasibility. In Part 1, cohorts of at least 2 subjects are planned to be dosed until a decision is made for MTD, however adjustment of cohort size might be considered due to enrollment and safety consideration. 13 subjects were enrolled to test 5 dose levels. At least 2 subjects are required for cohort 1 at the starting dose. Size of later cohorts may be adjusted based on feasibility. As noted earlier, if more than two subjects present simultaneously for the study, additional subject(s) may be dosed in a cohort to avoid unnecessary delays in treatment of this life-threatening disease.

### Part 2

In Part 2, 25 subjects were enrolled to evaluate up to 2 different dose cohorts with at least 6 subjects and up to approximately 10 subjects per cohort.

The driver of the sample size in Part 2 is the primary objective, safety. We are able with 95% confidence to rule out that the true incidence rate exceeds 50% of any class of adverse events if none in that class are observed in 6 subjects.

Furthermore, in an interim analysis of CHOP INTEND data from Part 1, CHOP INTEND scores were analyzed by a mixed linear model with covariates for dose, baseline CHOP INTEND, and calendar age. A compound symmetric covariance structure was assumed for observations within the same individual. This analysis pointed to a total estimated variability of 7 on a CHOP INTEND scale (sum of between and within subjects' variance components). The table below (Table 3-1) shows the power to detect a difference in CHOP INTEND score between two adjacent dose groups (by one-sided t test at nominal significance level 5%). It seems likely that differences exceeding 10 points on a CHOP INTEND scale will be identifiable with the planned sample size.

**Table 3-1 Power to detect a difference in CHOP INTEND score between two adjacent dose groups (by one-sided t-test at nominal significance level of 5 percent)**

| | N=6 | N=7 | N=8 | N=9 | N=10 |
|---|---|---|---|---|---|
| Effect size 8 points | 56% | 64% | 70% | 74% | 78% |

| | | | | | |
|---|---|---|---|---|---|
| Effect size 10 points | 74% | 80% | 85% | 89% | 92% |
| 12 points | 86% | 91% | 94% | 96% | 98% |

# 4 Change to protocol specified analyses

The following analyses were specified in the protocol but will not be performed or will be analysed differently:

- [redacted]
- The repeated measures analysis specified in section 11.5.1 (for part 1 and part 2 together, for continuous endpoint) was not performed. No repeated measures model was estimated.
- Listings for relevant medical history and current medical condition, concomitant therapies, [redacted] from the protocol will not be produced. Team assessed that tables with summary statistics are sufficient for the purpose of the CSR.
- The listing for laboratory will not display all data. Instead, if there is any value outside normal range of a parameter for a subject then all records for that parameter and this subject are listed.

[redacted]

[redacted]

- As time to death, permanent ventilation or tracheostomy is specified as efficacy assessment in the protocol summary, Kaplan Meier tables and plots for that endpoint will be provided, and not for time to death or permanent ventilation as specified in section 11.5.1 from protocol.

# 5 Appendix

## 5.1 Imputation rules

In any analysis or evaluation, if the visit date(s) is missing, no imputation will be implemented.

### 5.1.1 Study drug

Start date and end date of study drug on the respective CRF panel are mandatory; thus, no date imputation will be applied.

### 5.1.2 AE and concomitant medication date imputation

Incomplete start date or end date of an adverse event or concomitant medication taken will be handled by following rules:

**Table 5-1 Imputation of start dates (AE, CM)**

| Missing Element | Rule |
|---|---|
| day, month, and year | • No imputation will be done for completely missing dates |
| day, month | • If available year = year of study treatment start date then<br>  o If end date contains a full date and end date is earlier than study treatment start date then set start date = 01JanYYYY<br>  o Else set start date = study treatment start date.<br>• If available year > year of study treatment start date then 01JanYYYY<br>• If available year < year of study treatment start date then 01JulYYYY |
| day | • If available month and year = month and year of study treatment start date then<br>  o If end date contains a full date and end date is earlier than study treatment start date then set start date= 01MONYYYY.<br>  o Else set start date = study treatment start date.<br>• If available month and year > month and year of study treatment start date then 01MONYYYY<br>• If available month and year < month year of study treatment start date then 15MONYYYY |

**Table 5-2 Imputation of end dates (AE, CM)**

| Missing Element | Rule<br>(*=min(death date, safety cutoff date, withdrawal of consent date)) |
|---|---|
| day, month, and year | • Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period* |

| Missing Element | Rule (*=min(death date, safety cutoff date, withdrawal of consent date)) |
|---|---|
| day, month | • If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period * |
| day | • If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period* |

Notice if imputed end date is less than the start date (if complete), use the start date as the imputed end date.

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

For adverse events and any prior or concomitant medication, to decide whether the event or medication was prior or post-dosing is carried out as follows:

- If start date and time are not missing, then report as post-dosing if start date and time > dosing start date and time
- If start date is available, but not start time, then report as post-dosing if start date > dosing start date. This means that all events occurring on the dosing start day (even if they occurred prior to it) will be considered as post-dosing – similarly for medications, will be considered as concomitant.
- If both start date and time are missing, both adverse events and medications will be defined as being post-dosing.

### 5.1.3 Values outside limits of quantification

For descriptive analyses of laboratory parameters [redacted] the following values will be imputed:

- LLOQ with 0.5 * LLOQ
- ULOQ with 1.5 * ULOQ

The frequency (n, %) of values either below the LLOQ or above the ULOQ will also be reported.

For PK analyses, other rules apply (see Section 2.9.1).

## 5.2 AEs coding/grading

Not applicable.

## 5.3 Laboratory parameters derivations

For each subject, the estimated creatinine clearance values (without collecting urine) will be calculated using the Cockcroft-Gault formula (as specified in Table 5-3). In these calculations, the body weight is the last measurement collected on or before the day when the subject takes the laboratory test and age should also be calculated based on the time when the subject takes the laboratory test.

If the creatinine value is collected in the unit *µmol/L* (SI unit), it will be converted to *mg/dL* in order to use the formulas. The conversion is via the equation below:

- mg/dL = 88.4 µmol/L (e.g., creatinine = 2.0 mg/dL = 176.8 µmol/L).

**Table 5-3 Creatinine clearance calculation**

| Variable | Formula |
|---|---|
| Creatinine clearance [mL/min] using Cockcroft-Gault formula (Cockcroft and Gault 1976) | = $(140 - A) \times W / (72 \times C) \times G$<br>Where<br>*A* is age [years]<br>*W* is body weight [kg]<br>*C* is the serum concentration of creatinine [mg/dL]<br>*G* is a constant: *G*=1 for males and *G*=0.85 for females. |

The estimated creatinine clearance will be included as one of the laboratory parameters.

### 5.3.1 Laboratory test groups and subgroups

On presenting lab results, grouping parameters by family will ease the review. Table 5-4 below shows a possible set of lab parameters and their corresponding classification.

**Table 5-4 Laboratory tests**

| Order | Laboratory Group Subgroups | Tests [SI unit] |
|---|---|---|
| 1 | Hematology | Absolute Basophils [10E9/L]<br>Absolute Eosinophils [10E9/L]<br>Absolute Lymphocytes [10E9/L]<br>Absolute Monocytes [10E9/L]<br>Absolute Neutrophils [10E9/L]<br>Absolute other differentials [10E9/L]<br>Basophils [%]<br>Eosinophils [%]<br>Hematocrit [1]<br>Hemoglobin [g/L]<br>Lymphocytes [%]<br>Mean Platelet Volume [fL]<br>Monocytes [%]<br>Neutrophils [%]<br>Other differentials [%]<br>Platelet count direct [10E9/L]<br>RBC [10E12/L]<br>Reticulocytes [%]<br>WBC (Total) [10E9/L] |
| 2 | Chemistry | Albumin [g/L]<br>Alkaline Phosphatase [U/L]<br>ALT [U/L]<br>AST [U/L]<br>Bicarbonate [mmol/L]<br>Bilirubin (direct/conjugated) [umol/L]<br>Bilirubin (indirect/unconjugated) [umol/L]<br>Calcium [mmol/L] |

| Order | Laboratory Group Subgroups | Tests [SI unit] |
|---|---|---|
| | | Chloride [mmol/L]<br>Creatinine [umol/L]<br>Free Thyoxine (FT4) [pmol/L]<br>Glucose [mmol/L]<br>hsCRP (high sensitive C-Reactive protein) [mmol/L]<br>Potassium [mmol/L]<br>Sodium [mmol/L]<br>Thyroid hormones T4 [nmol/L]<br>Thyroid stimulating hormone [mU/L]<br>Urea [mmol/L] |
| 3 | Urinalysis | Bilirubin Dipstick test<br>Blood Dipstick test<br>Glucose Dipstick test<br>Ketone Dipstick test<br>Leukocytes Dipstick test<br>Nitrite Dipstick test<br>Protein Dipstick test<br>Sediment - Casts<br>Sediment - RBC<br>Sediment - WBC<br>Specific Gravity<br>Urobilinogen<br>pH |

### 5.3.2 Newly occurring liver enzymes abnormalities

Below lists the criteria for "events" of newly occurring liver enzymes abnormalities:

- ALT > 3, 5, 10, 20x ULN
- ALT or AST > 3, 5, 8, 10, 20x ULN
- ALT or AST > 3x ULN & TBIL > 1.5x ULN
- ALT or AST > 3x ULN & TBIL > 2x ULN
- ALP > 1.5, 2, 5x ULN
- TBIL > 1, 1.5, 2x ULN
- ALP > 3, 5x ULN & TBL > 2x ULN
- ALT or AST > 3x ULN & TBIL > 2x ULN & ALP ≤ 2x ULN
- ALT or AST > 3x ULN & (nausea or vomiting or fatigue or general malaise or abdominal pain or (rash and eosinophilia))

When a criterion contains multiple laboratory parameters (e.g., ALT > 3xULN & TBL > 2xULN), unless otherwise requested by the project clinical team/Brand Safety Leader (BSL), the criterion should be only considered to be met when the elevation in both parameters occurs on the same sample day (as evidenced by the same date that the lab samples were taken).

The "events" are defined in the Novartis safety guideline on hepatotoxicity (Novartis: Philippe Close 2011), Section: Safety parameters for special liver event analyses.

## 5.4 Analysis of the primary objective in Part 1

The primary objective of Part 1 is to estimate the Maximum Tolerated Dose (MTD) of branaplam, when administered orally on a once weekly schedule to subjects with Type 1 spinal muscular atrophy. The primary analysis method is an adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle (Neuenschwander et al 2008).

### 5.4.1 Primary endpoint in Part 1

The primary endpoint is the incidence of Dose Limiting Toxicity (DLTs) in the first two weeks after the first dose in Part 1. Estimation of the MTD of LMI070 will be based upon the estimation of the probability of DLT in the first 2 weeks after the first dose in the DDS. This probability is estimated by the model in Section 5.4.2.

For the analysis of the primary variables, the DDS analysis set will be used.

DLTs will be listed and their incidence summarized by primary system organ class, worst grade based on the CTCAE version 4.03, type of adverse event, and by treatment group. The DDS will be used for these summaries.

### 5.4.2 Statistical hypothesis, model, and method of analysis in Part 1

The dose-toxicity (DLT) relationship in each dose escalation will be described by the following logistic regression model:

$$\text{logit}(\pi_{(d)}) = \log(\alpha) + \beta \log(d/d^*),\ \alpha>0,\ \beta>0$$

where, $\text{logit}(\pi_{(d)}) = \ln(\pi_{(d)}/(1-\pi_{(d)}))$, and $\pi_{(d)}$ is the probability of a DLT at dose d, where d represents the total weekly dose in Part I. Doses are rescaled as d/d* with reference dose of d*= 40 mg/m$^2$ of branaplam. As a consequence, $\alpha$ is equal to the odds of toxicity at d*. Note that for a dose equal to zero, the probability of toxicity is zero.

The following sub-sections provide details for dose recommendation and prior distribution for the model parameters.

#### Dose recommendation

After each cohort is completed the posterior distributions for the probabilities of DLT at different dose levels will be obtained. The results of this analysis will be summarized in terms of the estimated probabilities that the true rate of DLT at each dose-level will lie within each of the following intervals:

- [0, 10%) under-dosing.
- [10%, 25%) targeted toxicity.
- [25%, 100%] excessive toxicity.

Following the principle of escalation with overdose control (EWOC), after each cohort of subjects the recommended dose will be the one with the highest posterior probability of the DLT rate falling in the target interval [10%, 25%) among the doses fulfilling escalation with overdose control (EWOC), i.e. it is unlikely (< 25% posterior probability) that the DLT rate at

the dose falls in the excessive toxicity interval i.e. P(DLT) is 0.25 or higher. In addition, the maximum dose escalation is limited to 100% of the previous dose.

Note that the dose that maximizes the posterior probability of targeted toxicity is the best estimate of the MTD, but it may not be an admissible dose according to the overdose criterion if the amount of data is insufficient. If vague prior information is used for the probabilities of DLT, in the early stages of the study this escalation procedure will reflect a cautious strategy. The dose recommended by the adaptive Bayesian logistic model may be regarded as guidance and information to be integrated with a clinical assessment of the toxicity profiles observed at the time of the analysis in determining the next dose level to be investigated.

### Prior specification

A vague bivariate normal prior for the model parameters (log(α), log(β)) is derived by assuming that the median DLT rate at reference dose d*=40 mg/m$^2$ equals the targeted toxicity 0.25, and that for the remaining doses, median DLT rates a priori are linear in logit scale as a function of log-dose.

The information to derive the prior distribution of model parameters is provided in Table 5-5.

**Table 5-5 Prior parameters for bivariate normal distribution of model parameters**

| Parameters | Means | Standard deviations | Correlation |
|---|---|---|---|
| log(α), log(β) | (-1.099, 0) | (3.2, 1) | 0 |

All information obtained on adverse events will be displayed by initial and administered dose and subject.

## 5.4.3 Interim analysis in Part 1

After each cohort of subjects finish first dosing and contribute safety data at week 2, an interim analysis (without requirement for database lock) will be conducted for dose escalation decisions. The analysis will be comprised of fitting a Bayesian logistic regression model (BLRM) based on the dose limiting toxicity (DLT) information. From this model, the posterior probability of DLT rate at different dose levels will be estimated and a dose will be recommended to guide dose selection for the next cohort or declaration of MTD. In general, the next dose will have the highest chance that the DLT rate will fall in the target interval [10%, 25%) and will always satisfy the escalation with overdose control (EWOC) principle that the posterior probability of DLT rate falling in overdosing interval (>25%) is below 25%. In all cases, the dose for the next cohort will not exceed a 100% increase from the previous dose. Final dose escalation decisions will be made by Investigators and Novartis study personnel. Decision will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study, including safety information, DLTs, and available PK data from evaluable subjects. Dose escalation will continue until identification of the MTD.

An interim analysis is planned after MTD determination in Part 1 to evaluate PD effects of the treatment and assist with decision making for Part 2. Data on muscle thickness, ratio of muscle thickness to subcutaneous tissue thickness and muscle echo intensity, growth measurements, respiratory function assessments and CHOP INTEND infant motor scale will be summarized at different time points and compared to baseline.

[redacted]

The Interim Analysis Team may communicate interim results (e.g. evaluation of PoC criteria or information needed for planning/modifying another study) to relevant Novartis teams for information, consulting and/or decision purposes.

# 6 References

Garwood F. (1936) Fiducial Limits for the Poisson Distribution. Biometrika 28, 437-442.

Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, Van Lente F for Chronic Kidney Disease Epidemiology Collaboration (2007). Expressing the Modification of Dietin Renal Disease Study Equation for Estimating Glomerular Filtration Rate with Standardized Serum Creatinine Values. Clinical Chemistry 53:4: 766–772

Neuenschwander B, Branson M, Gsponer T (2008) Critical aspects of the Bayesian approach to phase I clinical trials. Statist. Med. 27(13):2420-243.

Sahai H, Khurshid A (1993). Confidence intervals for the ratio of two Poisson means. The Mathematical Scientist, 18, 43–50.

Ulm K (1990). A simple method to calculate the confidence interval of a standardized mortality ratio. American Journal of Epidemiology 1990;131(2):373-375.