NOVARTIS

Novartis Research and Development

LMI070/Branaplam

Clinical Trial Protocol CLMI070X2201 / NCT02268552

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

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**Clinical Trial Protocol Template Version 2.0 (01-Aug-2018)**

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## Site Operations Manual (SOM) and Pharmacy Manual

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct. Pharmacy Manual will contain all important guidelines for site on how to store, dispense, maintain and return Investigational Medical Product (IMP).

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## List of abbreviations

| | |
|---|---|
| ADME | Absorption, distribution, metabolism and excretion |
| AE | Adverse Event |
| ALT | Alanine Aminotransferase |
| ALP | Alkaline Phosphatase |
| AST | Aspartate Aminotransferase |
| BLRM | Bayesian Logistic Regression Model |
| BSA | Body Surface Area |
| CDC | United States Centers for Disease Control and Prevention |
| CD-ROM | Compact Disc – Read Only Memory |
| CFR | Code of Federal Regulation |
| CHOP INTEND | Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders |
| CMAP | Compound Motor Action Potential |
| CPAP | Continuous Positive Airway Pressure |
| CM | Concomitant Medication |
| CNS | Central Nervous System |
| CRF | Case Report/Record Form (paper or electronic) |
| CSF | Cerebral Spinal Fluid |
| CSR | Clinical Study Report |
| CTC | Common Terminology Criteria |
| CV | coefficient of variation |
| CYP | Cytochrome P450 metabolizing enzyme |
| DDS | Dose determining set (for dose escalation) |
| DLT | Dose Limiting Toxicity |
| DMC | Data Monitoring Committee |
| ECHO | Echocardiogram |
| ECG | Electrocardiogram |
| EDC | Electronic Data Capture |
| ENR | Enrolled set |
| EWOC | Escalation With Overdose Control |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FIH | First in Human |
| GCP | Good Clinical Practice |
| h | Hour |
| hERG | Human-ether-a-go-go-related gene |
| HINE | Hammersmith Infant Neurological Examination |
| HIV | Human Immunodeficiency Virus |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IMP | Investigational medicinal product |
| IN | Investigator Notification |
| IRB | Institutional Review Board |

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|---|---|
| IVSTd | Intraventricular Septum Thickness diastole |
| LLOQ | lower limit of quantification |
| LVEDV | Left Ventricular End Diastolic Volume |
| LVEDI | Left Ventricular End Diastolic Volume Index |
| LVEF | Left Ventricular Ejection Fraction |
| LVESV | Left Ventricular End Systolic Volume |
| LVESVI | Left Ventricular End Systolic Volume Index |
| LVFS | Left Ventricular Fractional Shortening |
| LVIDd | Left Ventricular Internal Dimension Diastole |
| LVIDs | Left Ventricular Internal Dimension Systole |
| LVPWTd | Left Ventricular Posterior Wall Thickness diastole |
| MedDRA | Medical dictionary for regulatory activities |
| mg | milligram(s) |
| mL | milliliter(s) |
| mRNA | messenger RiboNucleic Acid |
| MTD | Maximum Tolerated Dose |
| MMRM | Mixed Model for Repeated Measurements |
| NCV | Nerve Conduction Velocities |
| NfL | Neurofilament-light chain |
| NTproBNP | N-Terminal pro B-type Natriuretic Peptide |
| PD | Pharmacodynamic(s) |
| pEFD | Preliminary Embryo  Fetal Development |
| PI | Principle Investigator |
| PIP | Pediatric Investigation Plan |
| PK | Pharmacokinetic(s) |
| PRO | Patient Reported Outcomes |
| PT | Preferred Term |
| QMS | Quality Management System |
| RAP | Report and Analysis Plan |
| RBC | red blood cell(s) |
| REB | Research Ethics Board |
| SAE | Serious Adverse Event |
| SAF | Safety Analysis Set |
| SBP | Systolic Blood Pressure |
| SD | standard deviation |
| SMA | Spinal Muscular Atrophy |
| SMN | Spinal Motor Neuron |
| SMN1 | Survival of Motor Neuron 1 |
| SMN2 | Survival of Motor Neuron 2 |
| SMQ | Standardized MedDRA Query |
| SNAPs | Sural Nerve Action Potentials |
| SOM | Site Operations Manual |
| STD10 | Severe Toxic Dose in 10% animals |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TEAE | Treatment Related Adverse Event |
| TR | Tricuspid Regurgitation |

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|---|---|
| ULN | upper limit of normal |
| WBC | white blood cell(s) |
| WHO | World Health Organization |
| WoC | Withdrawal of Consent |
| wt | Wild type |

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## Glossary of terms

| | |
|---|---|
| Additional treatment | Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy) |
| Assessment | A procedure used to generate data required by the study |
| AUC0-168h | The area under the plasma (or serum or blood) concentration-time curve from time zero, which is equal to the dosing time to 168 h [mass x time / volume] |
| AUCinf | The area under the plasma (or serum or blood) concentration-time curve from time zero to infinity [mass x time / volume] |
| AUClast | The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume] |
| AUCweek | The area under the plasma (or serum or blood) concentration-time curve for the time period of one week [mass x time / volume] |
| Biologic Samples | A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant |
| CL/F | The apparent systemic (or total body) clearance from plasma (or serum or blood) following extravascular administration [volume / time] |
| Cmax | The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume] |
| Cohort | A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time same time |
| Cycles | Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days) |
| Discontinuation from study | Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data. |
| Dosage | Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day) |
| Electronic Data Capture (EDC) | Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care |
| End of the clinical trial | The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol |
| Enrollment | Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants |
| Healthy volunteer | A person with no known significant health problems who volunteers to be a study participant |
| Investigational drug/ treatment | The drug whose properties are being tested in the study |

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| Other treatment | Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy) |
| Part | A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease |
| Participant | A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection |
| Participant number | A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc. |
| Patient | An individual with the condition of interest for the study |
| Period | The subdivisions of the trial design (e.g. Screening, Treatment, and Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis |
| Personal data | Participant information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes patient identifier information, study information and biological samples. |
| Remote | Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location |
| Screen Failure | A participant who did not meet one or more criteria that were required for participation in the study |
| Source Data/Document | Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource |
| Start of the clinical trial | The start of the clinical trial is defined as the signature of the informed consent by the first participant |
| Study treatment | Any single drug or combination of drugs or intervention administered to the participant as part of the required study procedures |
| Study treatment discontinuation | When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation |
| Subject number | A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc. |
| T1/2 | The terminal elimination half-life [time] |
| Tele-visit | Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the investigator will conduct the trial. |
| Tmax | The time to reach the maximum concentration after drug administration [time] |

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| Troponin | Complex of three regulatory proteins that is integral to muscle contraction in skeletal muscle and cardiac muscle |
| Variable (or endpoint) | The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event. |
| Vz/F | The apparent volume of distribution during the terminal elimination phase following extravascular administration [volume] |
| Withdrawal of study consent (WoC) / Opposition to use of data /biological samples | Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation.<br>Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent. |

[redacted]

# Amendments and rationale for amendments

## Amendment 11 (19-Jul-2021)

### Amendment rationale

The main purpose of this amendment is to implement increased cardiac enzyme monitoring from every six months to every three months based on new cardiac microscopic findings (cardiomyocyte vacuolation) from a wild type RasH2 mouse study with 4-week daily dosing of branaplam at ≥ 10 mg/kg/day. It is not known whether this finding translates to humans. At a dose of 4 mg/kg/day, that did not induce cardiac lesions in the mouse, the area under the plasma (or serum or blood) concentration-time curve for the time period of one week [mass x time / volume] (AUCweek) based exposure multiple for the new findings is 2.2-fold for Type 1 SMA patients (mean of male and female). The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume] (Cmax)-based exposure multiple is 1.2-fold (mean of male and female).

Following cardiac safety consultation, it was agreed to increase cardiac enzyme monitoring to every three months; and, if any abnormalities are found, an unscheduled ECHO assessment should be performed.

In addition:

- UFB112: The bioanalytical validation of UFB112 failed with initial sample collection and a new analysis method was not completed. To avoid unnecessary blood sample collection and to reduce the total blood volume collected, the determination of UFB112 in blood samples of patients enrolled into Part 3 has been removed from the protocol.

### Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

- List of abbreviations has been aligned with amendment 11
- Glossary of terms has been updated to align with Protocol Amendment Template v 4.0
- Protocol Summary has been updated to remove ‘Impossibility/inappropriateness of treatment with nusinersen’ as an inclusion criteria for Part 2 and to remove caloric intake as an additional assessment
- Section 1.1.1 Relevant data summary: Updated to add new findings from ongoing preclinical studies
- Section 2.2 Secondary objectives: Aligned and corrected Protocol Summary Section with the secondary objectives as follows:

  1. Part 1, Part 2, Part 3:

     a. Removed two endpoints namely ‘Discontinuation due to permanent ventilation (defined as more than 21 days for more than 16 hours/day of ventilation) or tracheostomy’ and ‘Removal of tracheostomy’ from the objective ‘To evaluate the

[redacted]

effect of branaplam on respiratory function' due to the removal of the secondary objectives

b. Clarified the timepoint of CHOP INTEND infant motor scale endpoint

2. For Part 2 and Part 3:

a. Removed the objective related to UFB112 PK and its endpoint due to failed bioanalytical validation and to avoid unnecessary blood sample collection

b. Removed one endpoint namely 'Change from baseline for Hammersmith Infant Neurologic Examination' from the objective 'To evaluate the efficacy of branaplam on motor and development milestones' since this level of detail is not needed in this section

3. For Part 2: Changed the timepoint of ability to sit without support assessed by HINE-2 from 'at 12 months of Treatment' to 'over time' since all patients have received more than 12 months of treatment at this point

[redacted]

- Section 3.5.1 Doses in Part 1: Updated the link to the reference for the International Council for Harmonization (ICH) S9 guidelines 2010 and removed repetitive text
- Section 3.5.3 Doses in Part 3: Updated the section to reflect the selection of the optimal dose
- Section 3.5.4 Safety margins: Removed details around the calculations for exposures measured in animals, details can be found in the current IB
- Section 3.8 Risks and benefits: Section was revised with new risks (ovarian and cardiac) as identified from the latest preclinical studies and re-ordered according to the newly added Table 3-1. The methods to minimize the cardiac risks to the patients have been updated and the following details have been removed - the benefits and risks of approved therapy nusinersen, the comparison of long-term risks (potential/clinical) to patients receiving branaplam and nusinersen, and the comparison of exposure and number of patient of branaplam and nusinersen (and deleted corresponding tables)
- Section 3.9 Rationale for Public Health Emergency Mitigation Procedures: Newly added regarding the Public Health Emergency Mitigation Procedures, in line with latest version of Protocol template (version 4.0, dated 15-Feb-2021). Section 7 has been updated with this related text
- Section 4 Population: Clarification added that no new patients will be enrolled in Parts 2 and 3
- Section 5.1.2 Treatment arms: Updated the section to reflect the selection of the optimal dose
- Section 5.4.3 Dose Modifications, Part 3: Updated the section to reflect the selection of the optimal dose and to update the wording to be consistent with Section 5.4.7
- Table 5-7 Criteria for interruption and re-initiation of branaplam treatment for AE possibly related to study medication: Added a new row for clinically significant increase in cardiac enzymes

[redacted]

- Section 5.4.7 Within-patient dose escalation: Updated the section to reflect the selection of the optimal dose
- Section 6 Informed consent procedures: Updated to reflect latest template (v4.0, dated 150Feb-2021) language as appropriate
- Section 7 Visit schedule and assessments: Updated to reflect latest template language
- Table 7-1 Additional instructions on Part 1 assessment schedule: Updated to clarify Part 1 of the study
- Table 7-2 Additional instructions on Part 1 Extended assessment schedule: Updated to clarify 'Part 1 Extended'
- Table 7-3 'Additional instructions' for all table footers: Updated to clarify 'Part  and Treatment Period'
- Table 7-4 Assessment Schedule – Part 3: Increased the frequency of cardiac enzymes collection from every 6 months to every 3 months (also updated in Section 7.4.1), with the additional information to repeat the test within 1 week if there is a clinically significant increase and to perform echocardiogram and ECG and if not already done for the visit, corrected PK collection at EoS visit
- Section 7.3 Efficacy: Added the subheading 'Appropriateness of efficacy assessments for consistency with Protocol template (v4.0, dated 150Feb-2021)
- Section 7.4.6 Echocardiogram: Section updated to add requirement of unscheduled assessment if there is a clinically significant increase in cardiac enzymes and to detail the standard parameters
- Section 7.5.1 and Section 11.5.3: Text related to UFB112 PK sample collection and evaluation/analysis has been removed
- Section 7.5.6 Appropriateness of safety measurements: Added section to align with the latest template version
- Section 8 Discontinuation and completion: Updated heading to align with the latest template version
- Section 8.1.1 Discontinuation of study treatment: Updated to align with the latest template version (version 4.0, dated 15-Feb-2021) and to include other approved SMA therapies as opposed to just nusinersen
- Section 8.1.2 Discontinuation of study: Section added to align with the latest template version
- Section 8.1.3 Withdrawal of informed consent/Opposition to use data/biological samples: Updated to align with latest template version
- Section 8.1.4 Lost to follow up: Updated to align with the latest template version (version 4.0, dated 15-Feb-2021)
- Section 9 Safety monitoring, reporting and committees: Updated heading to align with the latest template version (version 4.0, dated 15-Feb-2021)
- Section 9.1.3 SAE reporting: Updated to align with the latest template version (version 4.0, dated 15-Feb-2021)

[redacted]

- Section 9.2.2 Data Monitoring Committee: Revised to reflect possible changes in the members of the DMC
- Section 10.1 Data collection: Removed the option of receiving paper copies of the patient data after database lock (CD-ROM only) and updated section to align with the latest template version (version 4.0, dated 15-Feb-2021)
- Section 10.2 Database management and quality control: Section added to align with the latest template version
- Section 11.1 Analysis sets: added definition of ENR and updated definitions of FAS and SAF accordingly
- Section 11.3 Treatments: Added that the data for treatments will be listed by part as well
- Section 11.5 Analysis of secondary endpoints: mixed model for repeated measures specification updated; also for safety endpoints, some more detail added
- Section 11.5.1 Efficacy and/or Pharmacodynamics endpoint(s): Analysis of secondary endpoints more clearly defined
- Section 11.5.2 Safety endpoints: Analysis of endpoints more clearly defined

[redacted]

- Section 14 References: Removed two references that are no longer applicable to the document
- General changes made throughout document to reflect patients are in Part 3 only
- General grammatical, spelling, linking and referencing corrections and updates were made throughout the document

### IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

## Amendment 10 (13-Feb-2020)

### Amendment rationale

The main purpose of this amendment is to clarify the frequency of ophthalmology assessments in Part 3 of the study. The ophthalmology assessment, dilated direct and indirect ophthalmoscopy, can be performed at each onsite visit if considered applicable by the investigator. However, if the patient does not have any ocular related complaints and if at the previous ophthalmology assessments there were no clinical findings which, potentially could be attributed to branaplam, the examination will need to be performed every 12 months, from the date of the last ophthalmology assessment. (See Section 3.3 - Part 3 Study Design).

Further change to this protocol amendment is relevant for patients in Part 3. In Part 3, patients treated with 0.625 mg/kg dose, from Part 2, now have the possibility to have a dose increase to 2.5 mg/kg, if no further improvement becomes evident, or in case of disease progression. This dose increase is at the discretion of investigator and after consultation with the sponsor. Likewise, in case of any safety concern, patients who are receiving 2.5 mg/kg could have their dose decreased to 0.625 mg/kg, at the discretion of the investigator and after consultation with the sponsor. See 3.3 Part 3 Study Design, 3.5.3 Doses in Part 3 and 5.4.3 Dose modifications.

In addition to the above, other changes were also implemented to this protocol amendment, mainly correcting discrepancies and providing additional explanations that were lacking in protocol amendment 9 for Part 3 of the study.

- Monthly safety testing panel during safety visits was corrected to full liver function panel. Full liver function panel includes: Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), Total Bilirubin (Direct and Indirect if increase > 1.5 ULN), Albumin, Total Protein (Section 7.4.1).
- Table 7-4 Assessment Schedule – Part 3: Correction to replace “Weeks” with “Days”
- Table 7-4 Assessment Schedule – Part 3: Clarification that the assessments performed during the last visit of Part 1 or 2 do not need to be repeated on visit 1 of Part 3, if visit 1 of Part 3 is performed within 14 days of last visit of Part 1 or 2.
- Clarification that branaplam can be administered at home by the patient caregiver, however patients may visit the investigator site for dosing if preferable (Section 3.1)
- Clarification on the nerve conduction study (Section 7.4.7). It is a test commonly used to evaluate the function, especially the ability of electrical conduction by the motor and sensory nerves of human body. It is evaluated by performing the following assessments:
  - Compound Muscle Action Potential (CMAP)
  - Sural Nerve Action Potential (SNAP)
  - Nerve Conduction Velocity (NCV)
  - F wave
- Clarification on the primary objectives based on the clarification on the nerve conduction study (Section 2.1)

[redacted]

[redacted]

- Addition of a new PK parameter (Section 1.1.1 Relevant data summary, Table 7-3 Assessment Schedule – Part 2, Table 7-4 Assessment Schedule – Part 3, Section 7.5.1):
  - Beside the measurement of branaplam (LMI070) in plasma, the determination of its major metabolite UFB112 (M18) in plasma will be included into the bioanalytical analysis. PK parameters of UFB112 will be estimated if possible (Section 1.1.1).Update of subsection "Human pharmacokinetic data" with new findings on PK and UFB112
  - Collection of UFB112 added in the core protocol and on schedule of assessments for Part 2 (starting week 40) and Part 3. Blood volume sampling increases by 0.7 ml per PK sample to account for an additional tube in order to test UFB112 metabolite. Increased volume will be required in Part 2 Week 40 visit and for all PK samples in Part 3 (Table 7-3 Assessment Schedule – Part 2 and Table 7-4 Assessment Schedule – Part 3, Section 7.5.1).
  - Addition of UFB112 in secondary objectives (Section 2.2)

[redacted]

- Section 3.8 Risks and Benefits updated with new information available

[redacted]

## Amendment 09 (25-Apr-2019)

### Amendment rationale

The main purpose of this amendment is to provide to patients from Part 1 and Part 2 of this protocol the possibility for continuous treatment and long term safety and efficacy follow up in the newly added Part 3 of the study. Once all patients have transitioned into part 3, the parts 1 and 2 will be closed.

All patients treated in Part 1 and Part 2 of this protocol after completing at least 52 weeks of treatment, will be offered the possibility to further extend the treatment, for as long as branaplam treatment is in the best interest of the patient. If continued branaplam treatment is not in the best interest of the patient, investigator to discuss standard of care of the study site with the parents/caregivers.

Part 3 study duration will be as long as the branaplam treatment is in the best interest of the patient or other treatment options will be offered to the patients.

Patients who have completed at least 52 weeks of treatment either in Part 1 or Part 2 study are eligible to continue treatment under Part 3 of this protocol.

In addition to the above, other changes were also implemented to this protocol amendment, mainly correcting discrepancies and providing additional explanations that were lacking in protocol amendment 8 for Part 1 and 2 of the study.

Study description for Part 3 is also provided, in order to clarify the following points:

- Eliminate assessments that were present in Parts 1 and 2 and which are not necessary for part 3 (Three day food record, Survival of Motor Neuron Protein (SMN Protein), Survival of Motor Neuron2 mRNAs (SMN2 mRNAs) blood collections)
- Revise efficacy endpoints (CHOP-INTEND to be collected up to 3 years of age, i.e. 36 months)
- Change in schedule of assessments to reflect the reduced visit frequency
- Clarify and simplify the process of branaplam administration at home
- Extend the list of assessments which can be performed by Home Nurse, when applicable
- Reformatting and renaming sections of protocol amendment 9 to have them displayed in a more logical and sequential order for the ease of use

Additionally following clarification were made for Part 1 and Part 2:

- Consequently to Part 3 updates Eliminate Three day food record assessment
- Consequently to Part 3 updates: Clarify and simplify the process of branaplam administration at home

[redacted]

## Amendment 08 (October 2018)

### Amendment rationale

The main purpose and rationale for this from three to two, in order to better ensure that the studied doses are clinically distinguishable, and to more efficiently investigate the branaplam dose-response relationship in conjunction with the data generated in Part 1. In addition, several modifications were made to the inclusion and exclusion criteria to reflect evolving knowledge and practice in the diagnosis and treatment of Type 1 spinal muscular atrophy (e.g. allowing patients diagnosed before the onset of symptoms to be eligible for the study).

The data from Part 1, which utilized a within-patient dose escalation design, suggest that systemic exposure to branaplam is proportional to the dose across the full-range of doses studied (6 mg/m$^2$ [0.3125 mg/kg] to 60 mg/m$^2$ [3.125 mg/kg]). The originally selected three doses for Part 2 spanned a range of only 4-fold (0.625, 1.25, 2.5 mg/kg). The preliminary PK results of this study showed that Cmax and AUC values were not clearly separated between the middle dose and either the lower dose or the higher dose leading to difficulties in the interpretation of the dose-response. Since all three doses were associated with increases in CHOP-INTEND in Part 1, continuing the clinical characterization of the dose-response for branaplam with two doses separated by 4-fold (0.625 and 2.5 mg/kg) represents a more efficient study design and avoids exposing patients to unnecessary research. Due to the design of Part 1, which mandated within-patient dose escalation, it is not clear if continuous dosing with 12 mg/m$^2$ (0.625 mg/kg) may yet be effective and durable. In the event that the response to 12 mg/m$^2$ (0.625 mg/kg) appears inadequate and in order to ensure patient safety, Part 2 has a rescue provision that allows within-patient dose escalation. The lower dose cohort may be closed early and the higher dose cohort opened if three patients experience unacceptable responses to 12 mg/m$^2$ (0.625 mg/kg) as defined in Section 5.4.

The Part 2 study design and sample size were modified accordingly throughout the protocol.

Other changes include clarifications and harmonization throughout the protocol of:

- Relevant sections updated to reflect the latest edition of the Investigators' Brochure (IB)
- Definition of permanent ventilation
- Toxicity management and dose interruption guidance
- Inclusion criteria modified per comments from the Italian Health Authority (Istituto Superiore di Sanità, ISS) during their review of the protocol amendment 7
- Clarification that Part 1 patients following the Extended treatment Schedule of Assessment and patients enrolled in Part 2 may continue receiving study treatment in a separate branaplam protocol

The following Assessments have been modified:

- The nerve conduction studies and compound motor action potential (CMAP) assessments were modified. Novartis consulted external experts in the area of neurophysiology, who advised that the prolongation of the neurophysiology current protocol may increase the stress for patients and bear the risks of low quality results, missing parameters and/or withdrawal from the study. The recommended modifications address the safety concern to

detect potential neuropathy due to the study drug, as well as the feasibility in the study population

- The possibility for administration of the study drug at home by caregivers was added and an Instructions for administration of the study drug at home by caregivers developed
- Monitoring of patient dietary intake, per data monitoring committee (DMC) request, using a 3-day caloric intake record, has been added

### Changes to the protocol:

- List of abbreviations updated
- Protocol synopsis updated to reflect the changes to the protocol described below
- Preclinical Data: has been updated with most recent pre-clinical Pharmacokinetic data
- Human safety and tolerability data updated to reflect the most recent data available
- Human pharmacokinetic data updated to reflect the IB Edition 7.0 and
- Table 1-1 added
- Study purpose updated to clarify the rationale for Part 1 and Part 2
- Primary Objective (s):
  - Objective of Part 2 was rephrased as evaluation of two doses of branaplam administered weekly
  - Endpoint Part 1 and Part 2: Nerve conduction studies and ulnar nerve compound motor action potential assessments have been described and moved under safety endpoints
- Secondary Objective(s): Part 1and Part 2
  - Objective: To evaluate the effect of branaplam on respiratory function. The corresponding endpoint has been updated with the definition of permanent ventilation and removal of tracheostomy endpoint has been added to reflect the change in exclusion criterion number 8
  - Compound motor action amplitude potential endpoints moved to primary [redacted] objectives - ulnar nerves assessments are suitable to address safety concerns and peroneal nerve assessments changed to optional

[redacted]

- Study design:
  - Text referring to Part 2 updated with two doses
  - Text referring to the possibility for the Patient in Part 1 and Part 2 to continue receiving study medication under a separate branaplam protocol if in the best interest of the patient and assessed by the investigator has been added
  - Part 2 Study Design: Section updated to reflect the dose change and the cohort 1 dose escalation option after 3 patients treated for at least 13 weeks
  - Figure 3-2, cohort 2 and footnote removed
  - Screening paragraph: first sentence has been removed as unclear

[redacted]

  - End of Study: The option for the patient to continue receiving treatment under a separate branaplam protocol added
- Rationale for study design: updated with references
- Rationale for dose/regimen, duration of treatment
  - Doses in Part 1: the maximum dose text was moved under this section. No change to the content
  - Doses in Part 2: Second dose level rational paragraph has been added to describe the choice of the 2.5mg/kg
  - Dose escalation: text removed since it was not applicable
  - Safety margins: text was updated to reflect the IB Edition 7.0
  - Age effect was updated per IB Edition 7.0
- Table 3-3 Comparison of long-term potential risks of branaplam and nusinersen added with number of cases and duration of treatment per Italian Health Authority request
- Inclusion criteria Part 2:
  - Criterion # 2 modified to allow inclusion of symptomatic SMA Type 1 patient. Based on the current data, the Sponsor has determined that symptomatic patients could also benefit from branaplam
  - Criterion # 3 added per Italian Health Authority request
  - Criterion # 4: "as assessed by investigator" added. This addresses the differences of supportive care in countries and upon patient clinical status
  - Criterion # 5: the age was changed to include patients up to 180 days of age to reflect new practices in diagnosis such as newborn screening
  - Criterion # 9 reworded to help clarity
  - Criterion # 10 removed since local standard of care and compliance is already evaluated during site selection.
  - Criterion # 11 removed since difficult to assess and restricts both caregivers and physicians choice
- Exclusion criteria Part 2
  - Criterion # 4: Anemia grade 1 has been changed to Anemia grade 2. Mild anemia is frequent in this population with low weight. The cumulative part 1 data have not shown increase risks of anemia worsening.
  - Criterion # 8: presence of tracheostomy removed. The cumulated safety data from Part 1 support that patients could benefit from branaplam even with a tracheostomy
- Prohibited chronic treatment: new data related to some potential drug-drug interaction has been added and caution warning.
- General restrictions: reference to Pharmacy Manual corrected and replaced by the most recent version of the Instruction for administration of branaplam for phase I/II investigational human use.
- Treatment arms and Table 7-3 Treating the patient Part 2 updated with two doses
- Treating the Patient: the option to administer branaplam the patient's home by legal representative caregivers and reference to Appendix 2 –Administration of branaplam by caregivers - Instruction for site staff and caregivers added

[redacted]

- Dose cohort modification - Part 2: The text was updated with definition and time-point of potential intra-cohort 1 dose escalation in the event that the response to 0.625 mg/kg appears ineffective. The evaluation of a potential loss of positive effect is described
- Within-patient dose escalation - Part 2: The text was updated to clarify the possibility that a patient enrolled in cohort 1 may be escalated to the cohort 2 dose in the event of loss of durable positive effect
- Adverse events: reference to CTCAE vs 4 modified as "the most recent version" of the CTCAE
- Permitted dose adjustment and interruptions of study treatment: This section has been updated to reflect the Part 2 design and patients under Part 1 Extended treatment schedule. The references to dose-level decrease have been removed
- Concomitant treatment: "including vaccinations" has been added
- Discontinuation of study treatment: This section has been updated to reflect the Part 2 design and to be applicable for patients following the Extended schedule of assessment Part 1: "Patient has unresolved adverse events that require two dose de-escalations" removed and "Patients who never improve and decline in CHOP-INTEND by 5 or more points or lose one or more previously attained motor milestones" added
- Withdrawal of consent has been updated to reflect Novartis most recent protocol template
- Study Stopping rules updated to reflect status of the trial
- Table 7-2 Assessment Schedule – Part 1 – Extended treatment period and Table 7-3 Assessment Schedule – Part 2 has been updated :
    - with visits that study drug administration may be done in the patient's home by a qualified clinician or by the assigned and trained caregivers
    - add 3-day food record assessment
    - add footnotes to clarify optional peroneal CMAP, ophthalmologic assessment (to address errors and align with amendment 3), CHOP-INTEND assessment not required after patient/s have reached three years of age, and assessments that may be performed at a subsequent visit at the discretion of the investigator if patient/s experience an acute illness episode
    - Echocardiogram Part 1: 2 planned visit changed and echocardiogram Part 2:1 visit in period 2, 3 and 4 changed to reduce the burden of extra visits for the patient
    - [redacted]
- (CHOP-INTEND): The collection of the assessment will be terminated once patient reaches 3 years of age
- Laboratory evaluation: urine analysis: microscopic analysis replaced by bacterial analysis
- CMAP and Nerve conduction velocities (NCV). The list and order of the assessments and tests have been added
- Three –Day diary record added
- Pharmacokinetics: Total blood volumes have been added. EMA Good Clinical Practice and FDA Code for Federal regulation specify that blood volume should be minimized and justified in protocols
- CMAP and NCV Optional has been added. The section describes the optional CMAP assessment and NCV tests

[redacted]

[redacted]

- Data Monitoring Committee: Last paragraph has been removed. The study is open label. Data to the DMC are not generated by an Independent Statistical Team statistician.
- Analysis of the primary, secondary [redacted] variables. The sections have been updated to reflect the most recent Statistical Analysis Plan
- Sample size calculation Part 1 and Part 2. The section has been updated to reflect the actual total number of patients enrolled in Part 1, and the revised total number of patients in Part 2 considering the removal of the cohort 1.25mg/kg
- References has been updated
- Appendix 2 Administration of branaplam by caregivers- Instruction for study site staff and caregivers has been added

[redacted]

## Amendment 7 (December 2017)

### Amendment rationale

The main purpose of this amendment is to implement in all countries where the study is being conducted or being submitted to the Health Authorities the changes made based on the request of the German Health Authority during their review of the Amended Protocol version v06. These changes had so far been implemented in a local protocol amendment (Amendment 6 DE0.1) submitted and approved exclusively in Germany.

In addition the criteria used to decide interrupting and re-initiating treatment with branaplam in the event of thrombocytosis were added based on a commitment done to a Health Authority.

At the time of this amendment 8 patients are ongoing in Part 1 of the study and no new patients have been recruited in Part 2 of the study.

### Changes to the protocol

- All changes listed in the Amendment 6 DE0.1
- Notification of serious adverse events: the name of the Novartis department where serious adverse events (SAEs) need to be sent has been changed.
- Table 6-2 has been updated to include the dose conversion from BSA to weight for doses in Part 1 of the study since the previous amendment of the protocol did only specify the conversion for planned doses in Part 2 of the study.
- Table 6-5 Criteria for interruption and re-initiation of branaplam treatment has been updated to include specific recommendations for dose modifications in the event of thrombocytosis.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.
A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation.
The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

## Amendment 6 DE0.1 (August 2017)

### Amendment rationale

The main purpose of this amendment is to implement changes based on the request of the German Health Authority during their review of the Amended Protocol version v06 to better reflect that Spinraza® (nusinersen) is now approved in many countries for the treatment of 5q SMA and is considered standard of care. The impacts of this approval for study eligibility, study execution, study comparator and long term potential risks between an approved agent and branaplam have been added.

In addition in the Amended Protocol v06 (see corresponding Amendment rationale) it is foreseen to have the dose calculation for branaplam done based on the patient's weight instead of the body surface area. The rationale for the conversion of the dose administered from a body surface area calculation to a weight-based calculation has also been clarified.

### Changes to the protocol

- The List of abbreviations has been updated.
- Protocol synopsis: Changes were made in the synopsis to reflect all changes throughout the protocol as outlined below.

[redacted]

- Section 3.2 Rationale for study design and Section 3.4 Rationale for choice of comparator: these sections have been updated to indicate that Spinraza® (nusinersen) has now been approved in both the US and in the EU.
- Section 3.2 Rationale for study design: The section had been updated to clarify a sentence which was unclear about the initial study design and why the study had been designed to start directly in infants with Type I SMA
- Section 3.6 Risks and benefits: This section has been updated to specify the known benefits and risks of the approved therapy for 5q SMA. Table 3-1 and Table 3-2 had been added comparing potential risks observed in preclinical studies and of long-term administration of branaplam and nusinersen.
- Section 4.2.2 Part 2 Exclusion criteria: the use of nusinersen has been removed from the exclusion criterion #1 since nusinersen is an approved therapy and not an investigational drug and is now treated as a separate exclusion criterion. The need to check exclusion criterion #10 at baseline had been removed since Electrocardiogram (ECG) and echocardiogram (ECHO) are only performed at the screening visit.
- Section 5.2 Prohibited Chronic Treatment: nusinersen has been removed from Table 5-1 and listed separately to make a clear distinction between experimental therapies and approved therapies for the treatment of SMA.
- Section 6.3 Treatment arms: the explanation of how the dose conversion between BSA and weight was performed has been added. Data from PK samples collected in Part 1 of the study enabling this conversion have been added in Table 6-2. Table 6-3 has been

[redacted]

added to clarify the dose conversion from BSA to weight for provisional doses to be tested in Part 2 of the study.

- Section 5 Discontinuation of study treatment: the use of nusinersen during the study has been added as a reason to discontinue branaplam treatment, in agreement with Section 5.2 since this could interfere with the assessment of study endpoints.
- Section 7 Procedures and assessments: minor discrepancies have been corrected in the following assessment schedules:
  - Table 7-2: the nerve conduction velocities are planned to be performed every 3 months and not only at the end of study visit as previously indicated for Part 1 of the study in the clean version of the Amended Protocol v06.
  - Table 7-3: the number of the footnote specifying the frequency at which detailed neurologic examination needs to be performed has been corrected.
- Section 7.4 Physical examination: the wording defining the frequency of detailed physical examination has been corrected to match the Assessment Schedule.
- Section 14 References: the EMA report for Spinraza® had been added as a reference because it is mentioned in Section 3.6.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

[redacted]

## Amendment 6 (April 2017)

### Amendment rationale

The enrollment of the ongoing clinical study had been voluntarily and temporarily suspended following the implementation of a Urgent Safety Measure after preclinical findings in the 52-week, daily dosing toxicity study in juvenile Beagle dogs (see Amendment 5).The main purpose of this sixth amendment is to allow resumption of enrollment in the ongoing study as agreed by the independent Data Monitoring Committee (DMC). The DMC agreed that the benefit-risk was positive for new patients as well as for ongoing patients. This DMC recommendation was based on review of the available clinical data for the patients ongoing in the study as well as the results of the preclinical investigations as part of the chronic dog toxicology study. An independent benefit-risk assessment by Prof. [redacted] at Catholic University in Rome also found evidence of a continued positive benefit-risk for patients enrolled in the study. Following the DMC recommendation one of the safety monitoring measures put in place at the time of the third Urgent Safety Measure (USM), namely the expanded neurophysiologic examination will be modified to include the measurement of both median and sural nerve action potentials (SNAPs) to assess sensory as well as motor nerves in the monitoring plan. [redacted]

LMI070 now has a recommended International Nonproprietary Name (INN): branaplam which has passed the objection period and will thus be used in place of LMI070.

The study was initially designed as a multi-part study with Part 2 planning to evaluate the safety and efficacy of multiple dose regimens of branaplam. However in view of the available data collected in this ongoing clinical study as well as the preclinical findings reported in the 52-week, daily dosing toxicity study in juvenile Beagle dogs, and a dosing regimen more frequent than weekly administration was not supported. Part 2 of the study will thus be modified to obtain additional safety and efficacy data with oral administration of up to 3 dose levels of branaplam, already tested in Part 1, to identify the dose that is safe for long term use as well as that can provide durable efficacy. Part 2 will enroll up to approximately 30 patients (a minimum of 6 patients and a maximum of 10 patients will be enrolled in each cohort). Unlike in Part 1, no planned within-patient dose escalation will occur in Part 2, although rescue is allowed if response does not prove durable. No new patients will be enrolled in Part 1 of the study. The total number of patients planned to be enrolled is slightly increased, i.e. up to 45 patients (previously a maximum of 42 patients were planned to be enrolled).

The following inclusion and exclusion criteria for Part 2 have been modified or added compared to the ones for Part 1:

- the age of patients at screening is now expressed in days instead of months and restricted to 180 days of age (upper limit) because of the higher likelihood of motor response in younger patients, based upon Part 1 data from this study as well as responder age from other therapies in development
- A minimum CHOP INTEND score of 15 is required at baseline and patients must be able to feed orally for all nutritional needs and be greater than the 2$^{nd}$ percentile for weight on

[redacted]

the standard growth curves for the country of origin. This is undertaken to avoid inclusion of patients whose disease state is already too severe to expect clinical benefit

Since the relationship between weight and BSA is nearly linear in infants and individuals less than 50 kg the dose calculation will now be done based on the patient's weight only instead of the body surface area. This change will reduce burden in the study and simplify the dose calculation, and will apply to patients in both parts of the study. A conversion table based upon the linear relationship found for patients in part 1 of this study is included in Section 6.3.

Finally, where possible the number of assessments to be conducted has been reduced in order to lower burden on the patients.

### Changes to the protocol

- The List of abbreviations has been updated.
- Protocol synopsis: changes were made in the synopsis to reflect all changes throughout the protocol as outlined below.
- Section 1.1 – Figure 1-1 the figure describing the mode of action of branaplam has been modified to increase clarity.
- Section 1.1.1.4 has been updated to include the available information from all patients enrolled in the study at time of this amendment.
- Section 2.1 – Primary Objectives: the objective has been revised to reflect the dosing regimen and duration of treatment in Part 2 of the study.
- Section 2.2 – Secondary Objectives:
  - The endpoint corresponding to the pharmacokinetic objective has been re-written to be accurate.
  - The cry vital capacity which was an optional assessment foreseen to be conducted in Part 2 has been removed.
- The discontinuation due to permanent ventilation or tracheostomy has been added as an endpoint to evaluate the effect of branaplam on respiratory function
- The Hammersmith Infant Neurologic Examination has been added as an endpoint to evaluate the efficacy of branaplam on motor and developmental milestones for comparability to other molecules in development in SMA type I.
- The percentage of infants who are sitting without support at 12-months of Treatment has been added as a secondary objective for Part 2 of the study
- Peroneal compound motor action amplitude potential (CMAP) has been included in addition to the ulnar compound motor action amplitude potential.

[redacted]

[redacted]

- Section 3.1.1 Part 1 Study Design:
  - The actual number of patients enrolled in the study has been indicated since no more patients will be enrolled in Part 1 of the study.
  - The amount of time patients need to stay on site after administration has been removed and the decision is left to the investigator's decision. This is supported by safety data collected until now in the study.
- Section 3.1.2 Part 2 Study Design and Section 3.2 Rationale for study design: this section has been entirely adapted to reflect the 3 cohorts to be evaluated, the duration of treatment and the dose escalation.
- Section 3.3 Rationale for dose/regimen, duration of treatment: the choice of the starting dose for Part 2 has been described as well as the duration of treatment (52 weeks).
- Section 3.4 Rationale for choice of comparator: the section has been updated to take into account the recent approval of Spinraza® (nusinersen) for SMA in the United States.
- Section 3.5 Purpose and timing of interim analyses/design adaptations: the section has been updated to describe the actual interim analysis performed during Part 1 of the study and to specify that intra-patient dose escalation is not planned for patients enrolled in Part 2 of the study unless specific criteria are met.
- Section 3.6 Risks and benefits: the text has been updated with the most recent preclinical information on the effects of branaplam on peripheral nerve system.
- Section 4 Population: this section has been divided in 2 subsections for Part 1 and Part 2 since the eligibility criteria are different in each part of the study.
- Section 4.1. Inclusion criteria Part 2: Inclusion criterion #4 has been modified and inclusion criteria #7 and #8 have been added as described in the amendment rationale
- Section 4.2 Exclusion criteria Part 2:
  - Criterion #1 has been modified to take into account the availability of Spinraza® (Nusinersen) in some countries and the ongoing clinical trial with gene therapy.
  - Criterion #7 "Intractable seizure disorder" has been changed to "Intractable epilepsy" to clarify that infants with intractable epilepsy should be excluded from the study. Indeed these patients would not be expected to achieve motor milestones due to severe underlying brain disease and would interfere with secondary objectives of the study.
  - Criterion #8 has been modified to remove oral suctioning as a potential factor to determine eligibility in the study since this does not inform on the patient's respiratory function
  - Criterion #10 has been modified to specify that an echocardiogram needs to be performed at screening to exclude any clinical significant cardiac findings.
- Section 5.2 Prohibited chronic treatment: Spinraza® (nusinersen) and other non-approved experimental therapy for the treatment of SMA have been added in Table 5-1.
- Section 6.3 – Treatment Arms:
  - A conversion table from body surface area to weight is included for Part 1 and 2
  - The dose levels for Part 2 have been added

[redacted]

- Section 6.4 Treating the Patient: the text has been modified to include the details on the route of administration in Part 2. The possibility to have the administration performed in the patient's home once reviewed and agreed by the Investigator, Novartis and the DMC has been added.
- Section 6.5.2 Dose cohort modification: the details of the composition of cohorts in Part 2 as well as the dose escalation criteria have been included.
- Section 6.5.4 and Section 6.7.2 Intra-patient dose escalation and permitted dose adjustments and interruptions: sub-sections have been added for Part 2 to specify the rules to follow in order to decide when an intra-patient dose escalation could take place.
- Section 7.1 Discontinuation of study treatment: the criteria used to define the disease progression have been revised following discussion with the DMC.
- Table 7-2 Assessment Schedule – Extended treatment periods:
  - Speech and motor milestones and Hammersmith Infant Neurological Examination (HINE) have been added at the end of each treatment cycle and V777. The information on these milestones was previously collected but the frequency was left to the investigator's discretion.
  - Nerve conduction studies have been added based as per DMC feedback following the implementation of the third USM.
  - Physical examination, vital signs and body measurements, respiratory function assessments: the frequency of these assessments was reduced to monthly instead of weekly as previously scheduled. In view of the data collected so far in the ongoing study this reduced frequency is deemed sufficient and allows to reduce burden on patients.
  - [redacted]
  - The possibility to have drug administration performed in the patient's home has been added to reduce burden on the patients.
- Table 7-3 Assessment Schedule – Part 2: the schedule has been completely revised to match study Part 2 design. The schedule of assessments has been divided in 4 treatment periods of 13 weeks for readability. The possibility to have drug administration performed in the patient's home has also been added.
- Section 8.3.1 ulnar nerve compound motor action potential (CMAP) (expanded assessment) has been moved to the section describing safety assessments and to include peroneal nerves in the description of the assessment (Section 8.4.9)
- Section 8.3.2 Hammersmith Infant Neurologic Examination (HINE): this section has been added since this is a new assessment.
- Section 8.4.3 Body length, weight and head circumference: the calculation of the body surface area (BSA) has been removed since dose calculation will be performed based on weight only.
- Section 8.4.7 Respiratory function: the cry vital capacity has been removed.
- Section 8.4.8 GI function: the section has been deleted. Indeed the diary previously given to parents/caregivers Parents/Care-givers to record any adverse events when patients are

[redacted]

not in the clinic was focused only on the GI adverse events. As per the sites feedback the diary was too specific and not used. AEs are recorded as per standard practice.

- Section 8.4.10: Nerve conduction velocities (NCV): the section has been added since this is a new assessment.

[redacted]

- Section 11: The entire section has been adapted to reflect the changes in design in Part 2
- Minor spelling and administrative changes were made throughout the protocol to improve clarity.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

[redacted]

## Amendment 05 (August 2016)

### Amendment rationale

The main purpose of this amendment is to implement additional safety monitoring following a third urgent safety measure (USM), based on new non-clinical findings and dose lowering that was implemented, and later on reversed with a fourth urgent safety measure (USM) following serious clinical adverse events associated with a lower dose.

The new non-clinical findings that were considered adverse, potentially serious and unexpected and led to the third urgent safety measure (USM) have been reported to health authorities, ethics committees, and investigators. Histopathology data in the 52-week, daily dosing toxicity study in juvenile Beagle dogs, became available and identified three new target organs of toxicity: the nervous system, kidney and testes. In the ongoing CLMI070X2201 clinical study, where patients are dosed on a weekly basis, LMI070 continues to be well tolerated with signs of clinical benefit. However, following consultation with an external pediatric SMA expert, internal safety experts and in agreement with the external safety Data Monitoring Committee, Novartis had decided to take the following urgent safety measures which have been notified to all clinical sites and submitted to the Health Authorities:

- Reduction of the weekly dose of LMI070 administered to all patients having completed the initial 13 weeks of treatment to 6 mg/m$^2$. The dose of 6 mg/m$^2$ was selected as the dose for continued treatment of enrolled patients because it represented the lowest dose which exhibited clinical response (CHOP INTEND improvements) with a small safety margin over the lowest dose tested in dogs, based on systemic drug exposure.
- An expanded neurophysiologic examination to be conducted every 3 months to address the risk of nerve degeneration as identified in the 52-week chronic toxicology dog study.
- A detailed, serial neurologic examination focusing on both motor and sensory findings conducted monthly to document the patient's clinical status.
- A new benefit: risk determination by an independent physician for each patient enrolled in the study. Subsequent treatment for each enrolled patient would be conducted only if the benefit: risk assessment for this patient continued to be positive.

Also following recommendations from the independent Data Monitoring Committee (DMC) in response to the new non-clinical findings, the enrollment of new patients in the study has been voluntarily and temporarily suspended until data are available that allow for a better understanding of the pathophysiological mechanisms that may explain the observations in the chronic dog toxicology study.

However within 6-7 weeks following implementation of the lower dose of LMI070 as part of the third USM, new safety events, including serious adverse events indicating decrease of motor skills, generalized motor weakness and increased respiratory muscle weakness, occurred in 7 of 10 patients in the ongoing study whose dose was lowered to 6 mg/m$^2$. After consultation with Investigators and following recommendations from the internal safety board and as agreed to by the independent DMC, Novartis has decided to institute a fourth USM in response to these clinical events: to re-instate the weekly dose of LMI070 (either 48 mg/m$^2$ or 60 mg/m$^2$) that was administered prior to the dose reduction to 6 mg/m$^2$ for each patient. The evaluations

implemented in the third USM (additional neurologic and neurophysiologic examinations, risk/benefit determination by independent physician) remain implemented in the study. Also, as implemented in the third USM, enrollment of new patients remains suspended.

In addition, the following changes have been made to reduce the burden for patients already enrolled in the study:

- Option for safe oral administration of LMI070 to patients who have completed the initial 13 weeks of treatment has been introduced.
- The optional infant cry vital capacity assessment has been removed from Part 1 of the study.
- The number of PK samples taken and their frequency has also been reduced where possible.

At the time this amendment was written thirteen patients have been treated with LMI070 in Part 1 of the study. New information concerning the safety and pharmacokinetics in these patients is provided as part of this amendment.

### Changes to the protocol

- Protocol synopsis: changes were made in the synopsis to reflect all changes throughout the protocol as outlined below.
- Figure 1-1: The figure was replaced to reflect a more accurate number of mRNA splicing in SMN2.
- Section 1.1.1.1 has been updated with additional available preclinical information, mainly from the 52-week toxicology study in juvenile dogs.
    - Section 1.1.1.4 and Section 1.1.1.5 have been updated to include the available information from all patients enrolled in Part 1 of the study at time of this amendment.
- Section 2.1 – Primary Objective: addition of two following safety endpoints: neurologic examination and neurophysiologic examination following preclinical safety findings in the 52-week toxicology study in juvenile dogs and subsequent implementation of an USM.
- Section 2.2 – Secondary Objectives:
    - Correction of a discrepancy which indicated that LMI070 pharmacokinetics are evaluated in serum whereas it is actually performed in plasma samples only.
    - The compound motor action potential (CMAP) which used to be optional is now mandatory for all patients enrolled in the study as an additional safety monitoring assessment and thus the text has been adapted accordingly throughout the protocol.
- Section 3.1.1 – Part 1 Study design: Clarification that the dose escalation of LMI070 in Part 1 of the study could stop depending on PK results even if the MTD could not be reached.
- Section 3.1.2 – Study design: clarification on the data to be used for the determination of the dose regimen to be tested in Part 2.

[redacted]

- Section 3.3 – Rationale for dose/regimen, duration of treatment:
    - A typo has been corrected in the section explaining the calculation of the starting dose in patients.
    - The sub-section on the Maximum dose has been updated in view of the newly available preclinical data from the 52-week toxicology study in juvenile dogs.
    - The sub-section on age effect has been updated with the available information from the ongoing clinical study.
- Section 3.6: the benefit/risk assessment has been updated to reflect that with current information it does not justify enrollment of new patients (based upon new pre-clinical tox findings) but that the risk/benefit justifies continued dosing for currently enrolled patients (based on clinical data thus far).
- Section 4.1- Inclusion criteria: the inclusion criterion #6 has been updated to indicate that placement of a feeding tube for the administration of LMI070 in Part 1 should be applied only in patients who cannot be administered orally.
- Section 6.4 – Treating the Patient: this new section has been added to clarify when and under which conditions oral administration could be performed during the study.
- Table 8-1 and Table 8-3: the time points when the detailed neurologic examination should be performed and the fact that the expanded neurophysiologic examination is now mandatory for all patients have been added.
- Table 8-2: in addition to the changes listed above for Table 8-1 and Table 8-3 the following changes have been done: the Acceptability and palatability questionnaire has been added since in the extended treatment periods LMI070 can be administered orally; the frequency at which PK samples need to be drawn and their number have been reduced to take into account the patient's burden.
- Section 8.3.1 – Ulnar Nerve Compound Motor Action Potential (CMAP): this section has been updated since this examination becomes mandatory for all patients in the study.
- Section 8.4.1 – Physical Examination: this section has been updated to indicate when the detailed neurologic examination should be performed.
- Section 8.6.3 Acceptability and Palatability Questionnaire: this new section has been added since a new questionnaire has been introduced to evaluate the acceptability of LMI070 by patients when administered orally.
- Section 11.5 – Analysis of secondary [redacted] variables: this section was updated to remove the analysis of ultrasound data as this assessment is no longer performed
- Section 11.5.2 – Safety has been updated to take into account the additional safety findings reported in the different Urgent Safety Measures.
- Minor spelling and administrative changes were made throughout the protocol to improve clarity

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

[redacted]

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. Please note that the additional safety monitoring measures as described are already in effect as communicated by the Urgent Safety Measure notification.

[redacted]

## Amendment 04 (March 2016)

### Amendment rationale

The main purpose of this amendment is to implement additional cardiac monitoring following a second urgent safety measure (USM) based on two separate and distinct serious cardiac events that were reported in 2 patients enrolled in the study within the first 6 – 8 weeks following LMI070 treatment. While it is unlikely that the cardiac events were caused by LMI070, additional cardiac monitoring was implemented for every patient enrolled in the study as safety precaution. Measures were based on recommendations from both internal Novartis and external consulting cardiologists. Exclusion criterion #10 has been expanded to exclude a broader range of cardiac disease. Additionally, dose modification rules have been added for cardiac disorders and hypertension. The two higher dose levels (120 mg/m$^2$ and 240 mg/m$^2$), which exceed the available preclinical toxicology exposure, are removed in this amendment, based on the request of a Health Authority during their review of the Amended Protocol version v03. The highest dose level evaluated in the study will thus remain 60 mg/m$^2$ as initially foreseen. In addition, the measurement of quadriceps muscle thickness by ultrasound [redacted] are removed. The data collected so far in the study do not support the continuation of these assessments, and this will allow reducing the burden on patients in the study.

At the time this amendment was written twelve patients have been treated with LMI070 in Part 1 of the study. New information concerning the safety and pharmacokinetics in these patients is provided as part of this amendment.

### Changes to the protocol

- Protocol synopsis: changes were made in the synopsis to reflect all changes throughout the protocol as outlined below.
- Introduction-Section 1.1.1.1 has been updated with additional available preclinical information.
- Introduction-Section 1.1.1.4 and Section 1.1.1.5 have been updated to include preliminary information from the 12 patients enrolled in Part 1 of the study at time of this amendment.
- Section 2.1: addition of echocardiographic evaluation as an endpoint for Primary Objectives
- Section 2.2: Removal of the secondary objective meant to evaluate the effect of LMI070 on muscle by ultrasound.

[redacted]

[redacted]

- Study design – Figure 3-1 Part 1 study design: the 2 highest dose levels of 120 mg/m$^2$ and 240 mg/m$^2$ have been removed based upon the request of a Health Authority during their review of the Amended Protocol version v03. Subsequent sections of the protocol have been updated to remove reference to these two higher dose levels (e.g. Table 6-1), and the protocol now refers to 'up to 5 cohorts' instead of 'up to 7 cohorts'.
- Section 3.6: the benefit/risk assessment has been updated with the most recent information from non-clinical chronic toxicology studies and from the CLMI070X2201 clinical study.
- Section 4.2: exclusion criterion #10 was clarified in order to exclude patients with cardiac and/or vascular abnormalities. This modification is done based on the request from a Health Authority following their review of the USM.
- Section 6.7 - Table 6-5 Criteria for interruption and re-initiation of LMI070 treatment has been updated to include specific recommendations for dose modifications in the event of cardiac disorders or hypertension. This modification is done based on the request from a Health Authority following their review of the USM.
- Table 8-1 and Table 8-3: addition of echocardiographic examination at 1 and 2 months during the initial treatment period, in order to reflect the measures described in the USM. Removal of the ultrasound assessment [redacted]
- Table 8-2: addition of monthly echocardiographic examination in the event of a Grade 2 systolic function Adverse Event (AE). The assessments not performed during the extended treatment period have been removed, the footnotes updated accordingly and a mistake in the visit numbers has been corrected. Removal of the ultrasound assessment [redacted]
- Section 8.3.1: Removal the section describing the determination of muscle thickness by ultrasound.
- Section 8.4.5: addition of the QTcB in the list of parameters to be collected when an ECG is performed. The QTcB, which is more accurate at high heart rates will be used from now on for clinical decision instead of QTcF.

[redacted]

[redacted]

- Section 14: references listed in the Risks and Benefits section have been added and the references mentioned in the section describing the ultrasound assessment have been removed.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. Please note that the cardiac monitoring changes as described are already in effect as communicated by the Urgent Safety Measure notification.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

## Amendment 03 (November 2015)

### Amendment rationale

The main purpose of this amendment is to implement additional safety measures. First, ophthalmologic monitoring was added as part of the safety monitoring plan. This measure was already implemented at clinical sites in all countries, due to an immediate implementation request generated by a Health Authority following their review of newly available preclinical data. In addition, this amendment is also implementing requests for modification from the independent Data Monitoring Committee (DMC) following their review of the clinical safety data so far. Furthermore, based on feedback from site investigators and patient guardians, the measure of infant respiratory function (cry vital capacity) is considered too burdensome for many patients and therefore is no longer a required evaluation of the study and becomes an optional assessment. A different and much less burdensome assessment to evaluate respiratory function, measurement of chest circumference during quiet breathing, has been added. Also the requirement for parents/guardians to wear gloves during 48h after each administration has been removed since a toxicological safety assessment on accidental dermal exposure indicated that the calculated maximum systemic exposure following an accidental spill of LMI070 solution onto the skin is not considered to present an undue health risk to the caregiver. Finally, two dose levels are added since at the time of this amendment the MTD has not yet been reached. Moreover preliminary PK results obtained up to the 48 mg/m$^2$ dose level indicate the need to further evaluate the dose proportionality. This amendment thus plans to increase the total number of patients to be enrolled in Part 1 of the study up to approximately 30 in order to also include additional patients who may present in order not to delay their treatment.

At the time this amendment was written nine patients have been treated with LMI070 in Part 1 of the study. New information concerning the safety and pharmacokinetics in these patients is provided as part of this amendment.

### Changes to the protocol

- List of abbreviations: The list was updated and some abbreviations were added.
- Protocol synopsis
- Introduction – Section 1.1: the genetic background of SMA patients has been re-worded to increase clarity and the mechanism of action of LMI070 has been specified since it has been elucidated and published.
- Introduction – Section 1.1.1.1: the effect of LMI070 on the SMN protein level observed in mice has been re-worded to increase clarity. The preliminary observations from the ongoing 26-week juvenile rat including ophthalmologic examination findings have been added as well.
- Introduction – Section 1.1.1.4 and Section 1.1.1.5 have been updated to include preliminary information from the 10 patients enrolled as of today in Part 1 of the study.
- Section 2.1. Addition of ophthalmologic monitoring as an endpoint for Primary Objectives
- Section 2.2 Secondary objectives: the respiratory function endpoints have been modified to indicate that the cry vital capacity is now an optional assessment and to include the

measurement of chest circumference during quiet breathing instead since this is a non-invasive and another way to quantify the degree of respiratory muscle impairment. These changes are also reflected in Section 8.4.7 and in the different assessment schedules (Table 8-1 Assessment Schedule – Part 1 – Initial treatment period (Day -14 to Day 85) ; Table 8-2 Assessment Schedule – Part 1 – Extended treatment period ; Table 8-3 Assessment Schedule – Part 2)

- Section 3.1, Section 4 and Section 8.2.1: clarification on the number of SMN2 gene copies needed for eligibility in the study, which must be exactly 2.
- Section 3.1.1 and Section 4: the number of patients to be enrolled in study Part 1 had been increased and the study design figure has been updated with the 2 additional provisional dose levels.
- Section 3.1.1, Section 3.1.2 and Section 5.3: clarification on the guidance to be followed for the implementation of reflux precautions post-dosing.
- Section 3.1.1 – A recommendation for patients to stay within less than 120 minutes by ground transportation of the site for the time interval between signing the Informed Consent Form (ICF) and the end of the DLT (Dose Limiting Toxicity) period has been added.
- Section 3.1.2: clarification that data from chronic juvenile toxicity studies available at the time of initiation of Part 2 will be taken into account for determination of the dosing regimens to be tested in Part 2.
- Section 3.2 the sentence explaining the rationale for including infants between 1 and 7 months has been re-written to increase clarity. Also the description of Part 2 dosing regimen has been corrected. Finally clarification has been added on the possibility for patients to continue receiving treatment beyond the initial treatment period.
- Section 3.3 and Table 6-1: Clarification that the dose escalation is guided by the Bayesian logistic regression model (BLRM) with escalation with overdose control (EWOC) principle. The maximum dose level has been increased and the rationale for this change has been indicated.
- Section 3.5: clarification of the conditions for enabling or not to proceed to Part 2 as well as the criteria to stop dose escalation.
- Section 3.6: removal of a sentence repeated twice, addition of preclinical retinal findings and the rationale for the ophthalmologic monitoring.
- Section 4.1: re-wording of inclusion criterion #2 and criterion #8 to clarify the language

- Section 4.2: Re-wording of exclusion criterion #2 to clarify the language.
- Laboratory measurement values to define anemia, leukopenia and thrombocytopenia have been added in exclusion criterion #3 to have cut-off for these parameters adapted to the values observed in the pediatric population. In addition neutropenia has been added to exclusion criterion #3. Likewise numeric values for defining hepatic dysfunction have been added in exclusion criterion #4. These changes were requested by the independent Data Monitoring Committee.
- The formula to be used for the calculation of the renal function in infants has been specified in exclusion criterion #5 to ensure homogeneity of this evaluation at sites in a multi-center setting. The supportive reference has been added in Section 14. The Heilbronn formula initially indicated for the calculation of the body surface area has been removed since it is widely known and to increase clarity.
- Clarification of exclusion criterion #8 to indicate that either persistent hypoxemia or presence of a tracheostomy would lead to ineligibility of a patient as they are considered too advanced in their disease to participate in the study.
- Addition of changes in hematologic parameters or gastrointestinal dysfunction not otherwise specified in exclusion criterion #13 that may also pose a safety risk since LMI070 has cell cycle arrest properties that would increase the risk of such events.
- Section 5.4: Removed requirements for the use of gloves during handling of bodily fluids after dosing.
- Section 6.2: Clarification that only one strength of LMI070 is provided as well as modification of the storage temperature of the variant to be used from now on.
- Section 6.3–Table 6-1 had been updated with the 2 additional provisional dose levels to be evaluated in Part 1.
- Section 6.5.2: the number of patients per cohort for dose levels ≥ 48 mg/m2 has been increased and a clarification on inclusion of additional patients has been included.
- Section 6.5.4: language corrected to increase clarity in the event of intra-patient dose escalation.
- Table 6-4: update of some criteria for defining dose-limiting toxicities during dose escalation to account for differences in typical management of these events in infants
- Section 7.1: clarification of the study treatment discontinuation rules to specify time interval for measurement and define extent of disease progression.
- The original Assessment Schedule has been sub-divided in Table 8-1 and Table 8-2 to distinguish the assessments to be conducted during the initial treatment period (Day -14 up to Day 85) or during the extended treatment period since the number of evaluations have slightly decreased for the extended treatment period. Where reference was made to the Assessment Schedule it has been changed to the appropriate table throughout the document.
- Table 8-1, Table 8-2, Table 8-3: Addition of a time point for the [redacted] and mRNA blood collection at the end of each treatment period.
- Table 8-2: Removal of blood samples for PK analysis on Day 3 and Day 5 during the extended treatment period since a lighter PK profile is acceptable. As a consequence Day 5

[redacted]

visit could be removed as well to reduce burden for the patients while keeping a close safety monitoring in place.

- Section 8.3.1: clarification that the CHOP INTEND test allows measurement of the strength as well.
- [redacted].
- Section 8.4.2: clarification of the Blood Pressure measurements to be done by an oscillometric method. The supporting reference has been added in Section 14.
- Section 8.4.4: the reticulocyte count has been added to the existing measurements performed for the hematology sample to monitor for cell cycle arrest. The absolute neutrophil count calculation to be done has been added as well. Platelet volume has been added to better understand the impact of elevated platelet counts seen in the study on blood SMN pharmacodynamics measures as described in Section 1.1.1.4. Bicarbonate and high sensitivity C - reactive protein (CRP) are added to the existing measurements performed for the chemistry sample. No extra blood draw is necessary for any of these measurements.
- Section 8.4.5: clarification added regarding the calculation of the QTcF.
- Section 8.4.6: has been created to add echocardiogram as a new safety monitoring required following occurrence of a SUSAR in one patient enrolled in the study.
- Section 8.4.8: has been created to describe the ophthalmologic monitoring required by a Health Authority and previously implemented as an Urgent Safety Measure submitted to Health Authorities. This monitoring has also been added as an endpoint in Section 2.1 Primary Objective as well as in the different assessment schedules (Table 8-1 Assessment Schedule – Part 1 - Initial treatment period; Table 8-2 Assessment Schedule – Part 1 – Extended treatment period; Table 8-3 Assessment Schedule – Part 2).
- [redacted]
- Section 11.6.1: the number of patients to be included in each upcoming cohort of study Part 1 has been clarified.
- The Blood Logs (previously in the Appendix 2) have been removed from the Protocol since they are already present in the Site Operations Manual document.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. Please note that the ophthalmologic monitoring as described are changes already in effect triggered by requirements from a Health Authority, as communicated by the Urgent Safety Measure notification.

[redacted]

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

## Amendment 02 (February 2015)

### Amendment rationale

The purpose of this amendment is to address the requests from the European health authorities during their review for clinical trial authorization in Europe. The amendment provides clarification about the exclusion criteria, the dose limiting toxicities and the provisional dose levels. This amendment also corrects minor errors that are considered non-substantial. At the time this amendment was written the study was not open for enrollment.

### Changes to the protocol

- Protocol synopsis and Section 4.2: Clarification of exclusion criteria #3 and #4 to change the excluded values to grades from CTCAE.
- Protocol synopsis and Section 4.2: Clarification of exclusion criterion #5 to revise the excluded eGFR ranges to be appropriate for the pediatric target population as well as to specify which formula to use for the eGFR calculation.
- Protocol synopsis and Section 4.1; Clarification of inclusion criterion #6 to indicate that the tube should be placed for dosing LMI070 but could be removed between doses.
- Replacement of the assessment schedule in Section 3.1.1 with a study design figure to better explain the study flow. Moreover the assessment schedule is already present in Table 8-1.
- Indication of the days on which the study visits are scheduled both for Part 1 in Section 3.1.1 and for Part 2 in Section 3.1.2.
- Clarification in Section 3.1.2 of the different study visits and the assessments scheduled. Update of the provisional dose levels in Table 6-1 to show one possible dose escalation trajectory where the highest dose level equals the top dose 60 mg/ $m^2$.Revision of the dose limiting toxicity (DLT) criteria (Table 6-4) based on the patient population and on observations in preclinical data and based on recommendations from the external Data Monitoring Committee. These changes were based on realization that the earlier criteria were extremely unlikely to occur with present day standard of care (platelet and red blood cell transfusion, use of rescue growth factors, etc.) These changes were also made to standardize the DLT criteria across this multi-centre study as there are some small differences between countries and centres in their approach.
- Revision of the criteria for interruption and re-initiation of LMI070 treatment (Table 6-5) based on the revision of the DLT criteria and removal of the values to standardize the criteria.
- Clarification of when the End of study visit should be conducted in Section 3.1, in the study design figure (Figure 3-2-Section 3.1.2), in Section 7.2, in the Table 8-1 Assessment Schedule-Part 1 and Table 8-3 Assessment Schedule-Part 2.

[redacted]

- Correction of the Visit Numbers, clarification of the inclusion/exclusion criteria check that needs to be done at Baseline, and removal of the optional DNA collection in the Table 8-3 Assessment Schedule-Part 2 and in Appendix 2-Blood Logs Part 2.
- Removal of the reference made to the therapeutic misconduct in Section 8.1 since not relevant as part of the protocol.
- For the Bayesian analysis plan, changes to the reference dose from 14 mg/ $m^2$ to 40 mg/ $m^2$ in Section 11.4.2, and to one statistical prior parameter in Table 15-1 to update the non-informative prior that will be used. The new prior suits the dose range 6 mg/ $m^2$ to 60 mg/ $m^2$ better while it remains non-informative and conservative. Table 15-2 was updated to reflect the new prior.
- Addition of a new reference in Section 14 to support the use of the formula for the calculation of the eGFR. Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

## Amendment 01 (November 2014)

### Amendment rationale

The purpose of this amendment is to address the requests from a European health authority during the request for clinical trial authorization in Europe. The amendment provides clarification about the phases of the study, the sequential enrollment of patients into the cohorts and the safety monitoring of the patients after they receive their first dose of study drug. This amendment also corrects minor typographical errors that are considered non-substantial. At the time this amendment was written the study was not open.

### Changes to the protocol

Correction of the study phase from Phase II to Phase I/II. Phase I for part 1 of the study and Phase II for part 2 of the study which has been corrected through-out the document.

Additional information provided on the relationship between aneuploidy and carcinogenesis in Section 1.1.1.2

Clarification that continued observation in the study unit beyond 24 hours after the first dose is at the discretion of the investigator given the nature and severity of the disease. This has been corrected throughout the document.

[redacted]

Clarification that patient treatment will be sequential and will allow at least 24 hours between the treatment of 2 patients at any one dose level for the first dose. This has been corrected throughout the document.

Clarification that more than 2 patients could be enrolled into a cohort to prevent a patient waiting for the next cohort due to the life threatening nature of the disease.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

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## Protocol summary

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| Protocol number | CLMI070X2201 |
| Full Title | An open-label multi-part first-in-human study of oral LMI070 in infants with Type 1 spinal muscular atrophy |
| Brief title | An open-label study of branaplam (LMI070) in Type 1 spinal muscular atrophy (SMA) |
| Sponsor and Clinical Phase | Novartis<br>Phase I (Part 1)/ Phase II (Part 2)/ Phase II (Part 3) |
| Investigation type | Drug |
| Study type | Interventional |
| Purpose and rationale | The purpose of this study is to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy; and to estimate the Maximum Tolerated Dose (MTD) and optimal dosing regimen of orally administered branaplam in patients with Type 1 SMA. |
| Primary Objective(s) | Part 1<br>To determine the safety and tolerability of ascending weekly doses and estimate the MTD of oral/enteral branaplam in infants with Type 1 SMA<br>Part 2<br>To evaluate the long-term safety and tolerability of 2 doses of oral/enteral branaplam administered weekly for 52 weeks in patients with Type 1 SMA<br>Part 3<br>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 |
| Secondary Objectives | Part 1, Part 2, Part 3<br>• To evaluate branaplam pharmacokinetics in plasma after single and repeated doses of branaplam<br>• To evaluate the effect of branaplam on growth parameters<br>• To evaluate the effect of branaplam on respiratory function<br>• To evaluate the effect of branaplam on infant motor development<br><br>Part 2 (in addition to the above)<br>• To evaluate the efficacy of branaplam on motor and developmental milestones<br>• To evaluate the efficacy of branaplam on the ability to sit without support<br>Part 3 (in addition to the above)<br>• To assess the proportion of infants who are alive and are without permanent ventilation over time<br>• To assess the impact of treatment with branaplam on time-to-event (death, permanent ventilation) |
| Study design | This is a phase I/II, open-label, multi-part, first-in-human proof of concept study in infants with Type 1 spinal muscular atrophy, to evaluate safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy of orally administered branaplam.<br>Enrollment to this study is restricted to patients with Type 1 SMA with 2 copies of the survival of motor neuron 2 (SMN2) gene. |

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| | In Part 1 of the study patients will be dosed once weekly with branaplam until MTD is determined or when sufficient PK results confirm that the MTD cannot be reached due to a potential pharmacokinetic exposure plateau at higher doses. A Bayesian logistic regression model (BLRM) with escalation overdose control (EWOC) will be used to determine the dose levels used for each dose escalation. The 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 wash-out of branaplam to avoid accumulation of the compound and to improve understanding of the metabolic pathways of degradation and clearance of branaplam due to maturation of the CYP system. The data will be used to further develop the PK model. If PK data show the potential for accumulation, the dosing frequency may be decreased; For Part 1, patients completing 13 weeks of treatment (12 doses) will be considered to have completed the study. Patients who completed at least 52 weeks of treatment may continue treatment in Part 3 if in the best interests of the patient, as assessed by the investigator.<br>In Part 2 of the study, new patients will be enrolled and will participate for 52 weeks to assess efficacy and safety of branaplam. Patients will be dosed once weekly with branaplam. The decision for starting the next dose level cohort will be made after safety and efficacy data have been collected for at least 3 patients treated for 13 weeks following the first dose. Patients completing 52 weeks of treatment will be considered to have completed the study. However, they may continue treatment in part 3 of the protocol, if further treatment is in the best interest of the patient.<br>Part 3 of the study is long term safety and efficacy follow up of extended oral/enteral, once a week branaplam treatment. All patients 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. |
| Population | The study population will be comprised of infants with Type 1 SMA with 2 SMN2 gene copy numbers, aged approximately 1 to 7 months in Part 1 and up to 180 days of age at screening in Part 2. A total of 13 patients have been treated in Part 1 and 25 patients have been treated in Part 2. All patients from Part 1 and Part 2 of the study who completed at least 52 weeks of treatment or more are continuing receiving treatment in the Part 3 of the study |
| Inclusion criteria | Part 1<br>1. Written informed consent must be obtained from the parent / guardian before any assessment is performed.<br>2. Type 1 SMA, diagnosed clinically, with symptom onset <6 months of age and genetic confirmation of mutations in both alleles of the survival of motor neuron 1 (SMN1) gene, and with SMN2 copy number of 2.<br>3. Best supportive care in place and stable for at least 14 days before screening.<br>4. Age at screening between 1 and 7 months.<br>5. Must be able to demonstrate antigravity strength in both biceps.<br>6. Must have or agree to have placement of feeding tube for enteral access via nasogastric (NG), nasojejunal (NJ), percutaneous gastrostomy (PEG), or percutaneous jejunostomy (PEJ) tube for |

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| | dosing LMI070 (Part 1 only and for patients who cannot be administered orally; tube may be removed between doses).<br>7. Medical care meets and is expected to continue to meet guidelines set out in the Consensus Statement for Standard of Care in SMA (Wang et al 2007), in the opinion of the Site Investigator<br>8. At birth gestational age >32 weeks and body weight at birth >2 kg<br>9. Must live within 2 hours drive of study center. Clearance should be obtained from the site investigator and sponsor if the patient resides more than 2 hours ground travel from the study center.<br>10. Able to complete all study procedures, measurements and visits; and parent or guardian/patient has adequately supportive psychosocial circumstances, in the opinion of the Site Investigator.<br>Part 2<br>1. Written informed consent must be obtained from the parent / guardian before any assessment is performed.<br>2. Type 1 SMA, diagnosed with genetic confirmation of mutations in both alleles of the SMN1 gene, and with SMN2 copy number of 2.<br>3. Best supportive care in place and stable for at least 14 days before screening as assessed by the investigator.<br>4. Age at screening up to 180 days of age.<br>5. Must be able to demonstrate antigravity strength in both biceps.<br>6. Must have or agree to have placement of feeding tube for enteral access via nasogastric (NG), nasojejunal (NJ), percutaneous gastrostomy (PEG), or percutaneous jejunostomy (PEJ) tube for dosing branaplam (required for the first administration only, and subsequently only for patients who cannot be dosed orally; tube may be removed between doses).<br>7. Minimum CHOP INTEND score of 15 at baseline<br>8. Must be able to swallow solid and liquid even if tube feeding is used to support nutrition intake and must be the 5$^{th}$ percentile for length or weight on the international growth curves and must be proportional in height and weight<br>9. At birth gestational age >32 weeks and body weight at birth >2 kg<br>10. Able to complete all study procedures, measurements and visits; and parent or guardian/patient has adequately supportive psychosocial circumstances, in the opinion of the Site Investigator.<br>Part 3<br>1. Written informed consent must be obtained from the parent / guardian<br>2. Current participation in Part 1 or Part 2 of the study protocol and completion of at least 52 weeks of treatment with branaplam<br>3. Further treatment with branaplam is in the best interest of the patient as assessed by the Site Investigator<br>4. Able to complete all study procedures, measurements and visits; and parent or guardian/patient has adequately supportive psychosocial circumstances, in the opinion of the Site Investigator |
| Exclusion criteria | Part 1<br>1. Use of other investigational drugs within 14 days<br>2. Neurologic or neuromuscular conditions other than SMA.<br>3. Anemia (Hgb < 9.5 gm/dl ; <5.9 mmol/L), leukopenia (CTCAE Grade 2 or higher, <3000 /mm$^3$; <3.0 x10$^9$/L), neutropenia (Grade 2 or higher, <1,500/mm$^3$; < 1.5 X 10$^9$/L) or thrombocytopenia (CTCAE Grade 2 or higher, ≤ 75,000/mm$^3$), ≤75 X 10$^9$/L |

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| | 4. Hepatic dysfunction (AST or ALT CTCAE Grade 1 or higher, ≥ Upper Limit of Normal (ULN)); total bilirubin CTCAE Grade 1 or higher, ≥ ULN).<br>5. Age adjusted renal dysfunction with eGFR calculated using the following formula:<br>eGFR (in mL/min/1.73 $m^2$) = 0.45 X Length (cm) ÷ serum creatinine (mg/dl) (Schwartz and Work 2009),<br>- ≤ 26 mL/min/1.73 $m^2$ up to age 28 days of age<br>- ≤ 30 mL/min/1.73 $m^2$ for 1 to 3 months of age<br>- ≤ 40 mL/min/1.73 $m^2$ for 3 to 6 months of age<br>- ≤ 50 mL/min/1.73 $m^2$ for 6 to 12 months of age<br>6. Clinically significant abnormalities in hematology or clinical chemistry parameters, as assessed by the Site Investigator, at screening that would render the patient unsuitable for inclusion<br>7. Intractable seizure disorder (other than inactive febrile seizures).<br>8. Persistent (in the opinion of the Investigator) hypoxemia (O2 saturation awake <92% or O2 saturation asleep <91%, without ventilation support) or requiring oral suctioning >2 per day, or presence of a tracheostomy.<br>9. Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the screening period.<br>10. Current diagnosis of cardiac and/or vascular abnormalities including uncontrolled hypertension, intolerance of blood pressure and pulse assessment techniques such that consistent normal values cannot be measured, echocardiographic abnormalities (both structural and function) or ECG abnormalities (such as long QT, heart block or Torsade's) indicating significant risk of safety for infant patients participating in the study such as: Concomitant clinically significant pediatric cardiac arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second or third degree AV block<br>11. Prohibited Concomitant Medications used to treat SMA, including but not exclusively: oral albuterol or oral salbutamol, hydroxurea, riluzole, valproate, carnitine, creatine, sodium phenylbutyrate within 14 days prior to enrollment or during the study<br>12. Excluding SMA, any medically unstable condition including cardiomyopathy, hepatic dysfunction, kidney disorder, endocrine disorder, GI disorders, metabolic disorders, severe respiratory compromise and significant brain abnormalities or injuries including hypoxic-ischemic encephalopathy.<br>13. Acute or ongoing medical condition that, according to the Site Investigator and discussed with sponsor, would interfere with the conduct and assessments of the study. Examples are medical disability other than SMA that would interfere with the assessment of safety or would compromise the ability of the patient to undergo study procedures including be assessed by CHOP INTEND infant motor scale, changes in hematologic parameters or gastrointestinal dysfunction that would compromise the ability of adequate assessment of safety<br>Part 2<br>1. Use of gene transfer at any time or other investigational drugs within 14 days |

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| | 2. Patients who have received nusinersen at any time prior to screening<br>3. Neurologic or neuromuscular conditions other than SMA.<br>4. Anemia (CTCAE grade 2 of higher Hgb < 1.0 g/dl ; <6.2 mmol/L); leukopenia (CTCAE Grade 2 or higher, <3000 /$mm^3$ ; <3.0 x$10^9$/L), neutropenia (Grade 2 or higher, <1,500/$mm^3$; < 1.5 X $10^9$/L) or thrombocytopenia (CTCAE Grade 2 or higher, ≤ 75,000/$mm^3$), ≤75 X $10^9$/L<br>5. Hepatic dysfunction (AST or ALT CTCAE Grade 1 or higher, ≥ ULN); total bilirubin CTCAE Grade 1 or higher, ≥ ULN).<br>6. Age adjusted renal dysfunction with eGFR calculated using the following formula: eGFR (in mL/min/1.73 m2) = 0.45 X Length (cm) ÷ serum creatinine (mg/dl) (Schwartz and Work 2009), ≤ 26 mL/min/1.73 $m^2$ up to age 28 days of age ≤ 30 mL/min/1.73 $m^2$ for 1 to 3 months of age ≤ 40 mL/min/1.73 $m^2$ for 3 to 6 months of age ≤ 50 mL/min/1.73 $m^2$ for 6 to12 months of age<br>7. Clinically significant abnormalities in hematology or clinical chemistry parameters, as assessed by the Site Investigator, at screening that would render the patient unsuitable for inclusion<br>8. Intractable epilepsy<br>9. Persistent (in the opinion of the Investigator) hypoxemia ($O_2$ saturation awake <92% or $O_2$ saturation asleep <91%, without ventilation support).<br>10. Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the screening period.<br>11. Current diagnosis of cardiac and/or vascular abnormalities including uncontrolled hypertension, intolerance of blood pressure and pulse assessment techniques such that consistent normal values cannot be measured, echocardiographic abnormalities (both structural and function) or ECG abnormalities (such as long QT, heart block or Torsade's) indicating significant risk of safety for infant patients participating in the study such as: Concomitant clinically significant pediatric cardiac arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second or third degree AV block. Clinically significant findings identified by an echocardiogram performed at screening<br>12. Prohibited Concomitant Medications used to treat SMA: oral albuterol or oral salbutamol, hydroxyurea, riluzole, valproate, carnitine, creatine, sodium phenylbutyrate within 14 days prior to enrollment or during the study<br>13. Excluding SMA, any medically unstable condition including cardiomyopathy, hepatic dysfunction, kidney disorder, endocrine disorder, GI disorders, prematurity of <32 weeks gestation, metabolic disorders, severe respiratory compromise and significant brain abnormalities or injuries including hypoxic-ischemic encephalopathy.<br>14. Acute or ongoing medical condition that, according to the Site Investigator and discussed with sponsor, would interfere with the conduct and assessments of the study. Examples are medical disability other than SMA that would interfere with the assessment of safety or would compromise the ability of the patient to undergo study procedures including be assessed by CHOP INTEND infant motor scale, changes in hematologic parameters or gastrointestinal |

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| | dysfunction that would compromise the ability of adequate assessment of safety<br>Part 3<br>There are no specific exclusion criteria for part 3 study |
| Study treatment | Branaplam |
| Efficacy assessments | • CHOP INTEND infant motor scale (only for patients up to an age of 36 months)<br>• Physical examination including assessment of oral feeding, head control, rolling, sitting up, respiratory function<br>• Hammersmith Infant Neurologic Examination (HINE) (Including Independent sitting, standing and walking)<br>• Time to death or permanent ventilation from enrollment |
| Safety assessments | • Physical exam<br>• Vital signs<br>• Body length, weight, head circumference and respiratory function<br>• ECG and echocardiographic evaluation<br>• Safety laboratory parameters<br>• Neurologic examination<br>• Nerve conduction study (CMAP, SNAP, NCV)<br>• Ophthalmologic examination<br>• Adverse events (AE) |
| Other assessments | [redacted] PK, and speech and motor performance |
| Data analysis | The Safety Analysis Set (SAF) will consist of all patients in the Enrolled Set who received at least one dose of study drug and have at least one valid post-baseline safety assessment.<br>Part 1 only: The dose determining set (DDS) consists of all patients 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. Patients 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. An adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control principle (EWOC) will be used to determine MTD during the dose escalation phase of the study.<br>Part 1 and Part 2: the PK analysis set will include all patients who received at least one dose of LMI070 with available PK data and no protocol deviations with relevant impact on PK data.<br>The PD analysis set will include all patients who received at least one dose of LMI070 with available PD data and no protocol deviations with relevant impact on PD data.<br>The sample size for Part 1 is driven by feasibility. In Part 1, cohorts of at least 2 patients will be dosed until a decision is made for MTD. However, adjustment of cohort size might be considered due to enrollment and safety consideration. At least 2 patients are required for cohort 1 at the starting dose. Size of later cohorts maybe adjusted based on feasibility. In Part 2, |

[redacted]

| | |
|---|---|
| | 25 patients were enrolled to evaluate up to 2 different dose cohorts with at a minimum of 6 patients and a maximum of 10 patients per cohort.<br>The driver of the sample size in part 2 is the primary objective, safety. With the current sample size, 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 patients,<br>An interim analysis was performed after MTD determination in Part 1 to evaluate PD effects of the treatment. Data on growth measurements, respiratory function assessments and CHOP INTEND infant motor scale will be summarized at different time points and compared to baseline. Additional interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general or in case of any safety concerns.<br>Part 3<br>Sample size of part 3 will depend on the number of ongoing patients in Part 1 and Part 2 of the study protocol. Only patients who have participated in at least 52 weeks of treatment in either Part 1 or Part 2 are eligible to enroll in Part 3 Period. Additional interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general or in case of any safety concerns. Internal analysis of Part 2 will be conducted once all Part 2 patients completed 52 weeks of treatment. After all patients have transitioned from Part 1 and 2 of the study in the Part 3, additional interim analysis might be conducted |
| Key words | Type 1 Spinal Muscular Atrophy |

[redacted]

# 1 Introduction

## 1.1 Background

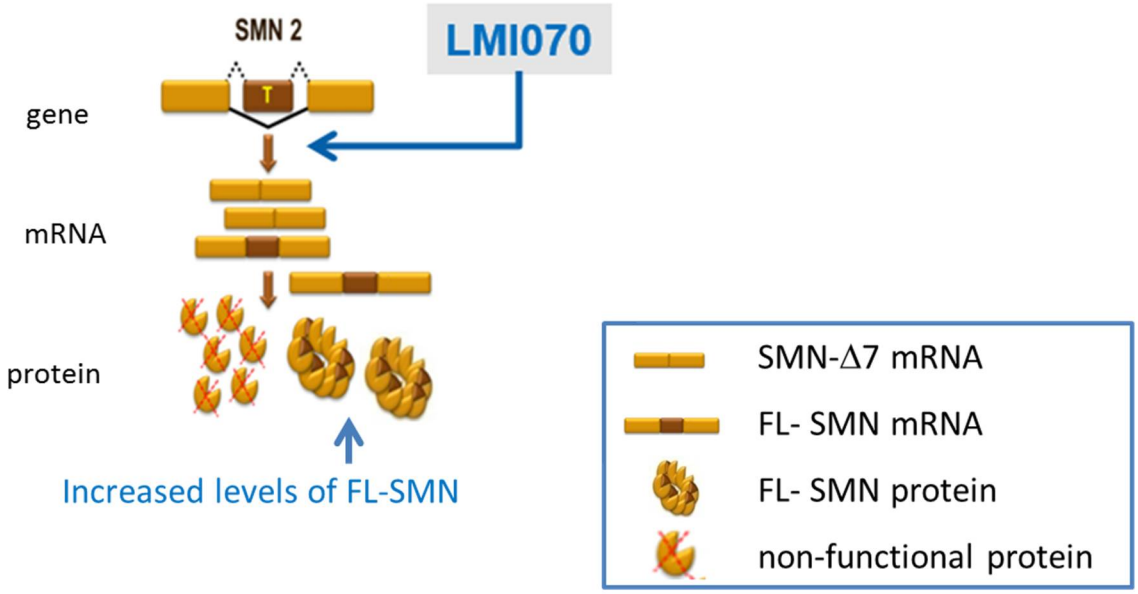
Type I SMA (Spinal Muscular Atrophy) is a fatal disease of infants who are deficient in SMN (Survival Motor Neuron), a key survival protein for alpha motor neurons in the spinal cord. Oral branaplam has been shown to systemically increase SMN production in animal models and prolongs survival of a most severe mouse model bearing the SMA mutation. In addition, an oral single dose of branaplam in preclinical models has shown upregulation of SMN protein in the spinal cord for up to 7 days. However, because it has potential toxicity (aneuploidy and cell cycle arrest) at high doses, it is being introduced into human use in infant patients who may benefit most from it despite the risks. The known risks (marrow suppression and GI disturbances) are monitorable, manageable and reversible; based on preclinical studies, toxicity can be controlled or can be mitigated by intermittent dosing.

In patients with spinal muscular atrophy (SMA), bi-allelic loss of function mutations of the SMN1 (Survival Motor Neuron 1) gene, leads to all SMN protein being produced by the inefficiently spliced SMN2 gene with loss of exon 7 (Figure 1-1). Up to 90% of the protein resulting from the SMN2 gene is truncated and unstable, resulting in a marked deficiency of SMN protein which in turn leads to premature cell death (apoptosis) of alpha motor neurons in the spinal cord. In type I SMA, the onset of symptoms for affected infants is in the first 6 months of life. This inappropriate and accelerated motor neuron cell death leads to muscle weakness and ultimately respiratory failure, paralysis, and death. The majority of patients with Type 1 SMA die by age of 22 months unless they receive mechanical feeding and ventilation supportive care, which can prolong life but does not reverse the loss of skeletal muscle function. Thus, infants with Type 1 SMA have the most to gain by a potential SMN splice modulator such as branaplam. As the neuromuscular system develops from birth throughout infancy, the survival of alpha-motor neurons of the spinal cord is crucial for the normal development of infants' motor skills.

Branaplam modulates SMN2 splicing and increases generation of full length SMN2 mRNA and functional SMN protein by stabilization of the transient double-strand RNA structure formed by the SMN2 pre-mRNA and the U1 small nuclear ribonucleic protein (snRNP) complex due to sequence selective increased binding affinity of U1 snRNP to the 5′ splice site of SMN2 (Palacino et al 2015). In humans it is postulated that splice modulation of SMN2 by branaplam will result in more full length SMN protein, leading to improved motor neuron survival, neuromuscular junction formation and motor unit development, which will facilitate muscle growth, motor gains and motor milestones, and lead to improved respiratory function and longer survival without ventilator dependence in SMA patients.

[redacted]

**Figure 1-1 Branaplam modulates survival motor neuron 2 (SMN2) gene splicing and increases generation of full length SMN2 mRNA, leading to increased functional SMN protein**




### 1.1.1 Relevant data summary

#### Preclinical data

#### Preclinical pharmacodynamics and efficacy

The pharmacodynamics of branaplam were assessed in *in vitro* and *in vivo* studies with 2 SMA mouse models, a severe neonatal efficacy model called the SMNDelta7 or hereon referred to as Delta7 mouse model (that phenotypically resembles clinical picture of Type I SMA) and a Pharmacodynamic (PD) model called the C/+ SMA mouse model. The C/+ model is a mild SMA mouse model in adult mouse which harbors a humanized exon 7 and 8 and a 42 kb fragment of human SMN2. These mice do not display an overt phenotype and show life expectancy matching that seen in normal wild type mice. This model offers an in vivo model to elucidate PK/PD effects of SMN2 splicing modulators. In all *in vivo* efficacy and PD studies, branaplam was administered orally, which is the clinical route of administration. The data generated support the potential for branaplam to elevate spinal cord SMN protein levels and based on the data, branaplam may be able to halt or slow down the debilitating disease progression of SMA in patients.

- Branaplam increases full length (FL)-SMN transcript and SMN protein in the brain and spinal cord of two SMA mouse models.
- A single dose of branaplam (30 mg/kg) in the adult C/+ model results in sustained elevation of SMN protein levels in the spinal cord for over 160 hrs. In parallel with elevated brain branaplam levels above the EC50. It is unknown if the elevated protein

[redacted]

levels represent prolonged SMN half-life or new synthesis from continued splice modulation.

- Studies with the Delta7 mouse models show that subcutaneous plus intracerebroventricular (ICV) delivery of SMN2 splice modulating antisense oligonucleotides, achieves superior life-extension effects over ICV delivery alone (Hua et al 2011). Branaplam can increase SMN protein in both peripheral and CNS tissues in mice.
- Branaplam elicits a dose-dependent (0.03-3 mg/kg) survival extension in the most severe neonate Delta7 mouse model. Additionally, enduring weight gain and survival extension were observed for up to two weeks after branaplam treatment was discontinued.
- Data published in peer reviewed literature show that early treatments which cause an increase in full length SMN protein (transgenic inducible promoters, antisense oligonucleotides) confer the greatest survival benefit in the Delta7 mouse (Le et al 2011, Hua et al 2011), underscoring the importance of early treatment in SMA.

### Preclinical pharmacokinetics

In adult rats and dogs, branaplam was moderately or completely absorbed. In rats there was some indication of first-pass elimination. Upon daily administration there was no accumulation of branaplam in adult animals.

In juvenile rats, an age-related change in PK was observed, with a ~3-5 fold decrease in branaplam plasma AUC on postnatal day 41 compared to postnatal day 7. After continued daily treatment (postnatal days 97 and 186) exposure levels increased but were comparable to day 7 values, i.e. 2-3 fold lower than the expected value if accumulation is taken into account. A reduction in systemic exposure with progressing age of the animals may be related to maturation of metabolizing enzymes and other physiological processes (e.g. hepatic blood flow). In juvenile dogs a similar but less pronounced decrease was observed in plasma exposure between postnatal day 28 and 56 (20-40% decline in AUC). These changes may be attributed to the maturation of drug metabolizing enzymes and/or transporters as well as tissue perfusion and permeability changes during growth and development in juvenile animals. Similar effects can be expected in humans over the first year to two years of life.

In juvenile mice and dogs, the brain to plasma exposure ratio was about 10, indicating that branaplam penetrated well into the brain. This is expected to decrease as a consequence of maturation of the blood brain barrier. As such, good central exposure is also anticipated in human infants, while a similar decrease in brain exposure may occur as infants grow.

The elimination of branaplam in rats occurred mainly via glucuronidation with subsequent excretion into feces. *In vitro* experiments indicated that UGT1A4, UGT1A7, and UGT1A9 were capable of branaplam direct glucuronidation. Experiments in human liver microsomes showed that CYP3A4 is the major enzyme involved in human hepatic metabolism of branaplam. Branaplam was also found to be a substrate of P-gp. Other transporters seem not to be involved in cross-membrane transport of branaplam.

[redacted]

Branaplam showed weak inhibition of CYP2C19, CYP2D6, and CYP3A4/5 (unbound $IC_{50}$ values of 9.9, 19, and 21 μM, respectively) and did not inhibit transporters (BCRP, P-gp, OATP1B1, OATP1B3). Overall, it is thus thought that the drug-drug interaction potential with branaplam is low and infants with SMA type I are not expected to be on chronic polypharmacy.

Branaplam showed some inhibition of MATE1 (IC50: 5.47 μM), MATE2-K (IC50: 0.183 μM), OCT1 (IC50: 0.299 μM) and OCT2 (IC50: 8.92 μM). Preliminary assessment on the drug-drug interaction potential of branaplam indicated a potential risk for MATE2-K and OCT1 inhibition. At the time of the amendment 8 this information is not available in the current IB and will be included in the next version.

PK/PD modeling based on animal data (C/+ mouse model) was performed to support the selection of the starting dose. As a PD effect, brain SMN protein levels in C/+ mice treated with branaplam were used. The results of the modeling suggested that the selected starting dose may also show minimal efficacy.

### Preclinical safety

The safety profile of branaplam was assessed in Safety Pharmacology, General Toxicity, Genotoxicity, Phototoxicity, and Reproductive studies. The data generated thus far support clinical safety and tolerability studies in SMA Type 1 patients.

- Cardiovascular safety pharmacology studies in vitro, CNS safety and respiratory safety studies in vivo do not raise a concern for patient safety.
- Repeat dose toxicity studies in adult and juvenile rats and dogs showed that weekly dosing is better tolerated compared to daily dosing. In all animal species effects on the hematopoietic system and gastrointestinal tract were observed when daily and high dose levels of branaplam were administered. The exposure at the highest dose Part 1 of the proposed study will dose patients on a weekly basis for this reason, as well as because the prolonged PD effect seen in animals suggests that intermittent dosing may be efficacious in infants.
- Observations from the 26-week juvenile rat study (daily dosing), showed findings of corneal opacities and retinal/choroid atrophy. The histological assessment showed minimal and focal atrophy of the retina near the ora serrata (the very periphery of the neurosensory retina where it meets the ciliary body) at all dose levels and the vehicle control. The incidence in rats given a high dose of branaplam was higher than in control animals. Focal retinal atrophy is not an uncommon microscopic observation in albino rats and is described as a congenital or age-related finding. No retinal changes were observed in any other toxicology studies conducted in mice, rats or dogs or monkeys. Liver microscopic findings were additionally observed in the 26-week rat study and consisted of hepatocellular necrosis and biliary hyperplasia. No safety margins could be established in the rat.
- Daily administration of branaplam to juvenile dogs for resulted in a minimal to mild axonal degeneration in the spinal cord and nerves (sciatic, peroneal, tibial and/or ulnar nerves), vascular proliferation and glomerulopathy in the kidney and testicular atrophy and degenerative changes in seminiferous tubules. No safety margin could be established in the dog.

[redacted]

- New findings were observed in the heart and ovary in a 4-week dose range finding study in the wild type RasH2 mouse strain and consisted of vacuolation of cardiomyocytes and decrease in corpora lutea and follicles in the ovary. The pathogenesis of the cardiomyocytes in the wild type RasH2 mice is unknown and is currently explored in-vivo and in-vitro. The heart was not identified as a target organ in previous chronic animal safety studies in rat or dog with daily administration of branaplam. No heart findings were observed in a 6-week monkey study with twice weekly branaplam dosing up to 6 mg/kg/dose. The exposure multiples for the AUCweek of the new mouse findings in the heart and ovary is 2.2-fold for Type 1 SMA patients (mean of male and female mice). The Cmax-based exposure multiple is 1.2-fold (mean of male and female mice).

### Genotoxicity

Branaplam was not genotoxic in a bacterial mutagenicity assay. Micronucleus (MN) tests in vitro and in vivo showed an induction of increased MN frequencies. An in vitro study in human lymphocytes demonstrated that increased MN frequencies were a consequence of aneugenic (i.e., chromosome maldistribution to daughter cells) but not clastogenic (i.e., DNA breaking) activity of branaplam. The aneugenic effect of branaplam is likely secondary to the cellcycle inhibiting properties of the compound and does not indicate a mutagenic potential because aneugenicity, unlike clastogenicity, does not damage DNA and is not propagated to subsequent daughter cells. *In-vitro* data show that branaplam can stabilize microtubulin polymerization.

The relationship between aneuploidy and carcinogenesis is complex and poorly understood. Moreover, it is confounded by the difference between aneuploidy and chromosomal instability, which is a feature of cancers caused by mutations in checkpoint genes that are known to be carcinogenic (Ricke and van Deursen 2013). Thus, although aneuploidy is a common characteristic of tumor cells, it is generally considered a consequence rather than a cause of tumorigenesis. Aneugenicity may be able to drive tumor growth by amplifying oncogene dosage or removing tumor suppressor activity. However, it is widely accepted that the occurrence of aneugenic cells is the consequence of cell selection during tumor growth rather than a causal event. A causal event may be a mutation in cell cycle checkpoint factors or other genes responsible for maintaining genomic integrity. The ability of aneuploidy-inducing agents to drive tumorigenesis remains unproven and is considered to be unrelated to tumor initiation (Marx 2002).

The aneugenic effects are expected based on the stabilization of microtubulin polymerization and consequently, cell cycle inhibition properties of branaplam. In this context it is important to note that an European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC) task force concluded that, although there is clear evidence of chemically induced aneuploidy in experimental systems, to date there are insufficient data to determine with certainty if chemically induced aneuploidy contributes to human disease (Aardema et al 1998). Therefore, the results of the micronucleus tests indicate that the aneugenic effect of branaplam is unlikely to pose a genetic or neoplastic threat to patients at therapeutic dose levels.

[redacted]

### Teratogenicity and reproductive toxicity data

Embryofetal toxicity studies have been conducted with branaplam in rats and rabbits. No teratogenic or embryo-toxic potential was observed in the rat (NOAEL 2.5 mg/kg, estimated AUCweek: 5838 h*ng/mL). The safety margins are 1.4-fold or 1.7-fold (AUC-based) higher compared to the highest dose used Type 1 SMA patients or recently selected dose for Part 3 of this study (3.125 mg/kg, Table 1-1, and 2.5 mg/kg, Table 1-2, respectively). Maternal toxicity and embryo-fetal toxicity were observed in the rabbit preliminary Embryo Fetal Development (pEFD) study at high dose levels (NOAEL 1.5 mg/kg, estimated AUCweek: 9380 h*ng/mL). The safety margin is approximately 2.2-fold (AUC-based) higher compared to the highest dose in Type 1 SMA patients (nominal dose: 3.125 mg/kg, Table 1-1).

Testicular findings (degenerative changes involving seminiferous tubules of testes and testicular atrophy) were observed in a 52-week (juvenile) dog study with daily dosing of branaplam and in a 4-week wild type RasH2 mouse study with daily dosing of branaplam. Testicular findings in the mouse consisted of minimal to severe atrophy/degeneration of testis seminiferous tubules, including germ cells. Testes findings are likely related to the known cell-cycle effects of branaplam.

Ovary findings (decrease of corpora lutea and follicles) were also observed in the wild type RasH2 mouse study with daily dosing of branaplam. Ovary findings are likely related to the known cell-cycle effects of branaplam.

### Human safety and tolerability data

At the time this protocol amendment is written 14 patients have been enrolled and 13 treated in the Part 1 of the study, and 25 patients have been enrolled and treated in the Part 2 of the study. In addition, patients from Part 1 and Part 2 of the study have all transferred to Part 3 of the study.

Thirteen patients aged 2-7 months were randomized to escalating weekly doses of branaplam (6, 12, 24, 48 and 60 mg/m2) for 13 weeks followed by an extension period, currently up to 190 weeks in part 1 of the study. First patient was dosed in April 2015. No dose limiting toxicity was found at the different doses. Improvements in motor function were seen as determined by the CHOP-INTEND score. Discovery of axonal degeneration in dogs led to an Urgent Safety Measure to reduce the dose in all patients to the lowest level (6 mg/m2). Following the dose reduction, the patients in the study experienced a clinically apparent worsening of symptoms. The clinical worsening associated with the dose reduction either led to or contributed to a fatal outcome in 5 patients. Surviving patients did not fully regain function (by CHOP-INTEND) despite resumption of the original dosing at 6 mg/m2..

In Part 1 and 3, the most commonly reported AEs were pyrexia and pneumonia followed by vomiting, upper respiratory tract infection and diarrhea. In Part 2 and 3, the most commonly reported AEs were pneumonia, followed by pyrexia and bronchitis, constipation and thrombocytosis.

The most common serious adverse events (SAEs) in Part 1 and 3 as seen in more than 30% of patients were pneumonia, atelectasis, respiratory distress, respiratory failure, and femur fracture.

[redacted]

Continuation to Part 2 of the study was warranted to evaluate the longer-term safety and tolerability of 2 doses of 0.625 mg/kg and 2.5 mg/kg without forced escalation or reduction. Up to 10 patients were planned for each cohort. In total, 25 patients aged 0-6 months have been enrolled. The most common SAEs in Part 2 and 3 in more than 10% of patients were pneumonia, respiratory failure, and bronchitis.

Suspected Unexpected Serious Adverse Reactions (SUSARs) were reported in 4 patients, 2 each in Part 1 and Part 2 of the study. There were no SUSARs reported in Part 3. The events consisted of PTs: left ventricular hypertrophy, sinus tachycardia, ejection fraction decreased (reported term: decreased systolic function of left ventricle EF45%), and hypertension, pericardial effusion, and laryngospasm.

There continues to be no evidence of dose-limiting toxicities of branaplam.

More detailed review of the safety events in this study are presented in the most recent Investigator Brochure.

### Human pharmacokinetic data

In Part 1 of present study, PK parameters were investigated across all observation periods at actual mean doses of 0.299, 0.644, 1.30, 2.51, and 2.99 mg/kg (respective nominal doses: 6, 12, 24, 48, and 60 mg/m$^2$, Table 1-1). Following oral branaplam administration across all observation periods, median Tmax values of branaplam in plasma ranged between 2.97 to 4.00 h. AUC and Cmax values increased with increasing dose after a single dose or across all observation periods. Both exposure parameters were considered to increase in an apparent dose proportional manner across all observation periods with a slight deviation from the upper 90% confidence interval for Cmax, which was considered to be clinically not relevant. Considering plasma profiles across all observation periods, mean apparent systemic clearance (CL/F) and volume of distribution (Vz/F) values were comparable across the dose levels and ranged between 735 and 1050 mL/h/kg and between 45600 and 63400 mL/kg, respectively. Branaplam concentrations decreased in plasma with mean apparent terminal elimination T1/2 values ranging between 37.4 h and 59.3 h. No obvious accumulation was observed in a subset of patients comparing exposure parameters of treatment cycle 1 and 2 after administration of same dose at both cycles.

**Table 1-1 Systemic exposure values of branaplam across all observation periods - Study CLMI070X2201 Part 1**

| Nominal dose (mg/m$^2$) | Actual dose [a] (mg/kg) | Arithmetic mean ± SD (%CV) n [b] | Cmax (ng/mL) | n [b] | AUC (h·ng/mL) [c] |
|---|---|---|---|---|---|
| 6 mg/m$^2$ | 0.299 ± 0.0240 | 11 | 8.84 ± 3.58 (40.5) | 10 | 413 ± 98.3 (23.8) |
| 12 mg/m$^2$ | 0.644 ± 0.0341 | 4 | 15.3 ± 4.10 (26.8) | 4 | 761 ± 170 (22.3) |
| 24 mg/m$^2$ | 1.30 ± 0.0858 | 6 | 37.8 ± 12.8 (33.8) | 6 | 1340 ± 381 (28.5) |
| 48 mg/m$^2$ | 2.51 ± 0.186 | 16 | 69.1 ± 15.7 (22.8) | 11 | 3310 ± 850 (25.7) |
| 60 mg/m$^2$ | 2.99 ± 0.159 | 52 | 96.5 ± 32.7 (33.9) | 41 | 4280 ± 1030 (24.2) |

All values were rounded to 3 significant digits;

a: mean ± Standard Deviation (SD); b number of PK profiles considered; please note, that a patient provides several PK profiles to the analysis; c: AUC corresponds to the area under the plasma (or serum or blood) concentration-time curve from time zero to infinity [mass x time / volume] (AUCinf) after the first dose and the area under the plasma (or serum or blood) concentration-time curve from time zero, which is equal to the dosing time to 168 h [mass x time / volume] (0AUC0-168h) after multiple doses

Dose-normalized AUC and Cmax values across the age range from 2.5 to 58.5 months ranged from 595 to 2360 (h*ng/mL)/(mg/kg) and from 10.3 to 57.0 (ng/mL)/(mg/kg), respectively, and seemed to be comparable across the age range investigated. Linear regression analysis, which considered all dose-normalized exposure values, indicated a minor age-dependent increase with a maximum of 1.2 (AUC) and 1.4-fold (Cmax) increase across the observed age range. Similar assessment has been executed across the body weight range (5.11 kg to 16.3 kg). Comparable observations were made when dose-normalized AUC and Cmax values were correlated with the body weight range from 5.11 to 16.3 kg. Exposure values seemed to be comparable across the body weight range investigated. Linear regression analysis indicated a minor body weight-dependent increase of dose-normalized AUC and Cmax by 1.4 and 1.3-fold, respectively, considering the minimum and maximum observed body weight. No obvious impact of the administration method (feeding tube versus oral) was observed on both plasma exposure parameters, AUC and Cmax.

In Part 2 of present study, PK parameters were investigated across all observation periods at actual mean doses of 0.625 and 2.5 mg/kg, Table 1-2). Following oral branaplam administration across all observation periods, median Tmax values of branaplam in plasma ranged between 3.75 and 4 h at all observation periods (after 1 dosing, at month 3 and months 9). Thereafter, branaplam decreased slowly from plasma with mean apparent terminal elimination T1/2 values of 42.2 h and 46.0 h at the low and high dose level, respectively. AUC and Cmax values increased approximately with increasing dose in a dose-proportional manner. Mean apparent systemic clearance (CL/F) were 660 and 781 mL/h/kg and volume of distribution (Vz/F) values 40000 and 52400 mL/kg for 0.625 mg/kg and 2.5 mg/kg, respectively. Overall, all PK parameters were comparable to those observed in Part 1 (see above).

**Table 1-2 Systemic exposure values of branaplam across all observation periods - Study CLMI070X2201 Part 2**

| Actual dose | Arithmetic mean ± SD (%CV) | | | |
|---|---|---|---|---|
| (mg/kg) | n [a] | Cmax (ng/mL) | n [a] | AUC (h·ng/mL) [b] |
| 0.625 | 29 | 21.7 ± 5.71 (26.3) | 28 | 1020 ± 278 (27.4) |
| 2.5 | 38 | 77.4 ± 27.5 (35.6) | 29 | 3470 ± 909 (26.2) |

All values were rounded to 3 significant digits
a: number of PK profiles considered; please note, that a patient provides several PK profiles to the analysis; b AUC corresponds to AUCinf after the first dose and AUC0-168h after multiple doses

## Human Pharmacodynamic data

Preliminary data on SMN protein and SMN2 mRNA splicing as well as efficacy data are presented in the Investigator Brochure.

[redacted]

## 1.2 Purpose

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 patients 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 allows to provide long term safety and efficacy follow up for patients treated with branaplam for more than 52 weeks.

# 2 Objectives and endpoints

## 2.1 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 weekly for 52 weeks in patients 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 |

## 2.2 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. |

[redacted]

| Objective | Endpoint |
|---|---|
| • To evaluate the effect of branaplam on infant motor development. | • CHOP INTEND infant motor scale up to 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<br>• |
| • 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 |

[redacted]

# 3 Study design

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

All patients must have confirmed SMA type 1 and 2 copies of the SMN2 gene.

In Part 1 of the study, patients will be dosed once weekly with branaplam. The branaplam dose will be escalated in subsequent cohorts until MTD was determined or when sufficient PK results would not confirm that the MTD could not be reached due to a potential pharmacokinetic exposure plateau at higher doses. Patients will be dosed at least 24 hours apart for the first dose

[redacted]

of each dose level to ensure patient 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, patients completing 13 weeks of treatment will be considered to have completed the study. Patients who are continuing to receive study medication follow the Assessment schedule-part1-Extended treatment period. The assessment schedule repeats until the patient discontinues the study or transfers to Part 3 the investigator agree that this is in the best interest of the patient.

Part 2 of the study did enroll new patients into one of 2 dose cohorts of 0.625 mg/kg and 2.5 mg/kg with once weekly dosing for 52 weeks. The branaplam dose was escalated in subsequent cohorts after 6 patients have been enrolled or at least 3 patients from the initial cohort have completed 13 weeks of treatment. After 52 weeks, patients may continue treatment in Part 3 of the study if in the best interests of the patient, as assessed by the investigator.

Part 3 of the study is long term safety and efficacy follow up of extended oral/enteral, once a week branaplam treatment. All patients 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.

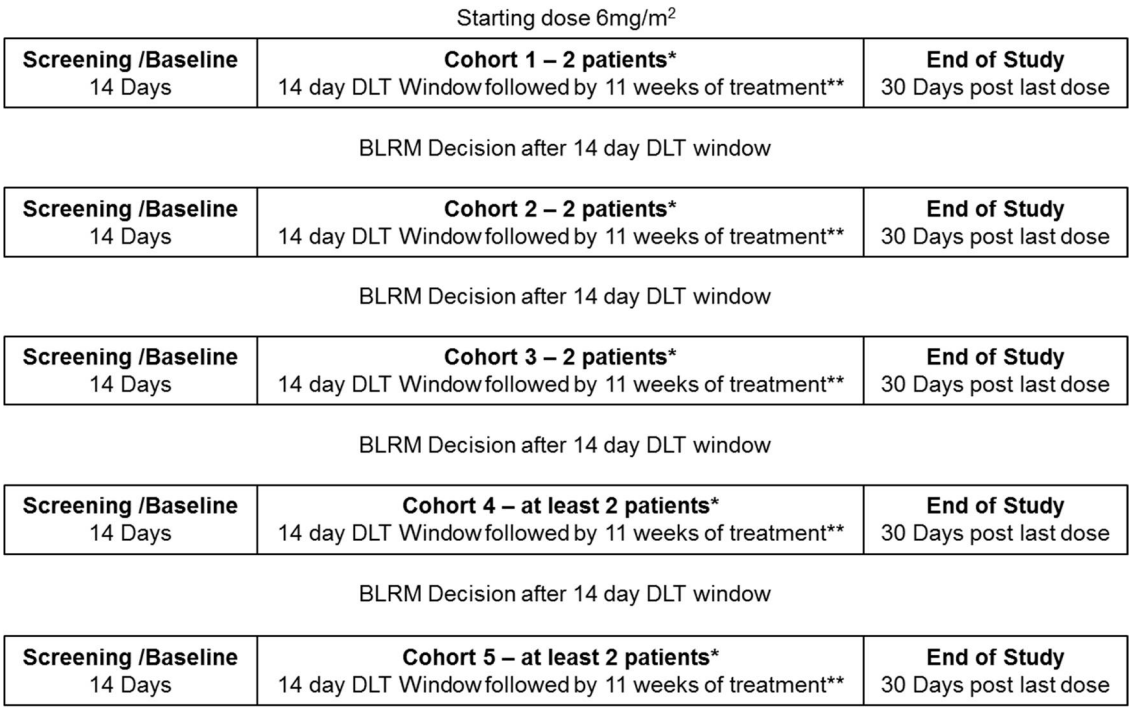
Continuation of the treatment will be done at the dose assigned while in Part 1 or Part 2 of the study. However, if at any later time an interim analysis of Part 1 or Part 2 study data suggest one optimal dose considering existing safety as well as efficacy data, the dose patients are receiving might be adjusted while participating in Part 3 of the study protocol.

## 3.1 Part 1 Study Design

14 patients have been enrolled and 13 patients treated in Part 1 (at least 2 patients planned in each of 5 cohorts). No new patients will be enrolled in Part 1.

[redacted]

**Figure 3-1 Part 1 study design**




* 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.

## Screening

Visit 1 – Day -14 to -8

Patients will be required to attend the investigator center for the screening visit (for logistical reasons more than 1 visit may be planned) where suitability for the study will be assessed by the investigator. Patients should stay within 120 minutes ground travel after signing the ICF through the end of the DLT period (Visit 9) and any longer travel should be discussed with and agreed to by the Sponsor.

Screening assessments will be completed per the Assessment Schedule.

To assess eligibility and confirm the diagnosis of SMA, SMN2 copy number will be determined in all patients in whom this has not been previously confirmed. As part of the inclusion and exclusion criteria, hepatitis and HIV screens will also be assessed at this visit. Similarly, general demographics and relevant and current medical history will be recorded.

Monitoring of concomitant medications, adverse events, and serious adverse events will be initiated during this visit.

Only patients who meet the inclusion/exclusion criteria at screening will be eligible to proceed to the baseline visit.

For a full list of assessments, please refer to Table 7-1.

## Baseline

### Visit 2 (Day -7 to -3) and Visit 3 (Day -2 to -1)

Due to the limited blood volumes available in infants, the baseline assessments have been split across two visits. The baseline visit may be combined into one day if appropriate.

All baseline eligibility assessment results must be available and confirmed by the investigator prior to progression into the treatment period.

## First dose – Visit 4 (Day 1)

Patients will attend the investigator site in the morning. They will remain at the site for at least 24 hours for safety monitoring, after which they will be discharged locally at the discretion of the investigator. Patients who do not live within 60 minutes travel from the site should be housed locally until the day 8 visit (Visit 8) either at family/friends, or in a hotel. After visit 8 they may return home until their next scheduled study visit.

Pre-dose assessments will be conducted according to Table 7-1.

Time of dosing will be collected in the eCRF and appropriate documentation of the patient specific dispensing process must be maintained. Dose administration should occur at approximately the same time of day at each dosing visit (morning or afternoon). The investigator should be in contact with the Sponsor before dosing to confirm that there is a 24 hour gap between patients receiving their first dose of study drug across all study sites. If two sites have patients scheduled for Visit 4 in the same week, they must be scheduled 24 hours apart, allowing for time zone variations.

[redacted]

Following study drug administration blood samples will be drawn for PK analysis at specified time points throughout the day.

Reflux precautions must be implemented post-dosing per local institutional standards.

For a complete list of assessments, please refer to Table 7-1 for the initial treatment period and to Table 7-2 for the extended treatment period.

### PK collections – Visits 5, 6, 7 and 8 (Day 2, 3, 5 and 8)

PK blood collections and safety assessments will be performed per Table 7-1 during the initial treatment period and per Table 7-2 during the extended treatment period and after the transfer into Part 3 per Table 7-4.

### Safety Review – Visit 8 (Day 8)

Safety assessments and respiratory function will be performed per Assessment Schedule. [redacted] a blood sample for PK will be obtained.

### Dosing Visits 9 (End of DLT review period) - 19 (Day 15 – Day 85)

If the first dose has been well tolerated during the 14-day DLT review period, patients will continue to be dosed on a weekly basis until end of study, or as long as it is in the best interest of the patient.

Patients will attend the investigator site in the morning. They will be discharged at the discretion of the investigator.

Safety and respiratory function assessments will be performed prior to dose administration per Table 7-1 during the initial treatment period and as per Table 7-2 during the extended treatment period.

Time of dosing will be collected in the eCRF and appropriate documentation of the patient specific dispensing process must be maintained. Dose administration should occur at approximately the same time of day at each dosing visit (morning or afternoon).

Reflux precautions must be implemented post-dosing per local institutional standards.

Patients entering treatment extension will undergo assessments as described in Table 7-2.

### End of Study – Visit 777

The End of Study visit will be performed 30 days after the last treatment.

End of study visit will become applicable only when further branaplam treatment is discontinued.

Study completion information is mandatory for this visit and must be completed regardless of the patient's completion / discontinuation status.

All other assessments within this visit should be completed wherever possible, depending on the patient's status and ability to tolerate assessments.

[redacted]

For a complete list of assessments, please refer to the Assessment Schedule.

Patients who are continuing to receive study medication follow the Assessment Schedule - Part 1 - Extended treatment period. The assessment schedule repeats until the patient discontinues the study or transfers to Part 3 of the study.

For patients who completed at least 52 weeks of treatment and who will continue treatment in Part 3, **no** end of study visit needs to be done.

## 3.2 Part 2 Study Design

In Part 2 of the study there are 2 different dose cohorts the patients will be enrolled to: cohort 1 at 0.625 mg/kg and cohort 2 at 2.5 mg/kg.

Those selected dose levels are based on previously obtained safety data from Part 1, as well as all data from preclinical chronic juvenile toxicity studies available at the time of initiation of Part 2. The rationale is described in Section 3.2.

A minimum of 6 and up to approximately 10 patients will be enrolled in each cohort.

Patients 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, patient(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 patient by patient level. If positive benefit cannot be confirmed for majority of the patients, the cohort 1 might be closed and ongoing patient will be escalated to 2.5 mg/kg.

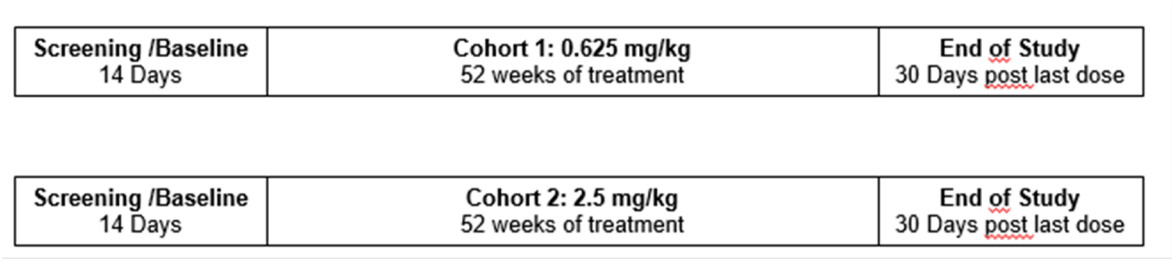
After completing 52 weeks of treatment, patients will have the possibility to continue receiving further branaplam treatment under Part 3 of this protocol.

However, in order to ensure patient 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 (non-durable effect). Efficacy and safety data will be reviewed after three patients 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 as defined in Section 5.4.7, the protocol will allow patients to receive the next higher dose.

Part 2 patients 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 patient, as assessed by the investigator will be enrolled to Part 3. For patients who will not be eligible to enter Part 3, End of Study of Part 2 will be performed.

[redacted]

**Figure 3-2 Part 2 study design**




## Screening

## Visit 1 – Day -14 to -8

Patients will be required to attend the investigator center for the screening visit

Screening assessments will be completed per the Assessment Schedule.

To assess eligibility and confirm the diagnosis of SMA, SMN2 copy number will be determined in all patients in whom this has not been previously confirmed. As part of the inclusion and exclusion criteria, hepatitis and HIV screens will also be assessed at this visit. Similarly, general demographics and relevant and current medical history will be recorded.

Monitoring of concomitant medications, adverse events, and serious adverse events will be initiated during this visit.

Only patients who meet all of the inclusion and none of the exclusion criteria at screening will be eligible to proceed to the baseline visit.

For a full list of assessments, please refer to the Assessment Schedule.

## Baseline/Randomization

Visit 2 (Day -7 to -3) and Visit 3 (Day -2 to -1)

Due to the limited blood volumes available in infants, the baseline assessments have been split across two visits. The baseline visit may be combined into one day if appropriate.

All baseline eligibility assessment results must be available and confirmed by the investigator prior to progression into the treatment period.

## First dose – Visit 4 (Day 1)

Patients will attend the investigator site in the morning.

Pre-dose assessments will be conducted according to the Assessment Schedule.

Time of dosing will be collected in the eCRF and appropriate documentation of the patient specific dispensing process must be maintained. Dose administration should occur at approximately the same time of day at each dosing visit (morning or afternoon).

[redacted]

Following study drug administration blood samples will be drawn for PK analysis at specified timepoints throughout the day.

Reflux precautions must be implemented post-dosing per local institutional standards.

For a complete list of assessments, please refer to the Assessment Schedule.

### Dosing Visits 8-67 (Day 8 - 358)

Patients will attend the investigator site in the morning.

Safety and respiratory function assessments will be performed prior to dose administration per the Assessment Schedule.

Time of dosing will be collected in the eCRF and appropriate documentation of the patient specific dispensing process must be maintained. Dose administration should occur at approximately the same time of day at each dosing visit (morning or afternoon).

Reflux precautions must be implemented post-dosing per local institutional standards.

### Home Visits

Home Visit can be performed at patient's home by Home Nurse professionals, if this service is available at the study site. The following activities can be performed at patient home depending on local regulations: Vital Signs (i.e. body temperature, blood pressure and pulse), Blood and urine draws for safety [redacted], blood draws for PK, ECG/Echocardiogram (ECHO), support with patients specific documents, study drug delivery, administration and return, Adverse Events and Concomitant Medication check

### End of Study – Visit 777

The End of Study visit will be performed 30 days after the last treatment. For patients from Part 2, after completing at least 52 weeks of treatment, who will continue treatment in Part 3, **no** end of study visit needs to be done.

End of study visit will become applicable only when further branaplam treatment is discontinued.

When end of study visit is applicable, study completion information is mandatory for this visit and must be completed regardless of the patient's completion / discontinuation status.

All other assessments within this visit should be completed wherever possible, depending on the patient's status and ability to tolerate assessments. For a complete list of assessments, please refer to the Assessment Schedule.

Patients will have the possibility to continue receiving branaplam treatment in Part 3 of the study if in the best interest of the patient, as assessed by the investigator.

[redacted]

## 3.3 Part 3 Study Design

Patients from Part 1 and Part 2 of the study 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 patient, as assessed by the investigator.

Part 3 of the study will have long-term safety follow up and monitoring as well as long term efficacy evaluation.

### Part 3 Visit 1 (14- to 1)

After completion of at least 52 weeks of branaplam treatment in Part 1 or Part 2 of the study, the investigator will assess whether continued branaplam treatment is in the best interest of the patient. When this is confirmed, a consent from parents/guardians will be collected and patient will transition to Part 3 of the study. Date of transition to Part 3 of the study will be collected in the eCRF and first dosing in Part 3 will ideally be done at site.

Visit 1 in Part 3 can be combined with last visit of either Part 1 or Part 2.

The assessments performed during last visit of either Part 1 or Part 2 do not need to be repeated at the first visit of Part 3, if the last visit of Part 1 or Part 2 occurred within the previous 14 days of the patient entering Part 3.

At Visit 1 of Part 3, investigator should always collect samples for PK, Troponin and N-terminal pro-brain natriuretic peptide (NTproBNP).

The ophthalmology assessments can be performed at Visit 1 if considered applicable by the investigator. However, if the patient does not have any ocular related complaints and if at the previous ophthalmology assessments there were no clinical findings which, potentially could be attributed to branaplam, the examination will be performed every 12 months from the date of the last ophthalmology assessment.

All consecutive doses in Part 3 can be administered at home, except if the dosing and site visit as per Assessment Schedule are overlapping, then patient will be dosed at the site.

If, in the opinion of the investigator, a patient receiving 0.625 mg/kg experiences no further clinical improvement of the condition or progression of disease, the dose may be increased to 2.5 mg/kg after consultation with the Sponsor. Similarly, if the investigator has any safety concerns for a patient receiving 2.5 mg/kg, the dose may be decreased to 0.625 mg/kg after consultation with the Sponsor.

If the caregivers do not wish to administer the IMP at home, the patient can visit the site for dosing anytime.

### Treatment and Long term follow up Period

The onsite visits will be performed as Regular (R) onsite visits every 3 months which will include all study assessments and Safety (S) onsite visits which will be done every month.

During Safety visits only Clinical Chemistry will be taken, weight of the patient collected and Adverse Events and Concomitant Medication checks done. Safety visits should be done on

[redacted]

site or at patient home performed by Home Nurse. If neither onsite visit nor home nurse visit is possible, investigator will perform a telephone call to caregivers. It is acceptable the patient will perform Clinical Chemistry locally and the results will be provided to investigator.

During Regular visits (R) following safety evaluations will be done:

- Blood samples for Hematology and Clinical Chemistry
- Urine Analysis
- Physical Examination
- Vital Signs
- Body Weight, Length and head and chest circumference
- Respiratory rate
- Electrocardiogram (ECG)
- Echocardiogram (ECHO)
- Respiratory Function
- Ophthalmology Examination
- Nerve Conduction Study (CMAP, SNAP, NCV)
- Adverse Events and Concomitant Therapies

All safety evaluations are described in Section 7.4.

Patient will follow the schedule of assessment of Part 3 as presented on Table 7-4.

### Telephone call interviews

In case patient is not able to visit the site for Safety Visit, site will perform telephone call interviews of the caregiver/legal guardians to assess the condition of the patient as well as verify patient's weight and study drug volume taken. The site will do all effort to reach the parents/caregivers. The contact will be reported in source documents. In case of adverse events and new concomitant medication, or patient's weight change these will be captured in applicable CRF pages.

### Unscheduled Visits

Unscheduled Visit can be performed by site at any time of the study under discretion of investigator. The site can perform some or all assessments listed in Assessment Schedule.

### Home Visits

Home Visit can be performed at patient's home by Home Nurse professionals, if this service is available at the study site. The following activities can be performed at patient home depending on local regulations: Vital Signs, Blood and urine draws for safety [redacted], blood draws for PK, ECG/ECHO, support with patients specific documents, study drug delivery, administration and return, Adverse Events and Concomitant Medication check.

[redacted]

### End of Study

End of study visit will be performed in case of patient discontinuation/early withdrawal. The End of Study visit will have to be performed 30 days after the last treatment.

Part 3 of the study currently does not have a study end defined, taking into account the lethal nature of the SMA Type 1 disease if left untreated. In case the study is discontinued for reasons other than branaplam related patient's safety, patient will continue treatment according to local standard of care, or if not available Novartis will offer available alternative treatment.

Study completion information is mandatory for this visit and must be completed regardless of the patient's completion / discontinuation status.

All other assessments within this visit should be completed, depending on the patient's status and ability to tolerate assessments. For a complete list of assessments, please refer to the Assessment Schedule as presented on Table 7-4.

### PK [redacted] collections

Blood collection for [redacted] PK will be performed every 6 months. Blood collection will require 2 time points for sample collection, pre dose ($C_{through}$ [redacted]) and post dose (C4h), therefore the study drug administration should be done onsite, at the day when PK [redacted] is scheduled. Actual PK sampling times must be documented in the eCRF. Actual date and the time of dosing for the preceding last dose, and the dosing date and time on the day of PK sampling, must be documented in the eCRF.

## 3.4 Rationale for study design

Due to the life-threatening severity of the disease, rapid clinical decline of these patients and the presence of effective therapy, that is also available in some European countries, it would be unethical to include a placebo treatment as part of the study design. Therefore, the proposed study design is an open label study with all patients on active treatment for the duration of the study. At the time of initiation of Part 1 based on the natural history over 13 weeks (about 3 months) in infants with type I SMA who have 2 copies of SMN2 and who are greater than 1 and less than 8 months of age, the following was agreed as a consensus: if symptomatic, no infant will hold their head up independently, or roll, sit, crawl, stand, or show antigravity leg strength. In addition, all infants will essentially lose proximal motor strength in all 4 limbs by 12 months of age (depends on how old they are when they enroll).

At the time of initiation of Part 2 additional sham control data are available: in symptomatic SMA Type 1 infants with onset of signs less than 6 months of age who have exactly 2 copies of SMN2 and who are at least 30 days and less than 180 days old, approximately 75% will be unable to maintain their head upright or kick horizontally, and almost all will be unable to complete any motor tasks in the HINE for rolling or sitting. No patients are expected to be able to crawl, stand or walk, and no acquisition of these skills is anticipated.

Type 1 SMA infants have severely impaired motor milestones indicating their motor neurons are dysfunctional and likely dying by the time of diagnosis, usually after 3 months of age. Thus, early treatment is vital if SMN protein elevation from splice modulation is to have any benefit.

[redacted]

Based on the available information to date, Novartis assumes that SMN2 splice modulation will not lead to generating new motor neurons, but it should enable the survival and recovery of existing dysfunctional ones.

The study population (Type 1 SMA) was initially selected because, given the cell cycle arrest liability of branaplam and thus narrow therapeutic window, it was not considered appropriate to expose healthy adult volunteers who could not benefit from the study drug. An additional consideration was the inability of an adult first-in-human study to adequately predict bioavailability of the drug in a young infant population in this Type 1 SMA infant study.

The diagnosis of SMA is usually prompted by referral for evaluation between 1 and 4 months of age (range: birth to 8 months). The diagnosis of Type 1 SMA is traditionally made on clinical grounds, ultimately dependent upon the demonstration that independent sitting is not achieved after a period of observation (EMA 2016). The patients in Part 1 of the study were aged between 1-7 months. Since newborn pre-screening is already in place in some countries, the age of the study patients in Part 2 will be defined as up to 180 days of age at screening.

Branaplam distributes to the brain in both rat and dog, both juvenile and adult animals, so significant brain penetration in infants is anticipated. If branaplam is to offer benefit, it is most likely to be in preserving motor neurons before they die off and thus age of patient at entry into study is crucial. The mechanism of action of branaplam is via increasing SMN protein in key cell types such as the alpha-motor neurons. Therefore, it is likely that branaplam will offer the maximal benefit if the target population of motor neurons are not irreversibly diminished, so recruitment for this study must be built around enrolling infants with SMA at the earliest stages of the disease process as possible.

Studies should be conducted in the patient population where there is the potential for benefit of the treatment. Novartis proposes that branaplam be tested in SMA patients with SMA Type I, because they suffer the most life-threatening form of SMA and have the greatest medical need for effective therapies and the highest prospect for direct benefit from participating in the planned study. By selection of 2 copy SMN2 SMA Type I patients, the study population is generally more homogeneous than other SMA types, which is anticipated to increase the probability to see treatment benefit in an open label study.

Patients with milder SMA Type II, III or IV have more slowly progressive disease, often characterized as a stable disease course. They typically survive to adulthood.

The study design has adopted a dose escalation design method to originally identify the MTD in **Part 1** similar to that used in oncology studies. Branaplam has known reversible cell-cycle arrest effects at high doses so the study design is planned to monitor and manage such effects (marrow or GI tissue) as delineated from standard pediatric oncology experience. The AE profile anticipated from potential cell-cycle arrest effects are considered to be clinically differential to the type I SMA clinical phenotype. Since Type 1 SMA is fatal, the prospect for direct clinical benefit is a fundamental mandate. In an adult Pharmacodynamic SMA mouse model, it has been demonstrated that a single oral dose of branaplam can drive up SMN protein in the brain and spinal cord and remains elevated for nearly a week. Weekly dosing is implemented after the initial 14-day safety review window, as this is expected to allow for a complete washout between doses. While more frequent dosing may be possible even in Part 1,

[redacted]

our approach is to avoid accumulation until we can be sure that branaplam does not harm patients. Patients will initially be dosed for 13 weeks, however dosing may be extended if recommended by the independent DMC.

PK will be analyzed to complement the safety data acquired. Similar FIH studies have been carried out in infants with fatal illnesses before (Kishnani et al 2007; Worgall et al 2008). It is not practical or ethical to enroll patients into a traditional single dose study and then have them wait potentially 3-6 months until a full cohort is treated at one dose before dose escalation, even with retreatment of the same patients. In that period, a great majority of their vulnerable motor neurons could die off and they would no longer be able to receive potential benefit from branaplam, though they would still be vulnerable to any AE's the drug may cause. We hypothesize that branaplam will rescue alpha-motor neurons from dying, but it is probably not capable of restoring or regenerating lost alpha-motor neurons; thus timing is key for patient entry at early stages of disease for receiving a potentially efficacious dose.

**Part 2** is designed to assess safety and tolerability of 0.625 mg/kg and 2.5 mg/kg of weekly oral branaplam for 52 weeks. Additionally, it will be investigated whether a change over time in infant growth and motor parameters can be detected and interpreted as an effect of branaplam treatment. Patients will initially be dosed for 52 weeks. After this initial 52 weeks, patients may continue receiving continuous treatment in Part 3 if the investigator confirms that this is in the best interest of the patient.

**Part 3** is designed to assess long term safety and tolerability and some long term efficacy of weekly oral branaplam treatment. Based on the interim analysis of Part 1 patients an improvement in motor function was seen as determined by the CHOP-INTEND score. Based on this improvement, and overall survival in Part 1, there is a strong rationale to extend treatment in participating patients and further assess efficacy and safety.

## 3.5 Rationale for dose/regimen and duration of treatment

### 3.5.1 Doses in Part 1

*Starting dose:* Due to the life-threatening nature of the Type I SMA disease, a starting dose must be selected which is intended to be safe but has the potential to show pharmacologically active effects e.g., SMN2 splice modulation. Therefore, an oncology approach was used to calculate the starting dose (14 References, International Council for Harmonization (ICH) S9 guidelines 2010) Doses were adjusted for body surface area since the toxicological reference studies in rats and dogs were done in juvenile animals.

In juvenile rats the highest dose evaluated was 10 mg/kg/day (60 mg/m$^2$/day), and neither lethality nor severe toxicity were observed at this dose; therefore, this dose is considered the rat STD10 (severely toxic dose in 10% animals). The Highest Non-Severely Toxic Dose (HNSTD) in juvenile dogs is considered to be 10 mg/kg/day (200 mg/m$^2$/day). Since 1/10th the rat STD10 scaled for body surface area is not severely toxic in dogs, which is the most sensitive species, the rat data are considered most appropriate for calculating the human starting dose.

The starting dose in patients is 1/10th of the rat STD10 (60 mg/m$^2$/day) = 6 mg/m$^2$/day. Assuming that a pediatric patient of 6.5 kg body weight and 62 cm has a body surface of 0.32 m$^2$,

[redacted]

(using the DuBois formula of BSA= $0.007184*W^{0.425}*H^{0.725}$) (DuBois and DuBois 1916), the starting dose for the first-in-human patient should be 6 mg/m$^2$/day x 0.32 m$^2$ ≈ 1.9 mg/day or approximately 0.3 mg/kg. The actual dose of each patient will be adjusted based on weight and length. Similarly, the dose in the extension may be adjusted based all available exposure data.

To uphold pediatric clinical trial guidance, the prospect for direct clinical benefit is built into this study design for all enrolled patients. Thus, the study design has a starting dose that is projected to be minimally efficacious and allows for dose escalation that is not limited by the enrollment pace of a sizeable cohort of patients with a rare disease. Once a patient has been treated for 13 weeks (end of part 1) and enters extended treatment, a patient *may* be switched to a higher dose once this higher dose has been deemed safe in other patients.

*Maximum dose:* At the highest tested dose of 60 mg/m$^2$ (corresponding to 3.125 mg/kg), the preliminary AUC0-24h value was 1470 ng.h/mL after single and repeated branaplam administration (Section 1.1.1). This exposure was about 6-fold higher than the projected efficacious AUC exposure based on nonclinical animal models. Due to the preliminary efficacy data of Part 1 of this study described in the current IB, no further increase of the dose is considered, although no dose limiting adverse event have been observed. Additionally, the available data from the 52-week toxicology study in juvenile dogs suggested not to exceed 60 mg/m$^2$ (corresponding to 3.125 mg/kg).

### 3.5.2 Doses in Part 2

*Starting dose:* The dose of 0.625 mg/kg was chosen as a starting dose in Part 2 based on safety and preliminary efficacy data collected in Part 1 of the study (see Table 7-1 and Table 7-2). Indeed, following an urgent safety measure (USM) in Part 1, treatment with branaplam continued but at a reduced dose of 6 mg/m$^2$ (0.3125 mg/kg) for all patients who had completed the initial 13 weeks of treatment. This dose was predicted to be efficacious based upon the preliminary clinical (CHOP INTEND) response of patients in Cohort 1. However, following the branaplam dose reduction to 6 mg/m$^2$ (0.3125 mg/kg) , safety events including decrease of motor skills, generalized motor weakness and increased respiratory muscle weakness have been reported (see also Section 1.1.1). While a mechanistic relation between these clinical observations and the preclinical nerve fiber degeneration following branaplam treatment cannot be completely excluded, due to the almost synchronous temporal association of the events with the decrease in dose and the similar course of the events in the 7 patients, it is most likely that branaplam was benefitting the patients and that the lower dose of branaplam is less effective. For that reason and also given the preliminary efficacy data collected in patients treated with branaplam 12 mg/m$^2$ (0.625 mg/kg)it was decided to take this dose as a starting dose in Part 2.

*Second dose level:* The dose of 2.5 mg/kg (48 mg/m$^2$) was selected as second dose in Part 2 being 4-fold higher than the starting dose of 0.625 mg/kg. Considering the preliminary PK exposure values and their variability determined in Part 1 (Section 1.1.1), the difference between 0,625 mg/kg and 2.5 mg/kg was considered to be sufficient to ensure appropriate separation in terms of systemic branaplam exposure and potentially also of efficacy endpoints. In addition, the magnitude of the dose difference would be sufficient to guide the dose-response. An increase of the selected second dose of 48 mg/m$^2$ to 60 mg/m$^2$ was not further considered as the dose difference is only 1.25-fold and exposure overlap was clearly observed in Part 1.

### 3.5.3 Doses in Part 3

In Part 3 patients will be treated at doses that have already be assigned in Part 1 and Part 2 of the study until an optimal selected dose has been determined. However, if in the opinion of the investigator, a patient from Part 2, receiving 0.625 mg/kg experiences no further clinical improvement of the condition or even progression of disease, the dose may be increased to 2.5 mg/kg after consultation with the Sponsor. Similarly, if the investigator has any safety concerns for a patient receiving 2.5 mg/kg, the dose may be decreased to 0.625 mg/kg after consultation with the Sponsor.

Following the Part 2 (52 weeks) analysis, a comparison of the two doses showed 2.5 mg/kg to have numerically better changes in HINE-2 scores compared to 0.625 mg/kg following one year of treatment, and comparable safety profiles. The SMN mRNA analysis also noted a greater target engagement favoring the higher dose as well (see Section 1.1.1). Thus, it is expected that this higher dose will maximize the potential long-term benefit for patients. Therefore, the dose of 2.5 mg/kg was selected as the optimal dose in Part 3 and the investigators from study sites were prompted to have all patients transition to this new dose, unless there are safety concerns or this change in dose is not in the best interest of the patient.

#### Dose escalation

In Part 1 dose escalation is guided by the Bayesian logistic regression model (BLRM) with escalation with overdose control (EWOC) principle. Based on modeling and simulation projections from preclinical toxicology and the most relevant mouse models for efficacy studies, the doses planned/anticipated after dose level 1 are no more than 100% increases of the previous dose level rather than the typical ½-log (3-fold) increase in order to be careful with these symptomatic infants.

The initial duration of treatment in Part 1 (13 weeks) and Part 2 (52 weeks) are designated to allow adequate time for SMN upregulation to not only rescue motor neurons from dying but also enable neuromuscular development to manifest observable gains in motor and respiratory function. Based on the safety and efficacy data analyzed so far, a benefit for the patients has been demonstrated and is justifying to continue with long term treatment.

Part 2 is designed to have two separate dose cohorts and no in-patient dose escalation from 0.625 mg/kg to 2.5 mg/kg is planned. However, in case of no improvement or progressive disease individual patients might be escalated from lower to higher dose.

In Part 3 patients will continue receiving doses that they have been receiving at time of transition into Part 3. If, in the opinion of the investigator a patient receiving 0.625 mg/kg experiences no further clinical improvement of the condition or even disease progression, the dose may be increased to 2.5 mg/kg. Similarly, if the investigator has any safety concerns for a patient receiving 2.5 mg/kg, the dose may be decreased to 0.625 mg/kg after consultation with the Sponsor.

After analysis of Part 2 data, if new information on the optimal dose of branaplam becomes available, dosing of all patients in Part 3 might be adjusted.PK/PD relationship

[redacted]

PK/PD modeling based on PK and brain SMN protein levels in mice suggested that 0.3 mg/kg (projected plasma AUC0-24h ~239 ng.h/mL in infants) could be a minimally efficacious dose. Since the SMN protein elevation observed at this dose corresponded to approximately a 35% increase above baseline brain SMN levels in these animals, it is anticipated that elevating SMN protein levels in Type I SMA patients to about 35% of the SMN levels in normal, unaffected individuals may elicit clinically meaningful effects. Given that peripheral (blood) SMN protein levels will be monitored as a surrogate for central SMN elevation and that the range of SMN protein levels in Type I individuals is ≤ 5-20% of normal levels, it is anticipated that a dose of branaplam that provides a 15-30% increase (over baseline levels of a given patient) in peripheral SMN levels is expected to be within an efficacious dose range.

### 3.5.4 Safety margins

In order to estimate multiples of animal exposures relative to human exposures, the exposures at dose levels not associated with severe toxicity were compared to preliminary exposures in human at the projected minimum efficacious dose level (6 mg/m$^2$, corresponding to 0.3125 mg/kg) and at the maximum dose levels tested in humans so far (60 mg/m$^2$ corresponding to 3.125 mg/kg). Details of the safety margin calculations are presented in the most current IB.

The estimated exposure at the No-observable-effect-level for genotoxicity (specifically, aneugenicity) in the rat (227 ng.h/mL) is similar to the projected efficacious exposure resulting in an exposure multiple of 1. For the maximum anticipated exposure, the exposure multiple would be 0.1 (for further details see the Investigator's Brochure). Since the aneugenic effect is considered secondary to the cell-cycle effects of branaplam the projected efficacious and maximum foreseen exposures are considered justified.

### 3.5.5 Age effect

Branaplam PK is expected to change with age as a consequence of maturation of metabolizing enzymes (UGTs and CYP3A4) and transporters (Pgp). This may reduce the bioavailability, impact the distribution to the brain (Pgp) and/or increase the clearance, leading to a reduction of exposure. Therefore, the doses in both parts have to be adjusted either to the BSA (Part 1) or body weight (Part 1 extension, Part 2) as described in Section 5.1.2. Since BSA and body weight increases with age in infants, the effect of age on the PK will, at least partially, be compensated by the BSA/body weight adjustment. However, this may not completely compensate for the changes in metabolic and absorption/distribution processes. Therefore, PK samples have been and will be collected in all study parts every 3 to 6 months for assessment of PK exposure parameters (Part 1 and Part 2) and of steady state concentrations (Part 3). Results of all of these assessments will be evaluated for potential dose adjustments even on an individual basis to maintain the same exposure (AUC) as observed after the first dose.

## 3.6 Rationale for choice of comparator

Because of the lethal and progressive nature of SMA Type I, no placebo control will be offered. No active comparator is proposed despite of the approval of nusinersen for SMA in the US and EU because this is an exploratory study to determine safety and initial efficacy of branaplam.

[redacted]

Nusinersen is not yet available in some countries where this study may be run. Supportive care will be used as background treatment throughout the study. Comparison to natural history studies may be used as well.

## 3.7 Purpose and timing of interim analyses/design adaptations

In Part 1, prior to dose escalation, a review of all safety/tolerability (continued review of physical examination, vital signs, safety laboratory assessments and adverse events), dose-limiting toxicity (DLT) and available PK data up to 14 days post-dose for at least 1 patient in the dose cohort will be performed and must be assessed as satisfactory to proceed. See Section 5.4 for definitions of dose limiting toxicities.

The decision for dose escalation will be based on a review of all relevant data available from all dose levels evaluated in the ongoing study and will be made jointly between the Sponsor and the Site Investigators. The recommended dose for the next cohort of patients will be guided by the Bayesian logistic regression model (BLRM) with escalation with overdose control (EWOC) principle.

Dose escalation will continue in Part 1 until a Maximum Tolerated Dose (MTD) is adequately defined for the weekly dosing regimen or when sufficient PK results confirm that the MTD cannot be reached due to a potential pharmacokinetic exposure plateau at higher doses.

When MTD or a pharmacokinetic exposure plateau is reached, PD as measured by either blood SMN protein upregulation from baseline or blood cell SMN2 mRNA splicing in Part 1 will confirm branaplam's mechanism of action occurring in human periphery. This is expected to be similar to the effect in brain stem and spinal cord motor neurons. If clinical efficacy is seen in Part 1 with positive PD whole blood SMN protein upregulation or other PD markers, and MTD is not determined, sponsor may not pursue establishing the MTD and may go into Part 2 with efficacious doses only.

Final analysis will be performed at the end of Part 3 which will evaluate PK/PD (blood SMN protein upregulation) and evaluate the change over time in clinical endpoints related to infant growth and motor function.

Patients enrolled in Part 1 who tolerate the assigned doses of branaplam may receive extended treatment beyond the initial treatment period if Novartis, the investigator and the DMC agree that this is in the best interest of the patient. Under this regimen, a patient may continue to receive weekly dosing at the originally assigned dose level, or they *may* be escalated to a higher dose (Part 1 only) once this higher dose has been deemed safe in other patients. Additional adjustment for age may also be required, as discussed earlier. However, for each patient, DLTs observed while taking doses subsequent to the initial 14-day safety review will not influence dose escalation decisions, in order to avoid bias of increased tolerance or toxicity to branaplam.

In Part 2 patients will be assigned to one of the two cohorts, 0.625 mg/kg or 2.5 mg/kg and patients from lower dose cohort will not be escalated to a higher dose than their originally assigned dose level unless there is a potential lack of efficacy/disease progression.

[redacted]

[redacted]

[redacted]

Additional information is presented in Section 11.7.

## 3.8 Risks and benefits

Overall, the benefit-risk of branaplam for newly diagnosed infants with type I spinal muscular atrophy appears to be favorable. The inclusion of new patients in Part 1 of the study was withheld in 2017 until data were available that allowed for a better understanding of the pathophysiological mechanisms that may explain the observations in the chronic dog toxicology study. For patients already enrolled in the Part 1 of the study at that time, the benefit-risk, the additional survival and functional data, and the new benefit-risk determination for each patient in the study by an independent physician support a continued positive benefit-risk ratio. In addition, an autopsy from a patient who died shortly following dose reduction showed no evidence of axonal degeneration. Clinical neurophysiologic [redacted] monitoring has been added to address this risk identified in the chronic dog toxicology study.

A total of 38 patients have been treated with branaplam to date in CLMI070X2201 study. Treatment has been well tolerated with few safety events. Investigators have reported seeing improvements in some patients that exceed the expected natural history of SMA type I disease, and assessment of the CHOP INTEND motor function measure after interim analyses in Part 1 are showing increases of CHOP INTEND over time at serial evaluations in most patients. Seven patients have reached a CHOP INTEND score of > 36, exceeding the results seen in historical control studies with infants with symptomatic Type I SMA (Finkel et al 2014; Kolb et al 2016). Similar changes have been seen in data in part 2. In result of these changes seen, branaplam may be beneficial to patients, enabling motor neurons to survive and indeed leading to acquisition of motor skills as hypothesized. The survival of motor neurons in this critical window of infancy requires sufficient amounts of functional SMN protein so that the muscle fibers remain innervated and function. The potential benefit of branaplam is to rescue motor neurons from dying out and enable neuromuscular development to occur which is required for muscle functions such as motor development e.g. rolling, sitting and walking in addition to independent respiratory function and eating/swallowing. Thus, the potential for benefit to patients from branaplam is motor skills acquisition, prolonged survival in this fatal disease with improved respiratory function, plus enhanced growth with better nutritional intake by improved feeding.

Since the initiation of the CLMI070X2201 study, the therapeutic landscape has changed with new therapies for treating SMA type 1. The following are approved therapies for SMA: Spinraza (nusinersen), an antisense oligonucleotide, Zolgensma (onasemnogene abeparvovec-xioi), an SMN1 gene replacing gene therapy, and Evrysdi (risdiplam), an SMN splice modulator. For full details please review product labels.

For detailed information on safety, including the number of SUSAR, please refer to the investigator brochure.

[redacted]

The table below summarizes the important potential risks from pre-clinical studies as well as human experience from this ongoing trial (CLMI070X2201) as well as recently completed Single Ascending Dose study and human absorption, distribution, metabolism and excretion (ADME) study in healthy volunteers.

**Table 3-1 Summary of Important Potential Risks**

| Class/Compound | Risk Classification | Risk Name | |
|---|---|---|---|
| Compound | Potential | Cell cycle effects | Bone marrow effects |
| | | | Gastrointestinal effects |
| | | | Nerve fiber degeneration |
| | | | Retinal atrophy |
| | | | Gonadal effects: Testicular/ovarian |
| | | | Reproductive toxicity: Pregnancy in Women of Childbearing Potential |
| | | | Genotoxicity (aneuploidy*) |
| | Potential | Liver function effects | |
| | Potential | Cardiovascular effects | |
| | Potential | Renal toxicity | |
| | Potential | Drug-drug interactions | |
| | Missing Information | Effects of Breastfeeding | |
| Class | None | None | |

*Branaplam was not mutagenic in a bacterial mutagenicity (Ames) test. Branaplam is aneugenic but not clastogenic. A neoplastic risk of branaplam as a consequence of the aneugenic effect is considered unlikely but cannot be excluded.

The risk to patients in this trial will be minimized by adherence to the eligibility criteria with experienced SMA pediatric clinical experts, close clinical monitoring, and close adherence to the stopping rules.

## Bone Marrow Effects

In this ongoing study some events of cytopenias consisting of neutropenia, anemia and thrombocytopenia were reported. However, these events were mild to moderate and reversible. Additionally, events of increased platelet counts were also reported which were also mild to moderate in severity and resolved spontaneously while on treatment. In the Single Ascending Dose (SAD) study in healthy volunteers, five participants dosed with 420 mg or placebo showed platelet count increases above the ULN (max increase up to 2x ULN) which were most pronounced in the 3 participants with liver events, which have not been observed at lower dose levels.

[redacted]

### Gastrointestinal Effects

In this ongoing study in Type 1 SMA patients the majority of gastrointestinal events were Grade 1 and 2, were not related to study drug and resolved while on treatment.

In the healthy volunteer study in healthy adult participants 7 out of 8 participants in this Cohort 4 (420 mg branaplam) reported diarrhea (5 branaplam and 2 placebo-treated) on Day 1 with a spontaneous recovery by Day 2.

### Nerve Fiber Degeneration

Nerve fiber degeneration (axonal degeneration) in peripheral nerves and spinal cord was found in one species (dogs) after 17 weeks of daily administration of branaplam. The onset of axonal degeneration preceded or coincided with an increased in Neurofilament light chain (NfL) concentration in serum and cerebral spinal fluid (CSF). A dose-dependent increase of NfL levels was observed in the serum and CSF of monkeys treated twice weekly with branaplam for a duration of 6 weeks in the absence of microscopic findings in the brain, spinal cord or peripheral nerves. [redacted] Furthermore, weekly dosing is expected to potentially mitigate this risk.

[redacted] So far there are no recorded adverse events indicative of neurotoxicity and the nerve conduction studies have not shown a clear indication of neurotoxicity.

In the SAD study in healthy adult volunteers, NfL levels in serum were monitored at several timepoints in the study. Individual serum NfL results showed overall no trend of increase within each cohort or across the investigated exposure range across the 4 cohorts and were not suggestive of any effects of branaplam on this variable.

The risk to patients in this trial will be minimized by adherence to the eligibility criteria with experienced SMA pediatric clinical experts, close clinical monitoring, and close adherence to the stopping rules.

### Renal Atrophy

Corneal opacities and retinal/choroid atrophy were observed in the 26-week study in juvenile albino rats which was considered rat specific.

In the current ongoing study in Type 1 SMA CLMI070X2201 no ocular events pertaining to retinal atrophy have been reported.

This risk will be monitored by ophthalmoscopic examinations.

### Testicular Effects

Degenerative changes involving seminiferous tubules of testes were observed after daily dosing with branaplam in a 4-week adult mouse study and 52-week juvenile dog study. This risk is considered unmonitorable in the sexually immature patients enrolled in this trial.

[redacted]

### Ovarian Effects

Ovary findings (decrease of corpora lutea and follicles) were observed in the adult mouse (wild type (wt) RasH2 strain) with daily dosing of branaplam. No ovarian findings in any other toxicological studies conducted in the rat and dog. This risk is considered unmonitorable in the sexually immature patients enrolled in this trial.

### Genotocicity (Aneuploidy)

A neoplastic risk of branaplam as a consequence of the aneugenic effect is considered to be unlikely but cannot be excluded. This potential risk may not present in the duration of this study.

### Liver Function Effects

Liver findings were observed in animals after daily dosing with high dose levels (mouse, rat and dog) or after chronic dosing in the rat.

In this ongoing study in Type 1 SMA patients there were some reported events of transient increases in aminotransferases. In the SAD study in healthy subjects all 6 subjects receiving single doses of 420 mg branaplam showed increases in AST and/or ALT with an onset on Day 8, which in of which 3 subjects were classified as "liver events" as per protocol defined criteria (ALT or AST increase >5x ULN or ALT increase >3x ULN accompanied by clinical symptoms) and were recorded as adverse events. A trend of ALT and AST increase within the normal range was already observed at doses of 210 mg (SAD study) and 140 mg (human ADME study).This risk is considered monitorable by history, physical exam, and liver function tests.

### Renal Effects

Kidney findings were observed after chronic daily dosing only in the dog. Blood pressure monitoring, serum chemistry measurements of electrolytes and renal function and urinalysis are included in the ongoing clinical study CLMI070X2201 as well as in the planned Clinical Pharmacology studies. In the current ongoing CLMI070X2201 study no relevant renal adverse events have been identified. In the SAD and humanADME study in healthy participants there have been no relevant abnormalities or changes in blood pressure, serum electrolyte levels or renal function variables or in the urinalysis assessments.

The risk to patients in this trial will be minimized by adherence to the eligibility criteria with experienced SMA pediatric clinical experts, close clinical monitoring, and close adherence to the stopping rules.

### Cardiac effects

Vacuolation of cardiomyocytes was observed with daily dosing of branaplam in the mouse study (wt RasH2 mouse strain). No heart functional changes were observed in the dog safety study and in the 6 weeks monkey study with twice-weekly dosing. The exposure at the highest dose in the monkey were 7.5-fold higher compared to exposures observed in Type 1 SMA patients. The safety margin for human-ether-a-go-go-related gene (hERG) channel inhibition is 37.8-fold higher than the highest Cmax observed in humans to date. Although these preclinical

findings are new findings, cardiac effects are already listed as a risk in the current Investigator's Brochure (IB).

At the time this protocol amendment is written, three cases of cardiac SUSARs have been reported in the CLMI070X2201 study (see Section 1.1.1). The events consisted of PTs: left ventricular hypertrophy, sinus tachycardia, ejection fraction decreased(reported term: decreased systolic function of left ventricle EF45%), and hypertension, and pericardial effusion.

The SMN protein is expressed in moderate levels in skeletal as well as cardiac muscle (Coovert et al 1997). Multiple preclinical in vivo studies and emerging clinical findings in SMA patients suggest that partial deficiency state of SMN in SMA may have an adverse effect on cardiac embryogenesis and function. Cardiac deficits, including bradycardia, arrhythmias and impaired blood flow have been described in several mouse models of SMA and are often the cause of death of these mice (Heier et al 2010). Drug treatments that elevate SMN levels have been shown to improve heart function in the same models. (Heier and DiDonato 2015).

In patients, severe forms of SMA, including Type I SMA, have been associated with autonomic dysfunction, congenital heart block, ASD, VSD, aortic stenosis, hypoplastic aortic arch, severe aortic coarctation, partial atrioventricular canal, tricuspid atresia, a single ventricle and hypoplastic left heart syndrome (Bach 2007; Bach et al 2007; Menke et al 2008; Rudnik Schöneborn et al 2008; for review see also Shababi et al 2014).

In summary, there appears to be an association of structural cardiac disease and autonomic findings, presenting as bradycardia and heart rate variability abnormality, with severe SMA that could potentially cause, or contribute to, the findings seen in study CLMI070X2201.

The risk to patients will be minimized by safety monitoring for cardiovascular function including monitoring of blood pressure at regular visits, cardiac biomarkers, such as troponin and NTproBNP every 3 months, ECGs every 3 months and echocardiography performed every 6 months or when clinically significant elevation in troponin and or NTproBNP levels are identified by the investigators. It is important that investigators ensure these protocol required investigations and get early pediatric cardiology consult if any abnormalities are identified.

### Additional risks

An additional risk to patients in this trial is that despite branaplam exposure and its toxicity risks, the SMA type I disease course may progress without evidence of stabilization or improvement or there may be loss of effect as patients age. In other words, there could be a lack of clinical efficacy despite participation in this trial.

There may also be unknown risks of branaplam that may be serious and unforeseen.

Please also refer to the current Investigator's Brochure.

## 3.9 Rationale for Public Health Emergency Mitigation Procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure patient safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed

[redacted]

with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

# 4 Population

### Part 1

The study population will be comprised of infants with Type 1 SMA with SMN2 copy number of 2, aged approx. 1 month to 7 months. Fourteen patients have been enrolled (amongst them, 13 were treated) in Part 1 of the study. No new patients will be enrolled in Part 1.

### Part 2

Twenty-five additional patients have been enrolled in Part 2. The study population will be comprised of infants with Type 1 SMA with SMN2 copy number of 2, aged up to 180 days of age at screening. The investigator must ensure that all patients being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator

Patient selection is to be established by checking through all eligibility criteria at screening and baseline. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from **any** entry criterion excludes a patient from enrollment into the study. No new patients will be enrolled in Part 2.

### Part 3

Patients treated currently with branaplam, who participated in Part 1 or Part 2 of this protocol and have completed at least 52 weeks of treatment with branaplam will be eligible to continue the study in Part 3. Except for previous participation in Part 1 or Part 2 of the study and completion at least 52 weeks of treatment, no further eligibility criteria will be implemented for Part 3. Patients will continue treatment as long as they are benefiting from it and it is in the best interest of the patients, or other treatment option(s) will be considered more appropriate. No new patients will be enrolled in Part 3.

## 4.1 Inclusion criteria

### 4.1.1 Part 1

| Screening | Baseline | Criteria |
|---|---|---|
| X | | 1. Written informed consent must be obtained from the parent / guardian before any assessment is performed. |

[redacted]

| Screening | Baseline | Criteria |
|---|---|---|
| X | | 2. Type 1 SMA, diagnosed clinically, with symptom onset <6 months of age and genetic confirmation of mutations in both alleles of the SMN1 gene, and with SMN2 copy number of 2. |
| X | | 3. Best supportive care in place and stable for at least 14 days before screening. |
| X | | 4. Age at screening between 1 and 7 months |
| X | X | 5. Must be able to demonstrate antigravity strength in both biceps. |
| X | X | 6. Must have or agree to have placement of feeding tube for enteral access via nasogastric (NG), nasojejunal (NJ), percutaneous gastrostomy (PEG), or percutaneous jejunostomy (PEJ) tube for dosing LMI070 (Part 1 only and for patients who cannot be administered orally; tube may be removed between doses) |
| X | X | 7. Medical care meets and is expected to continue to meet guidelines set out in the Consensus Statement for Standard of Care in SMA (Wang et al 2007), in the opinion of the Site Investigator. |
| X | | 8. At birth gestational age >32 weeks and body weight at birth >2 kg. |
| X | X | 9. Must live within 2 hours drive of study center. Clearance should be obtained from the site investigator and sponsor if the patient resides more than 2 hours ground travel from the study center. |
| X | X | 10. Able to complete all study procedures, measurements and visits; and parent or guardian/patient has adequately supportive psychosocial circumstances, in the opinion of the Site Investigator. |

### 4.1.2 Part 2

| Screening | Baseline | Criteria |
|---|---|---|
| X | | 1. Written informed consent must be obtained from the parent / guardian before any assessment is performed. |
| X | | 2. Type 1 SMA, diagnosed with genetic confirmation of mutations in both alleles of the SMN1 gene, and with SMN2 copy number of 2. |
| X | | 3. Best supportive care in place and stable for at least 14 days before screening as assessed by the investigator. |
| X | | 4. Age at screening up to 180 days of age |
| X | X | 5. Must be able to demonstrate antigravity strength in both biceps. |
| X | X | 6. Must have or agree to have placement of feeding tube for enteral access via nasogastric (NG), nasojejunal (NJ), percutaneous gastrostomy (PEG), or percutaneous jejunostomy (PEJ) tube for dosing branaplam (for the first administration only and for patients who cannot be administered orally; tube may be removed between doses) |
| | X | 7. Minimum CHOP INTEND score of 15 at baseline |

[redacted]

| Screening | Baseline | Criteria |
|---|---|---|
| X | X | 8. Must be able to swallow solid and liquid even if feeding is used to support nutrition intake and must be in the 5th percentile for length or weight on the international growth curves and must be proportional in height and weight. |
| X | | 9. At birth gestational age >32 weeks and body weight at birth >2 kg. |
| X | X | 10. Able to complete all study procedures, measurements and visits; and parent or guardian/patient has adequately supportive psychosocial circumstances, in the opinion of the Site Investigator. |

### 4.1.3 Part 3

| Baseline | Criteria |
|---|---|
| X | 1. Written informed consent must be obtained from the parent / guardian |
| X | 2. Current participation in Part 1 or Part 2 study and completion of at least 52 weeks of treatment with branaplam |
| X | 3. Further branaplam treatment is in the best interest of the patient as assessed by the Site Investigator |
| X | 4. Able to complete all study procedures, measurements and visits; and parent or guardian/patient has adequately supportive psychosocial circumstances, in the opinion of the Investigator. |

## 4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study.

### 4.2.1 Part 1

| Screening | Baseline | Criteria |
|---|---|---|
| X | | 1. Use of other investigational drugs within 14 days. |
| X | | 2. Neurologic or neuromuscular conditions other than SMA. |
| X | | 3. Anemia (Hgb < 9.5 gm/dl ; <5.9 mmol/L), leukopenia (CTCAE Grade 2 or higher, <3000 /mm3; <3.0 x109/L), neutropenia (Grade 2 or higher, <1,500/mm3; < 1.5 X 109/L) or thrombocytopenia (CTCAE Grade 2 or higher, ≤ 75,000/mm3), ≤75 X 109/L |
| X | | 4. Hepatic dysfunction (e.g. AST or ALT CTCAE Grade 1 or higher, ≥ ULN if considered to be consequence of hepatic dysfunction); total bilirubin CTCAE Grade 1 or higher, ≥ ULN). |

[redacted]

| Screening | Baseline | Criteria |
|---|---|---|
| X | | 5. Age adjusted renal dysfunction with eGFR calculated using the following formula: eGFR (in mL/min/1.73 $m^2$) = 0.45 X Length (cm) ÷ serum creatinine (mg/dl) (Schwartz and Work 2009).<br>≤ 26 mL/min/1.73 $m^2$ up to age 28 days of age<br>≤ 30 mL/min/1.73 $m^2$ for 1 to 3 months of age<br>≤ 40 mL/min/1.73 $m^2$ for 3 to 6 months of age<br>≤ 50 mL/min/1.73 $m^2$ for 6 to 12 months of age |
| X | | 6. Clinically significant abnormalities in hematology or clinical chemistry parameters, as assessed by the investigator, at screening that would render the patient unsuitable for inclusion |
| X | | 7. Intractable seizure disorder (other than inactive febrile seizures). |
| X | X | 8. Persistent (in the opinion of the investigator) hypoxemia ($O_2$ saturation awake <92% or $O_2$ saturation asleep <91%, without ventilation support) or requiring oral suctioning >2 per day |
| X | X | 9. Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the screening period. |
| X | X | 10. Current diagnosis of cardiac and/or vascular abnormalities including uncontrolled hypertension, intolerance of blood pressure and pulse assessment techniques such that consistent normal values cannot be measured, echocardiographic abnormalities (both structural and function) or ECG abnormalities (such as long QT, heart block or Torsade's) indicating significant risk of safety for infant patients participating in the study such as: Concomitant clinically significant pediatric cardiac arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second or third degree AV block. |
| X | X | 11. Prohibited Concomitant Medications used to treat SMA, including but not exclusively: oral albuterol or oral salbutamol, hydroxurea, riluzole, valproate, carnitine, creatine, sodium phenylbutyrate within 14 days prior to enrollment or during the study. |
| X | | 12. Excluding SMA, any medically unstable condition including cardiomyopathy, hepatic dysfunction, kidney disorder, endocrine disorder, GI disorders, prematurity of <32 weeks gestation, metabolic disorders, severe respiratory compromise and significant brain abnormalities or injuries including hypoxic-ischemic encephalopathy. |
| X | | 13. Acute or ongoing medical condition that, according to the Site Investigator and discussed with sponsor, would interfere with the conduct and assessments of the study. Examples are medical disability other than SMA that would interfere with the assessment of safety or would compromise the ability of the patient to undergo study procedures including be assessed by CHOP INTEND infant motor scale, changes in hematologic parameters or gastrointestinal dysfunction that would compromise the ability of adequate assessment of safety |

[redacted]

### 4.2.2 Part 2

| Screening | Baseline | Criteria |
|---|---|---|
| X | | Use of gene transfer at any time or other investigational drugs within 14 days. |
| X | | Patients who have received nusinersen at any time prior to screening |
| X | | Neurologic or neuromuscular conditions other than SMA. |
| X | | Anemia ( CTCAE Grade 2 or higher Hgb < 10 gm/dl ; <6.2 mmol/L ),Leukopenia (CTCAE Grade 2 or higher, <3000 /mm3; <3.0 x109/L), neutropenia (Grade 2 or higher, <1,500/mm3; < 1.5 X 109/L) or thrombocytopenia (CTCAE Grade 2 or higher, ≤ 75,000/mm3), ≤75 X 109/L |
| X | | Hepatic dysfunction (e.g. AST or ALT CTCAE Grade 1 or higher, ≥ ULN, if considered to be consequence of hepatic dysfunction); total bilirubin CTCAE Grade 1 or higher, ≥ ULN). |
| X | | Age adjusted renal dysfunction with eGFR calculated using the following formula: eGFR (in mL/min/1.73 m2) = 0.45 X Length (cm) ÷ serum creatinine (mg/dl) (Schwartz and Work 2009).<br>≤ 26 mL/min/1.73 $m^2$ up to age 28 days of age<br>≤ 30 mL/min/1.73 $m^2$ for 1 to 3 months of age<br>≤ 40 mL/min/1.73 $m^2$ for 3 to 6 months of age<br>≤ 50 mL/min/1.73 $m^2$ for 6 to12 months of age |
| X | | Clinically significant abnormalities in hematology or clinical chemistry parameters, as assessed by the Site Investigator, at screening that would render the patient unsuitable for inclusion |
| X | | Intractable epilepsy |
| X | X | Persistent (in the opinion of the Investigator) hypoxemia ($O_2$ saturation awake <92% or $O_2$ saturation asleep <91%, without ventilation support), |
| X | X | Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the screening period. |
| X | | Current diagnosis of cardiac and/or vascular abnormalities including uncontrolled hypertension, intolerance of blood pressure and pulse assessment techniques such that consistent normal values cannot be measured, echocardiographic abnormalities (both structural and function) or ECG abnormalities (such as long QT, heart block or Torsade's) indicating significant risk of safety for infant patients participating in the study such as: Concomitant clinically significant pediatric cardiac arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second or third degree AV block. Clinically significant findings identified by an echocardiogram performed at screening |
| X | X | Prohibited Concomitant Medications used to treat SMA: oral albuterol or oral salbutamol, hydroxurea, riluzole, valproate, carnitine, creatine, sodium phenylbutyrate within 14 days prior to enrollment or during the study. |
| X | | Excluding SMA, any medically unstable condition including cardiomyopathy, hepatic dysfunction, kidney disorder, endocrine disorder, GI disorders, metabolic disorders, severe respiratory compromise and significant brain abnormalities or injuries including hypoxic-ischemic encephalopathy. |

[redacted]

| Screening | Baseline | Criteria |
|---|---|---|
| X | | Acute or ongoing medical condition that, according to the Site Investigator and discussed with sponsor, would interfere with the conduct and assessments of the study. Examples are medical disability other than SMA that would interfere with the assessment of safety or would compromise the ability of the patient to undergo study procedures including be assessed by CHOP INTEND infant motor scale, changes in hematologic parameters or gastrointestinal dysfunction that would compromise the ability of adequate assessment of safety |

Note: In the case where a safety laboratory assessment at screening is outside of the range specified above, the assessment may be repeated once prior to dosing. If the repeat value remains outside of the specified ranges, the patient should not be dosed and may be excluded from the study after discussion between the principal investigator and the sponsor. In borderline situations, where the clinical relevance of the result is unclear, additional repetition of the assessment over a limited time frame may be considered.

#### 4.2.3 Part 3

There are no specific exclusion criteria.

# 5 Treatment

## 5.1 Study treatment

### 5.1.1 Investigational treatment

Details on the storage and management of study medication, instructions for dispensing, administering and return study treatment are outlined in the Pharmacy Manual. The investigational drug, branaplam, will be prepared by Novartis and supplied to the Investigator.

#### Storage

Branaplam is an oral solution and is provided in one dose strength: 3.5 mg/mL in 6 mL borosilicated glass, class 1, single use vials with a rubber stopper. Vials should be stored below 25°C, kept protected from light and not be frozen.

### 5.1.2 Treatment arms

#### Part 1:

14 patients have been enrolled into Part 1 in order to establish the MTD or determine with certainty that the MTD cannot be reached. All patients will be treated with branaplam with a weekly single dose. No new patients will be enrolled in Part 1.

[redacted]

**Table 5-1 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 patient with BSA of approximately 0.32 m$^2$.

**This table 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 patients in a new cohort.

## Part 2:

A total of 25 patients have been enrolled into Part 2 and assigned to either of the two doses, 0.625 mg/kg or 2.5 mg/kg, previously tested in Part 1 to further evaluate safety and tolerability and change over time in infant growth and motor parameters. All patients will be treated with branaplam.

Part 2 dose levels and regimens were decided from the data generated in Part 1. Actual dose levels and regimens will be confirmed in writing by Novartis and provided to all participating study sites before treatment of patients in Part 2.

In Part 2, dosing will be changed from dosing per m2 of body surface to per weight based dosing (mg/kg) in order to simplify study conduct by following a more common outpatient 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 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 6-2. The calculations were based on 13 patients 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 6-2, the calculated mg/kg doses were strongly correlated and increased linearly with the BSA normalized doses. Plasma exposure measured by AUC was dose-proportional up to 48 mg/m$^2$ with no additional increase in exposure at 60 mg/m$^2$. Thus, the 48 mg/m$^2$ value 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 5-3.

[redacted]

**Table 5-2 Dose conversion between BSA and weight for patients 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 5-3 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

In Part 3 subjects will be treated at doses that have already be assigned in Part 1 and Part 2 of the study until an optimal selected dose has been determined. However, if in the opinion of the investigator, a patient from Part 2, receiving 0.625 mg/kg experiences no further clinical improvement of the condition or even progression of disease, the dose may be increased to 2.5 mg/kg after consultation with the Sponsor. Similarly, if the investigator has any safety concerns for a patient receiving 2.5 mg/kg, the dose may be decreased to 0.625 mg/kg after consultation with the Sponsor.

**Table 5-4 Planned doses for Part 3**

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

## 5.2 Treating the patient

### 5.2.1 Preparation and dispensation

Branaplam will be administered to the patient via the following route of administration:

### Part 1:

- Enteral (via a feeding tube) during the initial treatment period of 13 weeks

[redacted]

- Either oral or enteral during the following extended treatment periods. The decision of the route of administration will be performed by the Investigator depending on the patient's ability to swallow.

Detailed information on how the transition from enteral to oral administration should be performed are given in the Site Operations Manual.

**Part 2:**

- Enteral (via a feeding tube) for the first administration on Day 1
- Either oral or enteral for the rest of the study. The decision of the route of administration will be performed by the Investigator depending on the patient's ability to swallow.

The option to administer branaplam orally may be reconsidered based on emerging PK data or if oral administration of the investigational drug is not tolerated by the patient following 2 consecutive attempts and as documented by the Acceptability and Palatability Questionnaire (see Table 7-3 and Section 7.5.1).

In Part 1 and Part 2 of the study branaplam may be administered at the study site, or at the patient's home by a qualified clinician or parent / legal guardian.

See the Site Operations Manual for further details. Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

**Part 3:**

- Similarly to Part 1 and Part 2 of the study, in Part 3 branaplam can be administered by oral or enteral application. The decision of the route of administration will be performed by the Investigator depending on the patient's ability to swallow.
- Patient will receive first dose at Visit 1 and continue weekly drug administration at home administrated by parents/caregivers or qualified personnel.
- At all of the visits where PK is collected the study drug administration should be performed at the site.
- Dispensation and return of study drug is described in Site Operations Manual

## 5.3 Other treatments

### 5.3.1 Concomitant therapy

All prescription medications including vaccinations, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

[redacted]

### 5.3.2 Prohibited medication

Except for medication which may be required to treat adverse events, and continuation of standard of care medications prescribed for SMA, no medication other than study drugs will be allowed from the first dosing until all of the Study Completion evaluations have been conducted.

Should a patient have an **incidental and limited** need for a medication to be taken within the restricted pre-dose timeframe (e.g. acetaminophen or ibuprofen, antibiotics, etc.), the sponsor should be advised, as administration of any concomitant medication *may* require the patient to be withdrawn. Administration of paracetamol/acetaminophen is acceptable, but must be documented

Uses of the treatments displayed in Table 5-5 is NOT allowed after screening:

**Table 5-5 Prohibited Chronic treatment for SMA**

| Medication |
|---|
| Other non-approved experimental therapy for the treatment of SMA |
| Oral albuterol or salbutamol (inhaled form is not prohibited) |
| Hydroxyurea |
| Riluzole |
| Valproate |
| Carnitine |
| Creatine |
| Sodium phenylbutyrate |

Such prohibited medications are postulated in some in-vitro studies as offering low levels of SMN splice modulation or alpha motor neuron cell survival benefits and could be considered confounding to this study; therefore, these drugs could interfere with assessment of study endpoints. The sponsor may consider removing the patient from study if prohibited medications are taken during the study. None of these are considered standard of care and are typically only used in experimental off-label use since none have been approved for SMA use. Note: Only if valproate is being used for a seizure disorder independently of treatment for SMA, this would not be considered prohibited.

As mentioned in Section 1.1, *in vitro* experiments showed that branaplam can be metabolized via CYP3A4 and glucuronidation. Therefore, there is a potential for inhibitors or inducers of CYP3A4 to alter the clearance of branaplam *in vivo* if oxidative metabolism is the major clearance pathway of branaplam. Branaplam should not be administered together with strong systemic inhibitors of CYP3A4 such as systemic boceprevir, clarithromycin, conivaptan, indinavir, itroconazole, ketoconazole, ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole or with strong systemic inducers such as carbamazepine, rifampin, phenytoin, St. John's Wort. Use of weak to moderate inhibitors of CYP3A4 should be avoided unless absolutely necessary.

Recent results indicated that branaplam showed a potential perpetrator risk on MATE2-K and OCT1 transporters (Section 1.1), which might alter the disposition of MATE2-K and OCT1 substrates. Therefore, co-administration should be avoided unless absolutely necessary or at

[redacted]

least caution should be taken when substrates of MATE2-K (evidence shown in clinics: fexofenadine, glycopyrronium, metformin) and OCT1 (clinical known substrates: cephalexin, dofetilde, pilsicainide, pindolol, procainamide, ranitidine, varenicline, umeclidinium, zidovudine) are co-administered.

The sponsor will remove the patient from study treatment if nusinersen is taken during the study as it would interfere with assessment of study endpoints.

### 5.3.3 Rescue medication

In general, medications used to treat specific signs and symptoms of SMA are acceptable as long as they are part of the standard of care and not listed in Table 5-1. Experimental treatments other than branaplam are not allowed. Use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies CRF after start of study drug.

### 5.3.4 Treatment blinding

This is an open-label study.

## 5.4 Dose escalation and dose modification

### 5.4.1 Dose escalation guidelines

The MTD is the highest drug dosage that is unlikely (<25% posterior probability) to cause DLT in more than 25% of the treated patients in the first 2 weeks of the LMI070 treatment.

A two-parameter Bayesian logistic regression model (BLRM) employing the escalation with overdose control (EWOC) principle (Neuenschwander et al 2008; Babb et al 1998) will be used during the dose escalation to guide dose level selection and to estimate the MTD. Dose escalation will continue until the MTD is reached or until Novartis and Investigators reach consensus that, based on a review of the totality of the clinical data (e.g., DLT, lower grade AE, PK, PD, etc.) there is no benefit to continue escalation.

Estimation of the MTD during the escalation part of the study will be based upon the estimation of the probability of DLT in the first 2 weeks in patients in the Dose-Determining Set (DDS). The corresponding statistical methodology is described in Section 11.4.2.

### 5.4.2 Definitions of dose limiting toxicities (DLTs)

A DLT is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant therapies that occurs within the first 14 days of treatment with LMI070 and meets any of the criteria listed in Table 5-6.

The National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) most recent version will be used for all grading. For the purpose of dose-escalation decisions, DLTs will be considered and included in the BLRM.

The investigator must notify Novartis immediately of any unexpected CTCAE grade $\geq 3$ adverse events or laboratory abnormalities. Prior to enrolling patients into a higher dose level, CTCAE grade $\geq 2$ adverse events will be reviewed for all patients at the current dose level.

[redacted]

### 5.4.3 Dose modifications

#### Part 1

For the purposes of dose escalation decisions, each cohort will consist of at least 2 newly enrolled patients who will be treated at the specified dose level, at least 24 hours apart. The first cohort will be treated with the starting dose of 6 mg/m$^2$. In cohorts being treated with doses ≥ 48 mg/m$^2$ up to a total of 5 patients will be initially treated. If more than five patients present at the same time, additional patients may be treated at the highest dose level deemed safe by Novartis and the DMC, in order to avoid unnecessary delays in treatment of this life-threatening disease.

Patients must complete the minimum safety evaluation at 2 weeks after the first dose or have had a DLT within the first 2 weeks after the first dose to be considered evaluable for dose escalation decisions. Dose escalation decisions will occur when the cohort of patients has met these criteria.

Dose escalation decisions will be made jointly by Investigators and Novartis study personnel. Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study, including safety information, DLTs, all CTCAE Grade ≥ 2 toxicity data during the 14 day DLT window and available PK data from evaluable patients. The recommended dose for the next cohort of patients will be guided by the Bayesian logistic regression model (BLRM) with escalation with overdose control (EWOC) principle.

The adaptive Bayesian methodology provides an estimate of all dose levels of LMI070 that do not exceed the MTD and incorporates all DLT information at all tested dose levels for this estimation. 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 see (Section 11.4.2). In all cases, the dose for the next cohort will not exceed a 100% increase from the previous dose. Smaller increases in dose may be recommended by the Investigators and Novartis upon consideration of all of the available clinical data. If needed to better define the dose-toxicity relationship additional patients may be enrolled to the current dose level, to a preceding dose level, or to an intermediate dose level before proceeding with further dose escalation.

If the first patient in previously untested dose level experiences a DLT during the first 2 weeks, enrollment to that cohort will stop, the BLRM will be updated and the next cohort will be opened at the next lower level or an intermediate dose level that is recommended and satisfied the EWOC criteria.

Enrollment will continue until at least 8 evaluable patients in Part 1 have provided DLT information during the first 2 weeks after the first dose. MTD will be identified based on recommendation of the model and review of all clinical data by Novartis and Investigators in a dose-escalation teleconference. MTD will not be declared as higher than the maximum dose level tested in Part 1 patients.

If a decision is made to escalate to a higher dose level but one or more additional patient(s) treated at the preceding dose level experiences a DLT during the first 2 weeks after the first

[redacted]

dose, then the BLRM will be updated with this new information before any additional patients are treated at that higher dose level. Patients ongoing will continue treatment at their assigned dose levels.

**Part 2**

In order to ensure patient safety, a dose increase for cohort 1 patients to the next level dose (2.5 mg/kg) will be allowed if there is lack of efficacy/progressive disease at the 0.625 mg/kg dose.

The following criteria will be applied to define lack of efficacy/progressive disease:

Loss of previously obtained motor skills after baseline of at least two points on the HINE Section 2, excluding voluntary grasp and/or more of five points on the CHOP-INTEND scales for two consecutive assessments. On the other hand, if decline of assessment occurred during an acute illness episode this would not be considered a loss of effect. Pulmonary events or loss of feeding will not be considered as loss of effect since these will not be distinguishable for normal disease progression without efficacy.

Decision to increase the dose for individual cohort 1 patients will be made jointly by Investigators, Novartis study personnel and DMC. Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study, including safety information, available PK data from evaluable patients, CHOP INTEND and HINE scores.

**Part 3**

In Part 3 patients will be treated at doses that have already be assigned in Part 1 and Part 2 of the study. However, if a patient from Part 2, receiving 0.625 mg/kg experiences no further clinical improvement of the condition or even disease progression, the dose might be increased to 2.5 mg/kg. This dose increase is at the discretion of investigator and after consultation with the sponsor. Likewise, in case of any safety concern, patients who are receiving 2.5 mg/kg could have their dose decreased to 0.625 mg/kg, at the discretion of the investigator and after consultation with the sponsor. After the 52-weeks analysis for Part 2, a comparison of the two doses showed 2.5 mg/kg to have numerically better changes in HINE-2 scores compared to 0.625 mg/kg following one year of treatment, and with comparable safety profiles. In addition, SMN mRNA analysis shows a trend for dose-dependent effects, with more target engagement favoring the 2.5 mg/kg dose. Thus, it is expected that the higher dose will maximize the potential long-term benefit which participating patients may be switched to as a selected optimal dose. After dose of 2.5 mg/kg was selected to be used as the treatment dose in Part 3, investigators from study sites were prompted to have all patients transition to this new dose, unless there are safety concerns or this change in dose is not in the best interest of the patient.

### 5.4.4 Implementation of dose escalation decisions

To implement dose escalation decisions, the available toxicity information (including adverse events and laboratory abnormalities that are not DLTs), the recommendations from the BLRM (Part 1 only), and the available PK and PD information will all be evaluated by the Investigators and Novartis study personnel (including the study physician and statistician) during a dose decision meeting by teleconference. The meeting will, at least, be composed of all investigators

[redacted]

who have included patients in the cohort for evaluation and a representative of the sponsor. The final dose escalation decisions will be made between the sponsor and the study investigators. Drug administration at the next higher dose level may not proceed until the investigator receives written confirmation from Novartis indicating that the results of the previous dose level were evaluated and that it is permissible to proceed to a higher dose level.

### 5.4.5 Intra-patient dose escalation

#### Part 1

Enrolled patients who tolerate the assigned doses of branaplam and continue to extended treatment *may* be escalated to a higher dose once this higher dose has been deemed safe in other patients as determined by BLRM with EWOC. This decision will be made on a patient by patient basis based on PK accumulation data from that patient, review of all available safety data, and PD response. Each time the dose will be escalated for a patient, a new cycle will have to be started again as described in Table 7-2.

Data at the new dose level will not be formally included in the statistical model describing the relationship between dose and occurrence of DLT. However, these data will be incorporated into the clinical assessment of safety when escalation to a new dose level is considered for the study.

Whenever a patient experiences a DLT, treatment with the study drug will be interrupted and the toxicity will be followed up as described in Section 5.4.6.

**Table 5-6 Criteria for defining dose-limiting toxicities during dose escalation – Part 1**

| TOXICITY | DLT CRITERIA |
|---|---|
| Blood and lymphatic system disorders | Anemia CTCAE Grade ≥ 3 |
| | Neutrophil count CTCAE Grade ≥ 4 |
| | Febrile neutropenia CTCAE Grade ≥ 3 |
| | Platelet count CTCAE Grade 3 or Grade 2 accompanied by clinically significant bleeding<br>Platelet count CTCAE Grade ≥ 4 |
| Gastrointestinal disorders | Diarrhea CTCAE Grade 3 ≥ 72 hrs., or dehydration > 5% requiring therapy<br>Diarrhea CTCAE Grade 4, |
| | Vomiting CTCAE Grade 3 ≥ 72 hrs., despite the use of anti-emetic therapy<br>Vomiting CTCAE Grade 4, despite the use of anti-emetic therapy |
| | Evidence of oral, peri-anal or gastric mucositis characterized by the presence of ≥ 2 of the following within 1 week;<br>Diarrhea CTCAE Grade 3 ≥ 48 hrs.<br>Vomiting CTCAE Grade 3 ≥ 48 hrs., despite the use of anti-emetic therapy<br>Ulceration CTCAE Grade 2 ≥ 48 hours<br>Haemorrhaging CTCAE Grade 2 ≥ 48 hours |

| TOXICITY | DLT CRITERIA |
|---|---|
| Investigations | Bilirubin[a] CTCAE Grade 2 for > 7 consecutive days<br>Bilirubin[a] CTCAE Grade ≥ 3 |
| | AST or ALT ≥3 ULN in conjunction with blood bilirubin ≥ 2 x ULN of any duration<br>AST or ALT ≥ 5 x ULN in conjunction with blood bilirubin ≥ 2 x ULN of any duration, for patients with elevated AST, ALT, or blood bilirubin at baseline |
| | AST or ALT CTCAE Grade 3 for > 7 consecutive days<br>AST or ALT CTCAE Grade 4 |
| | Serum alkaline phosphatase CTCAE Grade 4 > 7 consecutive days |
| | Serum Creatinine Grade 2 for more than 7 days<br>Serum Creatinine Grade ≥ 3 |
| | Serum lipase and/or serum amylase CTCAE Grade 3 > 7 consecutive days with clinical signs or symptoms of pancreatitis<br>Serum lipase and/or serum amylase (symptomatic and asymptomatic) CTCAE Grade 4 |
| Other toxicities | Any other CTCAE Grade ≥ 3 toxicity except:<br>An AE must be clinically significant to be defined as DLT: lymphopenia, study drug-related fever and electrolyte abnormalities (including K, Na, Cl, HCO3, Mg, Ca, PO4) that are ≤ CTCAE grade 3 abnormalities will not be considered a DLT unless clinically significant. Single incident of allergy to study drug will not be defined as DLT |
| | Any adverse event or serious adverse event that is suspected to be related to the study drug per investigator assessment and which leads to a temporary interruption of treatment with study drug for more than 14 consecutive days from the day of the first missed dose. |
| [a]An increase of indirect (unconjugated) bilirubin indicative of M. Meulengracht/Gilbert's syndrome is not considered a DLT | |

Patients may receive supportive care as per local institutional guidelines. Optimal therapy for vomiting or diarrhea will be based on institutional guidelines, with consideration of the prohibited medications listed in this protocol.

When there is ambiguity about whether an AE is related to the underlying disease as opposed to the study drug, the most conservative approach will be taken and the AE will be considered as study drug related.

### 5.4.6 Follow up for toxicities

For patients who do not tolerate the protocol-specified dosing schedule due to drug related toxicities, temporary dose interruptions are permitted.

If the patient has experienced evidence of clinical benefit and in the opinion of the investigator it is in the best interest of the patient to remain on study, then following discussion and agreement with the sponsor, the patient may continue on study treatment.

The guidelines in Table 5-5 should be applied. Novartis study team can at all times during the study ask the investigator to discontinue the treatment, also for reasons not specified in the

Table 5-5. For example, in case emerging PK data for an individual patient is showing higher exposure than anticipated, the investigator could be asked by Novartis study team to lower the dose, even if no toxicity has been observed. Any dose modification must be recorded on the Dosage Administration Record CRF.

The below guidance for interruption of study treatment is applicable when there is no clear clinical explanation for the toxicity other than possibly due to study treatment. It may not necessarily apply to abnormalities assessed by the Investigator as associated predominantly with the underlying disease or intercurrent illness. Such cases should be discussed with the Novartis medical team.

**Table 5-7 Criteria for interruption and re-initiation of branaplam treatment for AE possibly related to study medication**

| | |
|---|---|
| Worst toxicity CTCAE Grade[a] | 7 days post dose administration (including day of administration) |
| **Blood and lymphatic system disorders** | |
| **Anaemia** | |
| Grade 1 | Maintain dose |
| Grade 2 or higher | Suspend dose until resolved to Grade ≤ 1 or baseline<br>If not resolved after 14 days then discontinue of study treatment |
| **Neutropenia (ANC)** | |
| Grade 1 | Maintain dose |
| Grade 2 | Maintain dose |
| Grade 3 and Grade 4 | Suspend dose until resolved to Grade ≤ 1 or baseline<br>If not resolved after 14 days then discontinue of study treatment |
| Febrile neutropenia | |
| Grade 3 | Suspend dose until resolved<br>If not resolved after 14 days then permanently discontinue of study treatment |
| Grade 4 | Suspend dose and discontinue of study treatment |
| Thrombocytopenia | |
| Grade 1 | Maintain dose |
| Grade 2 or higher | Suspend dose until resolved to Grade ≤1 or baseline<br>If not resolved after 21 days , then permanently discontinue of study treatment |
| Thrombocytosis | |
| Grade 1, no evidence of clinical thrombosis and platelet counts < 1,000K | Maintain dose and current monitoring plan |

[redacted]

| | |
|---|---|
| | |
| Grade 2, no evidence of clinical thrombosis and platelet count ≥ 1,000K | Suspend dose until resolved to Grade ≤1 or baseline<br>If not resolved by 14 days, then obtain hematology consultation<br>If not resolved after 21 days, then permanently discontinue study treatment |
| Grade 3 or Grade 4, evidence of clinical thrombosis event | Suspend dose and permanently discontinue patient from study treatment |
| Investigations | |
| Serum creatinine | |
| Grade 1 | Maintain dose |
| Grade 2 | Suspend dose until resolved to Grade ≤1 or baseline<br>If not resolved after 21 days, this discontinue of study treatment |
| Grade 3 or Grade 4 | Suspend dose and permanently discontinue patient from study treatment |
| Bilirubin[b] | |
| Grade 1 | Maintain dose |
| Grade 2 | Suspend dose until resolved to Grade ≤ 1 or baseline<br>If not resolved after 21 days then discontinue of study treatment |
| Grade 3 | Suspend dose until resolved to Grade ≤ 1 or baseline, then: |
| Grade 4 | Suspend dose and discontinue patient from study treatment |
| AST or ALT | |
| Grade 1 | Maintain dose |
| Grade 2 and bilirubin < CTCAE grade 2 | Maintain dose |
| Grade 2 and bilirubin ≥ CTCAE grade 2 | Suspend dose until resolved to Grade ≤ 1 or baseline<br>If not resolved after 21 days , then discontinue of study treatment |
| Grade 3 | Suspend dose until resolved to Grade ≤ 1 or baseline<br>If not resolved after 21 days, then discontinue of study treatment |
| Grade 4 | Suspend dose and discontinue patient from study treatment |
| Amylase and/or lipase elevation | |
| Grade 1 | Maintain dose |
| Grade 2 | Maintain dose |
| Grade 3 with clinical signs or symptoms of pancreatitis | Suspend dose until resolved to ≤ Grade 2, then: |
| Grade 4 | Suspend dose and discontinue patient from study treatment |
| Gastro intestinal disorders | |
| Vomiting | |
| Grade 1 | Maintain dose |
| Grade 2 | Maintain dose |

[redacted]

| | |
|---|---|
| | |
| Grade 3 | Suspend dose (only if vomiting cannot be controlled with optimal anti-emetic treatments) until resolved to Grade ≤ 1<br>If not resolved after 14 days, then discontinue of study treatment |
| Grade 4 | Suspend dose and discontinue patient from study treatment |
| Diarrhea | |
| Grade 1 or 2 | Maintain dose |
| Grade 2 | Suspend dose (only if diarrhea cannot be controlled with optimal anti-diarrhea treatments) until resolved to ≤ Grade 1<br>If not resolved after 14 days, then discontinue of study treatment |
| Grade 3 | Suspend dose (only if diarrhea cannot be controlled with optimal anti-diarrhea therapy) until resolved to Grade ≤ 1<br>If not resolved after 14 days, then discontinue of study treatment |
| Grade 4 | Suspend dose and discontinue patient from study treatment |
| Ulceration | |
| Grade 1 | Maintain dose |
| Grade 2 | Suspend dose until resolved to Grade ≤ 1, then<br>If not resolved after 21 days , then discontinue of study treatment |
| Grade 3 or Grade 4 | Suspend dose and permanently discontinue patient from study treatment |
| Hemorrhage | |
| Grade 1 | Maintain dose |
| Grade 2 | Suspend dose until resolved to Grade ≤ 1<br>If not resolved after 21 days , then permanently discontinue of study treatment |
| Grade 3 or Grade 4 | Suspend dose and permanently discontinue patient from study treatment |
| Cardiac Disorders | |
| Clinically significant increase in cardiac enzymes (Troponin and NTproBNP) | Recommendation: Repeat test within 1 week. If it remains elevated get pediatric cardiology consult, perform echocardiogram and ECG if not already done. Continuing study treatment should be done in consultation with a pediatric cardiologist. Manage per standard of care. Continue checking Troponin/NTproBNP levels at a frequency determined by the cardiologist and investigator until resolution. |
| Grade 1 | Maintain dose |
| Asymptomatic Grade 2 | Maintain dose |
| Symptomatic Grade 2 | Suspend dose until resolved to Grade ≤ 1 or baseline<br>If not resolved after 21 days, then permanently discontinue of study treatment |
| Symptomatic Grade 3 with history of asymptomatic grade 2 | Suspend dose until resolved to ≤ Grade 1 or baseline<br>If not resolved after 21 days, then permanently discontinue of study treatment |

[redacted]

| | |
|---|---|
| Grade 3 – if Grade 2 was symptomatic | Suspend dose and permanently discontinue patient from study treatment |
| Grade 4 | Suspend dose and discontinue permanently patient from study treatment |
| Hypertension | |
| Grade 1 | Maintain dose |
| Grade 2 | Suspend dose until resolved to Grade ≤ 1 or baseline (with or without HTN monotherapy)<br>If not resolved with 21 days, then permanently discontinue of study treatment |
| Grade 3 | Suspend dose until resolved to ≤ Grade 2, (with or without HTN monotherapy),<br>If two agents required for control, Suspend dose and discontinue patient from study treatment |
| Grade 4 | Suspend dose and permanently discontinue patient from study treatment |
| Other adverse events | |
| Grade 1 or 2 | Maintain dose |
| Grade 3 | Suspend dose until resolved to Grade ≤ 1 or baseline, then↓ 1 dose level |
| Grade 4 | Suspend dose and discontinue permanently patient from study drug treatment |
| [a] Common Toxicity Criteria for Adverse Events ( most current version of the CTCAE dictionnary.0)<br>[b] An increase of indirect (unconjugated) bilirubin in the absence of transaminase increase, indicative of M. Meulengracht/Gilbert's syndrome, is considered a reason to permanently discontinue the study medication. | |

In the event of several organs being affected with any grade of AE, and with the AE being possibly drug related, then the study medication should be either discontinued until resolution to baseline or permanently discontinued. The decision must be made by the site investigator, in consultation with the Sponsor and independent DMC.

All grade 4 AEs regardless of causality will result in the study medication being permanently discontinued.

For all grade 1 to 3 AEs that are non-related to the study medication, the decision to discontinue the study treatment is at the discretion of the investigator.

### 5.4.7 Within-patient dose escalation

In Part 2 and Part 3 of the study no intra-patient dose escalation was planned. However, the potential loss of a positive effect over time of the starting dose may occur. Loss of effect is defined as loss of previously obtained motor skills from baseline, independent of ventilation of at least 2 points on the HINE Section 2, excluding voluntary grasp and/or more of five points on the CHOP-INTEND scale for two consecutive assessments. On the other hand, if decline of assessment occurred during an acute illness episode this would not be considered a loss of effect.

[redacted]

Pulmonary events or loss of feeding will not be considered as loss of effect since these will not be distinguishable for normal disease progression without efficacy.

After the 52-weeks analysis for Part 2, a comparison of the two doses showed 2.5 mg/kg to have numerically better changes in HINE-2 scores compared to 0.625 mg/kg following one year of treatment, and with comparable safety profiles. It is expected that the higher dose (2.5mg/kg) will maximize the potential long-term benefit which participating patients may be switched to as a selected optimal dose in Part 3 of the study.

The decisions will be made jointly by the investigator and Sponsor, with consultation by the independent DMC.

## 5.5 Treatment assignment

### Part 1

In Part 1, treatment numbers will be assigned in ascending, sequential order to eligible patients (see Site Operations Manual for details). The investigator will enter the treatment number on the eCRF.

### Part 2

In Part 2, treatment numbers will be assigned in ascending, sequential order to eligible patients (see Site Operations Manual for details). The investigator will enter the treatment number on the eCRF. Once assigned to a patient, a treatment number will not be reused.

The treatment number becomes the definitive patient number as soon as a patient receives the first dose of the respective dosing regimen.

There should be a source document maintained at the site which links the screening number to the treatment number (once assigned). This source document should be provided to all appropriate parties (i.e. Central Laboratory, ECG Laboratory) as soon as this is available.

Patients who are withdrawn from the study before having completed the first 13 weeks of treatment for reasons unrelated to branaplam may be replaced by an equal number of newly enrolled patients.

### Part 3

In part 3, patients will remain with study numbers already assigned in Part 1 and Part 2 of the study.

## 5.6 Additional treatment guidance

### 5.6.1 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all patients treated with branaplam.

Compliance will be inherent as patients will be dosed by medical staff in the clinic.

[redacted]

### 5.6.2 Recommended treatment of adverse events

All complications of SMA should be treated by the attending physician according to local standard of care and treatment guidelines. Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

### 5.6.3 Emergency breaking of assigned treatment code

Not applicable.

## 5.7 Restrictions for Study Patients

During recruitment, screening/informed consent review, and baseline visit, the patient's parent or guardian must be informed and reminded of the following restrictions:

### 5.7.1 Dietary restrictions

Patients will be treated with typical age-appropriate nutrition, each patient will be fed per direction of pediatric standards of care. Feeding tube or gastrostomy tube may also be used to provide supplemental nutrition.

- In order to ensure hydration for urine collection, patients should be encouraged to have adequate fluid intake throughout the day.

A normal feeding schedule should be followed for patients. However, at least one hour should be allowed between dosing with branaplam and feeding (before and after dosing), in order to avoid complications such as gastroesophageal reflux, which could interfere with the dose administration. Reflux precautions must be implemented post-dosing and post-feeding per local institutional standards.

### 5.7.2 General restrictions

Special handling instructions are required for branaplam as described in the most recent Instruction for administration of LMI/branaplam for phase I/II investigational human use.

## 5.8 Preparation and dispensation

Preparation, dispensation and return of study drug was described in Section 5.1 and Section 5.2 of the protocol.

# 6 Informed consent procedures

Eligible participants may only be included in the study after a legally acceptable representative(s) or parent of the participant has provided (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

Site investigators will have detailed discussions about the purpose of this clinical trial to ensure there are realistic expectations from participating in this study.

[redacted]

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

[redacted]

# 7 Visit schedule and assessments

The Assessment Schedules below list all of the assessments for each part of the study when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedules or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue from study treatment are to return for the end of treatment visit as soon as possible, as indicated in the Assessment Schedules.

Participants who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the CRF.

The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

As per Section 3.9, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the patient´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the patient to visit the site again.

## Table 7-1 Assessment Schedule – Part 1 – Initial treatment period (Day -14 to Day 85)

| | Screening | Baseline | Baseline Cont. | Treatment Period 1 | | | | | | | | | | Treatment Period 2 | | | | | | | | | | EOS[6,7] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Visit Numbers (internal use only)*[1] | *1* | *2* | *3* | *4* | | | | | *5* | *6* | *7* | *8* | *9* | *10* | *11* | *12* | *13* | *14* | *15* | *16* | *17* | *18* | *19* | *777* |
| Day | D -14 to -8 | D -7 to -3 | D-2 to -1 | 1 | | | | | 2 | 3 | 5 | 8 | 15 | 22 | 29 | 36 | 43 | 50 | 57 | 64 | 71 | 78 | 85 | - |
| Week | - | - | - | 1 | | | | | | | | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | - |
| Time (h) | - | - | - | 0 | 1 | 2 | 4 | 8 | 24 | 48 | 96 | 168 | - | - | - | - | - | - | - | - | - | - | - | - |
| Obtain informed consent | X | | | | | | | | | | | | | | | | | | | | | | | |
| Inclusion /Exclusion criteria | X | X | | | | | | | | | | | | | | | | | | | | | | |
| Relevant med history / current medical conditions | X | | | | | | | | | | | | | | | | | | | | | | | |
| SMN2 copy number[3] | X[3] | | | | | | | | | | | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | | | | | | | | | | |
| Physical examination | X | | | X | | | | | | | | X | X | X | X[4] | X | X | X | X[4] | X | X | X | X[4] | X[2] |
| Hepatitis and HIV screen | X | | | | | | | | | | | | | | | | | | | | | | | |
| Drug administration | | | | X | | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | |
| **Vital signs and body measurements** | | | | | | | | | | | | | | | | | | | | | | | | |
| Body weight/ Body length/ BSA | X | | | X | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X[2] |
| Head & Chest Circumference | X | | | X | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X[2] |
| Body temperature | X | | | X | | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[2] |
| Blood pressure / Pulse rate/ Respiratory rate | X | | | X | | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[2] |
| ECG evaluation | X | | | | | X | | | | | | X | | | | | | | | | | | X | X[2] |
| Echocardiogram | X | | | | | | | | | | | | | | X | | | | X | | | X | | X[2] |
| Hematology, Blood chemistry, Urinalysis | X | | X | | | | | | | X | | X | X | | X | | X | | X | | X | | X | X[2] |
| Ophthalmologic examination | | X | | | | | | | | | | | | | | | | | | | | X | | X[2] |
| CHOP-INTEND (SMA type I infant motor scale) | | | X | | | | | | | | | | | | | X | | | | | | | X | X[2] |
| **Respiratory function** | | | | | | | | | | | | | | | | | | | | | | | | |
| Pulse Oximetry | | | X | | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X[2] |
| Paradoxical Breathing | | | X | | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X[2] |
| Breathing pattern: chest circumference during quiet breathing (sleep) | | | X | | | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X[2] |
| Ulnar compound motor action amplitude potential (CMAP) | | X | | | | | | | | | | | | | | | | | | | | | X | X[2] |
| | | | | | | | | | | | | | | | | | | | | | | | | |
| mRNA blood collection | | X | | | | | | | | | | | | | | | | | | | | | X | X[2] |
| PK blood collection | | | | X | X | X | X | X | X | X | X | X | | | X | | X | | | | | | | |
| Videotaping of motor activities[5] | As required[8] | | | | | | | | | | | | | | | | | | | | | | | |
| Adverse Events | As required | | | | | | | | | | | | | | | | | | | | | | | |
| Concomitant meds/Therapies | As required | | | | | | | | | | | | | | | | | | | | | | | |
| Study completion information | | | | | | | | | | | | | | | | | | | | | | | | X[2] |

## Additional instructions on Part 1 assessment schedule:

[1] Visit structure given for internal programming purposes only

[2] To be completed where possible based on completion/discontinuation status

[3] Unless already obtained at point of diagnosis. Must be clearly documented in source notes

[4] Detailed neurologic examination must be performed at least monthly (and more often if deemed necessary by the investigator)

[5] Optional - Informed Consent must be obtained before this assessment

[6] For all patients, the end of Study must be completed 30 days after **last** study drug administration.

[7] if patients continue in the extended treatment period then assessment schedule as per Table 8-2 should be followed.

[8] up to the discretion of the investigator or parents/guardians

[redacted]

## Table 7-2 Assessment Schedule – Part 1 – Extended treatment period

| | Treatment Period | | | | | | | | | | | | | | | EOS[9] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Visit Numbers (internal use only)* [1] | *20* | | *21* | *22* | *24* | *25* | *26* | *27* | *28* | *29* | *30* | *31* | *32* | *33* | *34* | *35* | *777* |
| **Day** | 92 | | 93 | 94 | 99 | 106 | 113 | 120 | 127 | 134 | 141 | 148 | 155 | 162 | 169 | 176 | - |
| **Week** | 14 | | | | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | - |
| **Time (h)** | 0 | 4 | 24 | 48 | 168 | - | - | - | - | - | - | - | - | - | - | - | - |
| Current medical conditions | As required | | | | | | | | | | | | | | | | |
| Drug administration[2] | X | | | | X | X[2] | X[2] | X | X | X[2] | X[2] | X | X[2] | X[2] | X | X | |
| Acceptability and Palatibility Questionnaire[3] | X | | | | X | X | | | | | | | | | | | |
| **Safety** | | | | | | | | | | | | | | | | | |
| Physical examination[4] | | | | | | | | X | | | | X | | | | X | X |
| Body weight/ Body length | | | | | | | | X | | | | X | | | | X | X |
| Head & Chest Circumference | | | | | | | | X | | | | X | | | | X | X |
| Body temperature | | | | | | | | X | | | | X | | | | X | X |
| Blood pressure / Pulse rate/ Respiratory rate | | | | | | | | X | | | | X | | | | X | X |
| ECG evaluation | | | | | | | | | | | | | | | | X | X |
| Echocardiogram[5] | | | | | | | X | X | | | X | X | | | X | | X |
| Hematology, Blood chemistry, Urine analysis | | | | | | | | X | | | | X | | | | X | X |
| Nerve conduction study [12] | | | | | | | | | | | | | | | | X | X |
| Ophthalmologic examination [10] | | | | | | | | | | | | | | | X | | X |
| Adverse Events | As required | | | | | | | | | | | | | | | | |
| Concomitant meds/Therapies | As required | | | | | | | | | | | | | | | | |
| **Pharmacodynamics** | | | | | | | | | | | | | | | | | |
| CHOP INTEND (SMA type I infant motor scale) [11] | | | | | | | | | X | | | | | | | X | X |
| Speech and motor milestones | | | | | | | | | X | | | | | | | X | X |
| HINE (Hammersmith Infant Neurological Examination) | | | | | | | | | X | | | | | | | X | X |
| Videotaping of motor activities[6] | As required[7] | | | | | | | | | | | | | | | | |
| **Respiratory function** | | | | | | | | | | | | | | | | | |
| Pulse Oximetry | | | | | | | | X | | | | X | | | | X | X |
| Paradoxical Breathing | | | | | | | | X | | | | X | | | | X | X |
| Breathing pattern: chest circumference during quiet breathing (sleep) | | | | | | | | X | | | | X | | | | X | X |
| **Other assessments** | | | | | | | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | | | | | |
| PK blood collection [redacted] | X | X | X | X | X | | | | | | | | | | | | |

[redacted]

## Additional instructions on Part 1 Extended assessment schedule:

[1] Visit structure given for internal programming purposes only and indicated for the second treatment cycle only. For following cycles the visit numbering should be done sequentially

[2] Administration may be done in the patient's home by a qualified clinician or by the assigned and trained caregivers .

[3] Questionnaire to be completed **ONLY** when LMI070 is administered orally

[4] Detailed neurologic examination must be performed at least monthly (and more often if deemed necessary by the investigator)

[5] If a Grade 2 systolic function AE occurs, echocardiograms will be performed monthly until resolution or until the treatment is withdrawn. Otherwise echocardiograms are to be performed every 3 months.

[6] Optional - Informed Consent must be obtained before this assessment

[7] Up to the discretion of the investigator or parents/guardians

[8] Sampling to be performed only once every other period in the extended treatment phase if the route of administration and the dose level are unchanged.

[9] For all patients, the end of Study must be completed 30 days after **last** study drug administration. For patients continuing in the extended treatment period a new cycle will start, without performing the end of study visit.

[10] if there are no adverse changes detected at both Week 12 and Week 25 visits that can be attributed to branaplam and the branaplam dose is unchanged, then the examination will be performed yearly

[11] The CHOP-INTEND will not be collected for patient older than 3 years old

[12] If the patient experience an acute illness episode , these assessments should be performed at a subsequent visit at the discretion of the investigator

[redacted]

**Table 7-3 Assessment Schedule – Part 2**

## Treatment period 1

| | Screening | Baseline | Baseline Cont. | Treatment Period 1 | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Visit Numbers (internal use only)* | *1* | *2* | *3* | *4* | | | | | *5* | *6* | *8* | *9* | *10* | *11* | *12* | *13* | *14* | *15* | *16* | *17* | *18* | *19* |
| **Day** | **D -14 to -8** | **D -7 to -3** | **D-2 to -1** | **1** | | | | | **2** | **3** | **8** | **15** | **22** | **29** | **36** | **43** | **50** | **57** | **64** | **71** | **78** | **85** |
| **Week** | - | - | - | 1 | | | | | | | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| **Time (h)** | - | - | - | 0 | 1 | 2 | 4 | 8 | 24 | 48 | 168 | - | - | - | - | - | - | - | - | - | - | - |
| Obtain informed consent | X | | | | | | | | | | | | | | | | | | | | | |
| Inclusion /Exclusion criteria | X | X | | | | | | | | | | | | | | | | | | | | |
| Relevant med history / current medical conditions | X | | | | | | | | | | | | | | | | | | | | | |
| SMN2 copy number[1] | X[1] | | | | | | | | | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | | | | | | | | |
| Hepatitis and HIV screen | X | | | | | | | | | | | | | | | | | | | | | |
| Drug administration[2] | | | | X | | | | | | | X | X | X | X | X | X[2] | X[2] | X | X[2] | X[2] | X | X |
| Acceptability and Palatibility Questionnaire[3] | | | | | | | | | | | X | X | X | | | | | | | | | |
| **Safety** | | | | | | | | | | | | | | | | | | | | | | |
| Physical examination | X[4] | | | X[4] | | | | | | | X | | | X[4] | | | | X[4] | | | | X[4] |
| Body weight/ Body length | X | | | X | | | | | | | X | | | X | | | | X | | | | X |
| Head & Chest Circumference | X | | | X | | | | | | | X | | | X | | | | X | | | | X |
| Body temperature | X | | | X | | X | | | X | X | X | | | X | | | | X | | | | X |
| Blood pressure / Pulse rate/ Respiratory rate | X | | | X | | X | | | X | X | X | | | X | | | | X | | | | X |
| ECG evaluation | X | | | | | X | | | | | X | | | | | | | | | | | X |
| Echocardiogram | X | | | | | | | | | | | | | X | | | | X | | | X | |
| Hematology, Blood chemistry, Urine analysis | X | | X | | | | | | | X | X | | | X | | | | X | | | | X |
| Nerve conduction study[7] | | X | | | | | | | | | | | | | | | | | | | | X |
| Ophthalmologic examination | | X | | | | | | | | | | | | | | | | | | | X | |
| Adverse Events | As required | | | | | | | | | | | | | | | | | | | | | |
| Concomitant meds/Therapies | As required | | | | | | | | | | | | | | | | | | | | | |
| **Motor Scales** | | | | | | | | | | | | | | | | | | | | | | |
| CHOP INTEND (SMA type I infant motor scale)[7] | | | X | | | | | | | | | | | | X | | | | | | | X |
| Speech and motor milestones[7] | | | X | | | | | | | | | | | | | | | | | | | X |
| HINE (Hammersmith Infant Neurological Examination)[7] | | | X | | | | | | | | | | | | X | | | | | | | X |
| Videotaping of motor activities[5] | | As required[5] | | | | | | | | | | | | | | | | | | | | |
| **Respiratory function** | | | | | | | | | | | | | | | | | | | | | | |
| Pulse Oximetry | | | X | | | | | | | | X | | | X | | | | X | | | | X |
| Paradoxical Breathing | | | X | | | | | | | | X | | | X | | | | X | | | | X |
| Breathing pattern: chest circumference during quiet breathing (sleep) | | | X | | | | | | | | X | | | X | | | | X | | | | X |
| **Other assessments** | | | | | | | | | | | | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | | | | | | | | | | |
| PK blood collection [redacted] | | | | X | X | X | X | X | X | X | X | | | X | | | | X | | | | |

[redacted]

## Additional instructions on Part 2, Treatment Period 1 assessment schedule:

[1] Unless already obtained at point of diagnosis. Must be clearly documented in source notes
[2] Administration is allowed in the patient's home by a qualified clinician.
[3] Questionnaire to be completed ONLY when LMI070 is administered orally
[4] Detailed neurologic examination must be performed at least monthly (and more often if deemed necessary by the investigator)
[5] Optional - Informed Consent must be obtained before this assessment-up to the discretion of the investigator or parents/guardians
[7] If the patient experience an acute illness episode , these assessment should be performed at a subsequent visit at the discretion of the investigator

[redacted]

## Treatment period 2

| | Treatment Period 2 | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Visit Numbers (internal use only)* | *20* | | *21* | *22* | *24* | *25* | *26* | *27* | *28* | *29* | *30* | *31* | *32* | *33* | *34* | *35* |
| **Day** | **92** | | **93** | **94** | **99** | **106** | **113** | **120** | **127** | **134** | **141** | **148** | **155** | **162** | **169** | **176** |
| **Week** | 14 | | | | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 |
| **Time (h)** | 0 | 4 | 24 | 48 | 168 | - | - | - | - | - | - | - | - | - | - | - |
| Current medical conditions | As required | | | | | | | | | | | | | | | |
| Drug administration[1] | X | | | | X | X[1] | X | X | X | X[1] | X[1] | X | X[1] | X[1] | X | X |
| Acceptability and Palatibility Questionnaire[2] | X | | | | X | X | | | | | | | | | | |
| **Safety** | | | | | | | | | | | | | | | | |
| Physical examination[3] | | | | | | | | X | | | | X | | | | X |
| Body weight/ Body length | | | | | | | | X | | | | X | | | | X |
| Head & Chest Circumference | | | | | | | | X | | | | X | | | | X |
| Body temperature | | | | | | | | X | | | | X | | | | X |
| Blood pressure / Pulse rate/ Respiratory rate | | | | | | | | X | | | | X | | | | X |
| ECG evaluation | | | | | | | X | | | | | | | | | X |
| Echocardiogram[4] | | | | | | | X | | | | X | X | | | X | |
| Hematology, Blood chemistry, Urine analysis | | | | | | | | X | | | | X | | | | X |
| Nerve conduction study [7] | | | | | | | | | | | | | | | | X |
| Ophthalmologic examination | | | | | | | | | | | | | | | X | |
| Adverse Events | As required | | | | | | | | | | | | | | | |
| Concomitant meds/Therapies | As required | | | | | | | | | | | | | | | |
| **Motor Scales** | | | | | | | | | | | | | | | | |
| CHOP INTEND (SMA type I infant motor scale) [7] | | | | | | | | | X | | | | | | | X |
| Speech and motor milestones [7] | | | | | | | | | X | | | | | | | X |
| HINE (Hammersmith Infant Neurological Examination) [7] | | | | | | | | | X | | | | | | | X |
| Videotaping of motor activities[5] | As required[6] | | | | | | | | | | | | | | | |
| **Respiratory function** | | | | | | | | | | | | | | | | |
| Pulse Oximetry | | | | | | | | X | | | | X | | | | X |
| Paradoxical Breathing | | | | | | | | X | | | | X | | | | X |
| Breathing pattern: chest circumference during quiet breathing (sleep) | | | | | | | | X | | | | X | | | | X |
| **Other assessments** | | | | | | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | | | | |
| PK blood collection [redacted] | X | X | X | X | X | | | | | | | | | | | |

[redacted]

**Additional instructions on Part 2, Treatment Period 2 assessment schedule:**

[1] Administration may be done in the patient's home by a qualified clinician or by the assigned and trained caregivers .

[2] Questionnaire to be completed ONLY when LMI070 is administered orally

[3] Detailed neurologic examination must be performed at least monthly (and more often if deemed necessary by the investigator)

[4] If a Grade 2 systolic function AE occurs, echocardiograms will be performed monthly until resolution or until the treatment is withdrawn. Otherwise echocardiograms are to be performed every 3 months

[5] Optional - Informed Consent must be obtained before this assessment--up to the discretion of the investigator or parents/guardians

[7] If the patient experience an acute illness episode , these assessment should be performed at a subsequent visit at the discretion of the investigator

[redacted]

## Treatment period 3

| | Treatment Period 3 | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Visit Numbers (internal use only)* | *36* | *40* | *41* | *42* | *43* | *44* | *45* | *46* | *47* | *48* | *49* | *50* | *51* |
| **Day** | **183** | **190** | **197** | **204** | **211** | **218** | **225** | **232** | **239** | **246** | **253** | **260** | **267** |
| **Week** | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 |
| **Time (h)** | 0 | 168 | - | - | - | - | - | - | - | - | - | - | - |
| current medical conditions | As required | | | | | | | | | | | | |
| Drug administration[1] | X | X | X[1] | X | X | X | X[1] | X[1] | X | X[1] | X[1] | X | X |
| Acceptability and Palatibility Questionnaire[2] | X | X | X | | | | | | | | | | |
| **Safety** | | | | | | | | | | | | | |
| Physical examination[3] | | | | | X | | | | X | | | | X |
| Body weight/ Body length | | | | | X | | | | X | | | | X |
| Head & Chest Circumference | | | | | X | | | | X | | | | X |
| Body temperature | | | | | X | | | | X | | | | X |
| Blood pressure / Pulse rate/ Respiratory rate | | | | | X | | | | X | | | | X |
| ECG evaluation | | | | X | | | | | | | | | X |
| Echocardiogram[4] | | | | X | | | | X | X | | | X | |
| Hematology, Blood chemistry, Urine analysis | | | | | X | | | | X | | | | X |
| Nerve conduction study [6] | | | | | | | | | | | | | X |
| Ophthalmologic examination [9] | | | | | | | | | | | | X | |
| Adverse Events | As required | | | | | | | | | | | | |
| Concomitant meds/Therapies | As required | | | | | | | | | | | | |
| **Motor Scales** | | | | | | | | | | | | | |
| CHOP INTEND (SMA type I infant motor scale) [7] | | | | | | X | | | | | | | X |
| Speech and motor milestones [7] | | | | | | X | | | | | | | X |
| HINE (Hammersmith Infant Neurological Examination) [7] | | | | | | X | | | | | | | X |
| Videotaping of motor activities[5] | As required[5] | | | | | | | | | | | | |
| **Respiratory function** | | | | | | | | | | | | | |
| Pulse Oximetry | | | | | X | | | | X | | | | X |
| Paradoxical Breathing | | | | | X | | | | X | | | | X |
| Breathing pattern: chest circumference during quiet breathing (sleep) | | | | | X | | | | X | | | | X |
| **Other assessments** | | | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | |
| PK blood collection [redacted] | | | | | | | | | | | | | |

[redacted]

## Additional instructions on Part 2, Treatment Period 3 assessment schedule:

[1] Administration may be done in the patient's home by a qualified clinician or by the assigned and trained caregivers ..

[2] Questionnaire to be completed ONLY when LMI070 is administered orally

[3] Detailed neurologic examination must be performed at least monthly (and more often if deemed necessary by the investigator

[4] If a Grade 2 systolic function AE occurs, echocardiograms will be performed monthly until resolution or until the treatment is withdrawn. Otherwise echocardiograms are to be performed every 3 months

[5] Optional - Informed Consent must be obtained before this assessment- up to the discretion of the investigator or parents/guar

[6] If the patient experience an acute illness episode , these assessment should be performed at a subsequent visit at the discretion of the investigator

[9] if there are no adverse changes detected at both Week 12 and Week 26 visits that can be attributed to branaplam and the branaplam dose is unchanged, then the examination will be performed yearly

[redacted]

## Treatment Period 4

| | Treatment Period 4 | | | | | | | | | | | | | | | | EOS[10] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Visit Numbers (internal use only)* | *52* | | *53* | *54* | *56* | *57* | *58* | *59* | *60* | *61* | *62* | *63* | *64* | *65* | *66* | *67* | *777* |
| **Day** | **274** | | **275** | **276** | **281** | **288** | **295** | **302** | **309** | **316** | **323** | **330** | **337** | **344** | **351** | **358** | - |
| **Week** | 40 | | | | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | - |
| **Time (h)** | 0 | 4 | 24 | 48 | 168 | - | - | - | - | - | - | - | - | - | - | - | - |
| Current medical conditions | As required | | | | | | | | | | | | | | | | |
| Drug administration[1] | X | | | | X | X[1] | X | X | X | X[1] | X[1] | X | X[1] | X[1] | X | X | |
| Acceptability and Palatability Questionnaire[2] | X | | | | X | X | | | | | | | | | | | |
| **Safety** | | | | | | | | | | | | | | | | | |
| Physical examination[3] | | | | | | | | X | | | | X | | | | X | X |
| Body weight/ Body length | | | | | | | | X | | | | X | | | | X | X |
| Head & Chest Circumference | | | | | | | | X | | | | X | | | | X | X |
| Body temperature | | | | | | | | X | | | | X | | | | X | X |
| Blood pressure / Pulse rate/ Respiratory rate | | | | | | | | X | | | | X | | | | X | X |
| ECG evaluation | | | | | | | X | | | | | | | | | X | X |
| Echocardiogram[4] | | | | | | | X | | | | X | X | | | X | | X |
| Hematology, Blood chemistry, Urine analysis | | | | | | | | X | | | | X | | | | X | X |
| Nerve conduction study[6] | | | | | | | | | | | | | | | | X | X |
| Ophthalmologic examination[9] | | | | | | | | | | | | | | | X | | X |
| Adverse Events | As required | | | | | | | | | | | | | | | | |
| Concomitant meds/Therapies | As required | | | | | | | | | | | | | | | | |
| **Motor Scales** | | | | | | | | | | | | | | | | | |
| CHOP INTEND (SMA type I infant motor scale)[7] | | | | | | | | | X | | | | | | | X | X |
| Speech and motor milestones[7] | | | | | | | | | X | | | | | | | X | X |
| HINE (Hammersmith Infant Neurological Examination)[7] | | | | | | | | | X | | | | | | | X | X |
| Videotaping of motor activities[5] | As required[5] | | | | | | | | | | | | | | | | |
| **Respiratory function** | | | | | | | | | | | | | | | | | |
| Pulse Oximetry | | | | | | | | X | | | | X | | | | X | X |
| Paradoxical Breathing | | | | | | | | X | | | | X | | | | X | X |
| Breathing pattern: chest circumference during quiet breathing (sleep) | | | | | | | | X | | | | X | | | | X | X |
| **Other assessments** | | | | | | | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | | | | | |
| PK blood collection [redacted] | X | X | X | X | X | | | | | | | | | | | | |

[redacted]

## Additional instructions on Part 2, Treatment Period 4 assessment schedule:

[1] Administration may be done in the patient's home by a qualified clinician or by the assigned and trained caregivers

[2] Questionnaire to be completed ONLY when LMI070 is administered orally

[3] Detailed neurologic examination must be performed at least monthly (and more often if deemed necessary by the investigator)

[4] If a Grade 2 systolic function AE occurs, echocardiograms will be performed monthly until resolution or until the treatment is withdrawn. Otherwise echocardiograms are to be performed every 3 months

[5] Optional - Informed Consent must be obtained before this assessment- up to the discretion of the investigator or parents/gua

[7] If the patient experience an acute illness episode , these assessment should be performed at a subsequent visit at the discretion of the investigator

[9] if there are no adverse changes detected at both Week 12 and Week 26 visits that can be attributed to branaplam and the branaplam dose is unchanged, then the examination will be performed yearly

[10] For all patients, the end of Study must be completed 30 days after **last** study drug administration.

[redacted]

**Table 7-4 Assessment Schedule – Part 3**

| **Part 3** | **Visit 1** | **Treatment and long term follow up** (after study month 12 visit the cycle should be repeated every year) | | | | | | | | | | | | **Unscheduled Visit** | **End Of Study** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Month** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | Any time Investigator considers as necessary | 30 days after last dose |
| **Days** | 0 | 28 | 56 | 84 | 112 | 140 | 168 | 196 | 224 | 252 | 280 | 308 | 336 | Some or all assessments can be performed as required | 30 days after last dose |
| **Visit Window (days)** | -14-to 1 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | | +/-7 |
| **Visit types:** R-Regular, S-Safety | **R** | **S** | **S** | **R** | **S** | **S** | **R** | **S** | **S** | **R** | **S** | **S** | **R** | **R/S** | **R** |
| Obtain informed consent | X | | | | | | | | | | | | | | |
| Inclusion /Exclusion criteria | X | | | | | | | | | | | | | | |
| Current medical conditions | X | | | | | | | | | | | | | | |
| Drug dispensation/Return | X | | | X | | | X | | | X | | | X | X | X |
| Acceptability and Palatability Questionnaire | X | | | X | | | X | | | X | | | X | X | X |
| **Safety** | | | | | | | | | | | | | | | |
| Physical examination | X | | | X | | | X | | | X | | | X | X | X |
| Body weight | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Body length | X | | | X | | | X | | | X | | | X | X | X |
| Head & Chest Circumference | X | | | X | | | X | | | X | | | X | X | X |

[redacted]

| **Part 3** | **Visit 1** | **Treatment and long term follow up** (after study month 12 visit the cycle should be repeated every year) | | | | | | | | | | | | **Unscheduled Visit** | **End Of Study** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Month** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | Any time Investigator considers as necessary | 30 days after last dose |
| **Days** | 0 | 28 | 56 | 84 | 112 | 140 | 168 | 196 | 224 | 252 | 280 | 308 | 336 | Some or all assessments can be performed as required | 30 days after last dose |
| **Visit Window (days)** | -14-to 1 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | | +/-7 |
| **Visit types:** R-Regular, S-Safety | **R** | **S** | **S** | **R** | **S** | **S** | **R** | **S** | **S** | **R** | **S** | **S** | **R** | **R/S** | **R** |
| Body temperature | X | | | X | | | X | | | X | | | X | X | X |
| Blood pressure / Pulse rate | X | | | X | | | X | | | X | | | X | X | X |
| ECG evaluation | X | | | X | | | X | | | X | | | X | X | X |
| Echocardiogram | X | | | | | | X | | | | | | X | X | X |
| Hematology, Urine analysis | X | | | X | | | X | | | X | | | X | X | X |
| Clinical chemistry | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Nerve conduction study | X | | | X | | | X | | | X | | | X | X | X |
| Ophthalmologic examination | (X) | | | (X) | | | (X) | | | (X) | | | (X) | (X) | X |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant Medications/Therapies | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

[redacted]

| **Part 3** | **Visit 1** | **Treatment and long term follow up** (after study month 12 visit the cycle should be repeated every year) | | | | | | | | | | | | **Unscheduled Visit** | **End Of Study** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Month** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | Any time Investigator considers as necessary | 30 days after last dose |
| **Days** | 0 | 28 | 56 | 84 | 112 | 140 | 168 | 196 | 224 | 252 | 280 | 308 | 336 | Some or all assessments can be performed as required | 30 days after last dose |
| **Visit Window (days)** | -14-to 1 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | | +/-7 |
| **Visit types:** R-Regular, S-Safety | **R** | **S** | **S** | **R** | **S** | **S** | **R** | **S** | **S** | **R** | **S** | **S** | **R** | **R/S** | **R** |
| **Motor Scales** | | | | | | | | | | | | | | | |
| CHOP INTEND (SMA type I infant motor scale) | X | | | X | | | X | | | X | | | X | X | X |
| Speech and motor milestones | X | | | X | | | X | | | X | | | X | X | X |
| HINE (Hammersmith Infant Neurological Examination) | X | | | X | | | X | | | X | | | X | X | X |
| Videotaping of motor activities | Optional | | | | | | | | | | | | | | |
| **Respiratory function** | | | | | | | | | | | | | | | |
| Pulse Oximetry / Respiratory rate | X | | | X | | | X | | | X | | | X | X | X |
| Paradoxical Breathing | X | | | X | | | X | | | X | | | X | X | X |
| Breathing pattern: chest circumference during quiet breathing (sleep) | X | | | X | | | X | | | X | | | X | X | X |

[redacted]

| **Part 3** | **Visit 1** | **Treatment and long term follow up** (after study month 12 visit the cycle should be repeated every year) | | | | | | | | | | | | **Unscheduled Visit** | **End Of Study** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Month** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | Any time Investigator considers as necessary | 30 days after last dose |
| **Days** | 0 | 28 | 56 | 84 | 112 | 140 | 168 | 196 | 224 | 252 | 280 | 308 | 336 | Some or all assessments can be performed as required | 30 days after last dose |
| **Visit Window (days)** | -14-to 1 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | +/-7 | | +/-7 |
| **Visit types:** R-Regular, S-Safety | **R** | **S** | **S** | **R** | **S** | **S** | **R** | **S** | **S** | **R** | **S** | **S** | **R** | **R/S** | **R** |
| **Other assessments** | | | | | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | | | |
| PK blood collection (Before dosing and 4 hours post dose) | X | | | | | | X | | | | | | X | X | |
| PK blood collection (single blood draw) | | | | | | | | | | | | | | | X |
| Troponin / NTproBNP | X | | | X | | | X | | | X | | | X | X | X |

[redacted]

### Additional instructions on the assessments to be performed in Part 3

- Visit 1 can be combined with last visit of Part 1 or Part 2. Visit 1 of Part 3 can be combined with last visit of Part 1 or Part 2. It means that assessments of Visit 1 in Part 3 do not need to be repeated if they already were performed in Part 1 or Part 2 within 14 days before entering Part 3. PK, Troponin and NTproBNP should always be collected on Visit 1 of Part 3.
- Investigational Medicine Product (IMP) will be administered at site at Visit 1 and then can be administered either weekly at home by parent / legal guardian or qualified medical personnel, or at study site by qualified medical personnel.
- Physical examination will include neurological examination by an experienced pediatric physician, neurologist or neuromuscular specialist.
- Safety Visits (S) – will be performed every month in between Regular visits (R). Safety Visits should be performed on site or at patients' home by Home Nurse. If neither onsite visit nor home nurse visit is possible, investigator will perform a telephone call to caregivers. In case none of above is possible, it is acceptable the patient will perform Clinical Chemistry locally and the results will be provided to the investigator.
- Clinical Chemistry at Safety Visits will include total bilirubin (direct and indirect should be differentiated in case of increase > 1.5 ULN), AST, ALT, ALP, total protein and albumin.
- Home Visits: According to local regulations following procedures can be done at patient home by Home Nurse professionals: Vital Signs, Blood draws and urine for safety, blood draws for PK [redacted], IMP delivery, support with patients specific documents, administration and return of IMP, ECG/ECHO, AE and Concomitant Medication check.
- End of study visit will be performed in case of patient discontinuation/early withdrawal. The End of Study visit will have to be performed 30 days after the last treatment. Part 3 of the study currently does not have a study end defined, taking into account the lethal nature of the SMA Type 1 disease if left untreated. In case the study is discontinued for reasons other than branaplam related patient's safety, Novartis will offer to ongoing patient alternative treatment.
- CHOP INTEND will be collected until 36 months of age.
- Ophthalmology assessments: The ophthalmology assessments can be performed at each onsite visit. However, if the patient does not have any ocular related complaints and if at the previous ophthalmology assessments there were no clinical findings which, potentially could be attributed to branaplam, the examination will need to be performed every 12 months, from the date of the last ophthalmology assessment. This is marked in the schedule of assessments as "(X)".
- Every PK assessment includes two blood draws: one blood draw just before dosing the patient, and another one 4 hours after dosing, except for a single PK blood draw at EoS.
- For any clinically significant increase in cardiac enzymes (Troponin / NTproBNP), repeat test within 1 week, if enzymes remain elevated, obtain pediatric cardiology consult, perform unscheduled echocardiogram and ECG if not already done for the visit.

[redacted]

Continuance of study treatment should be done in consultation with a pediatric cardiologist. Please refer to Table 5-7 for more details.

## 7.1 Screening

### 7.1.1 Information to be collected on screen failures

For Part 1 and Part 2 patients a following information may be collected as minimum: Demographics, Informed Consent sign off date and/or withdrawal, adverse events. Full description is Screen Failures process data collection is described in eCRF Completion Guide. For Part 3 is not applicable.

## 7.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data will be collected on all patients.

Relevant medical history/current medical conditions data includes data until signature of informed consent. Where possible, diagnoses and not symptoms will be recorded.

Investigators have the discretion to record abnormal test findings on the medical history CRF whenever in their judgement, the test abnormality occurred prior to the informed consent signature.

### 7.2.1 Mandatory DNA for patient enrollment

As a mandatory condition of participation all patients will be genotyped at Visit 1 (screening) to determine their SMN2 copy number, if not already determined at diagnosis. Only patients with exactly 2 copies (alleles) of the SMN2 gene will be included. SMN2 copy number will be determined in a validated reference laboratory using a mandatory blood sample.

## 7.3 Efficacy

### 7.3.1 Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)

The CHOP INTEND is a reliable, easily administered and well tolerated motor test measure for SMA Type 1 and similarly weak infants with neuromuscular disease. The CHOP INTEND can provide a useful measure of motor skills and strength in this population.

The assessment will be stopped for patients older than 36 months of age.

### 7.3.2 Hammersmith Infant Neurological Examination (HINE Section 2)

The HINE is a simple and scorable method for assessing infants between 2 and 36 months of age, including different aspects of neurological examinations as cranial nerves, posture, movements, tone and reflexes. It provides a summary of motor developmental milestones giving not only the opportunity to record the age at which the various milestones were achieved but also allowing one to quantify intermediate steps leading to the full achievement of the milestone (HINE Section 2).

The HINE section 2 will be performed as specified in the Assessment Schedule. Methods for assessment and recording are specified in the Site Operations Manual.

### 7.3.3 Videotaping of the patient's motor activities (optional)

Videotaping is to explore the potential effect of LMI070 on motor activities. Videotaping will be up to the discretion of the investigator and parents/guardians, if it is deemed desirable to capture any significant changes in the patient's motor activities that are not already captured by the CHOP INTEND. Methods for this assessment are described in the Site Operations Manual.

## 7.4 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the Assessment Schedule detailing when each assessment is to be performed.

### 7.4.1 Laboratory evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

#### Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count, platelet volume, reticulocyte count will be measured. Absolute neutrophil count will be calculated.

#### Clinical chemistry

Following routine clinical chemistry will need to be done according to Assessment Schedule: Sodium, potassium, creatinine, urea, chloride, bicarbonate, high sensitivity CRP, albumin, calcium, alkaline phosphatase, total bilirubin, AST, ALT, TSH (if abnormal, T4 should be assessed), glucose.

In Part 3, routine clinical chemistry will be done at 3-month interval visits. In addition, liver function tests will be done at 1-month interval safety visits; albumin, total protein, ALT, AST, ALP, and total bilirubin. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

Additionally, in Part 3, troponin and NTproBNP levels will be assessed at 3-months interval visits.

#### Urine analysis

Urine test by dipstick e.g. Combur9: leucocytes, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood/ hemoglobin

[redacted]

If the dipstick result is positive for a combination of nitrite, leucocytes and/or blood and protein, it is recommended that the sample is sent for bacteriological culture. Investigators may use clinical judgement for this additional assessment.

### 7.4.2 Physical examination

A full physical examination (PE) that evaluates all major organ systems will be performed at time points indicated in the Assessment Schedule. This should include a physical and neurological examination by an experienced pediatric physician, neurologist or neuromuscular specialist. Detailed instructions for the neurologic examination are specified in the Site Operations Manual, with the Assessment Schedule detailing when this examination should be performed.

Other PEs should be focused on clinical signs and symptoms including evidence of potential cell cycle arrest impact on the GI system such as stomatitis, mucositis or lesions of the peri-anal area.

Significant findings that were present prior to the signing of ICF must be included in the Relevant Medical History/Current Medical Conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

### 7.4.3 Vital signs

- Body temperature in degrees Celsius (°C)
- Blood pressure (BP) will be measured at by an oscillometric method at the times indicated in the different Assessment Schedules and further described in the Site Operations Manual
- Pulse

### 7.4.4 Body length, weight and head circumference

- Length (measured from the top of the head to the sole of the foot) in cm
- Body weight in kg
- Head circumference in cm
- Chest circumference across nipple line in cm

### 7.4.5 Electrocardiogram (ECG)

- Age-appropriate PR interval, QRS duration, heart rate, RR, QT, QTc, QTcB
- The Bazette QT correction formula (QTcB), calculated with the RR interval expressed in seconds, should be used for clinical decisions

### 7.4.6 Echocardiogram

An echocardiogram will be performed at the timepoints defined in the Assessment Schedule or if clinically significant elevation of Troponin and/or elevated NTproBNP (as unscheduled)in consultation with pediatric cardiologist (refer toTable5-7). The following standard parameters will be obtained during the study:

[redacted]

- Biplane four and two chamber Left Ventricular End Diastolic Volume(LVEDV)
- Biplane four and two chamber Left Ventricular End Systolic Volume(LVESV)
- Left Ventricular Ejection Fraction from LVEDV and LVESV(LVEF)
- Left Ventricular Internal Dimension Diastole) 2-D guided M-mode measurements from parasternal long axis (LVIDd)
- Left Ventricular Internal Dimension Systole (LVIDs) 2-D guided M-mode measurements from parasternal long axis
- Left Ventricular Fractional Shortening (LVFS)
- Intraventricular Septum Thickness diastole (IVSTd) 2-D guided M-mode measurements from parasternal long axis
- Left Ventricular Posterior Wall Thickness diastole (LVPWTd) 2-D guided M-mode measurements from parasternal long axis
- tricuspid regurgitation(TR) peak velocity (continuous wave Doppler)
- Left Ventricular End Diastolic Volume Index(LVEDVI) = LVEDV/ BSA
- Left Ventricular End Systolic Volume Index(LVESVI) = LVESV/ BSA

### 7.4.7 Other safety evaluations

#### Respiratory function

- Respiratory rate
- Pulse oximetry
- Paradoxical breathing
- Breathing pattern: chest circumference measured during quiet breathing or sleep

#### Ophthalmologic examination

An ophthalmologic examination without sedation using dilated direct and indirect ophthalmoscopy will be performed at the time points defined in the Assessment Schedule. Any ocular change, compared to baseline or previous assessment that is considered clinically significant will need to be documented and reported as a new AE.

In addition, where feasible, hand-held Optical Coherence Tomography (OCT) will be performed as well at the same time points as the routine ophthalmologic examination, as described in Table 7-1 for the initial treatment period, Table 7-2 for the extended treatment period in Part 1. Please refer to Table 7-3 for Part 2 and Table 7-4 for Part 3. Further details can be found in the Site Operations Manual.

Any ocular change, compared to baseline or previous assessment that is considered clinically significant will need to be documented and reported as a new AE.

#### Nerve Conduction Studies

Nerve conduction study is a test commonly used to evaluate the function, especially the ability of electrical conduction by the motor and sensory nerves of human body. Nerve conduction

[redacted]

velocity (NCV) and F wave are common measurements made during this test. A NCV test measures how quickly electrical impulses move along a nerve. Velocities will be assessed in upper and lower limbs. The Compound Motor Action Potential (CMAP) is recorded by electrical stimulation of a motor nerve and measured in millivolts.

The Sensory Motor Action Potential (SNAP) is obtained by electrically stimulating sensory fibers and is measured in microvolts.

The **same order** should be followed at all centers, starting from (1) and going as far as patient can tolerate. Numbers with a/b refer to the fact that these measurements are yielded from one and the same stimulation.

The following tests will be assessed as safety parameters:

### Nerve conduction study safety parameters

| A maximum of 3 measurements are performed per nerves. | | | |
|---|---|---|---|
| 1a | Sural SNAP | Measurement #1 #2 #3 | Safety (+) |
| 1b | Sural sensory NCV | Measurement #1 #2 #3 | Safety (+) |
| 2a | Ulnar CMAP | Measurement #1 #2 #3 | Efficacy |
| 2b | Ulnar motor NCV | Measurement #1 #2 #3 | Efficacy |

(+) If an investigator is unable to detect a reliable sural SNAP at the first neurophysiological assessment, he/she should switch to the median SNAP and use this in that individual patient further on. In these cases, (1a) would turn to “median SNAP”, (1b) to “median NCV”.

The following tests will be assessed as optional parameters:

### Nerve conduction study optional parameters

| | | | |
|---|---|---|---|
| 1 | Ulnar F-wave latency, wrist | Measurement #1 (*) | Efficacy |
| 2 | Peroneal CMAP (EDB muscle) | Measurement #1 #2 #3 | Efficacy |
| 3(b) | Peroneal motor NCV (EDB muscle) | Measurement #1 #2 #3 | Efficacy |
| 4 | Peroneal F-wave latency, ankle | Measurement #1 (*) | Efficacy |

(*) refers to the minimum latency out of 10 F-waves - One measurement, comprising 10 stimuli, is sufficient.

Detailed instructions are described in the Site Operations Manual. The Assessment Schedule does specify the frequency at which this expanded neurophysiologic examination should be performed.

[redacted]

## 7.5 Additional assessments

### 7.5.1 Pharmacokinetics

PK samples will be collected at the timepoints defined in the Assessment Schedule.

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data. The total blood volume drawn including safety, PK [redacted] assessments will not exceed 10 ml per visit over 13 weeks treatment period in Part 2 and 8.2 ml per visit over a 13 week period in an Extended treatment period in Part 1. In Part 3, the sample volume will not exceed 10 mL per visit over 13 weeks.

Further details on sample collection, numbering, processing and shipment can be found in the Site Operations Manual and Laboratory Manual.

Pharmacokinetics (PK) of branaplam will be evaluated in all patients at all dose levels in Parts 1, 2, and 3. PK plasma samples for branaplam analysis from venous blood or capillary blood (approximately 75 – 200 µL blood per sample). Further details of PK plasma sample collection method and associated procedure can be found in the Site Operations Manual.

Branaplam will be determined by a validated LC-MS/MS method; the anticipated Lower Limit of Quantification (LLOQ) is 0.500 ng/mL for both analytes. Concentrations will be expressed in mass per volume units and will refer to the free base. Concentrations below the LLOQ will be reported as "zero" and missing data will be labeled as such in the Bioanalytical Data Report.

[redacted]

#### Part 1 and 2

The following pharmacokinetic parameters will be determined for branaplam using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 8 or higher): $C_{max}$, $T_{max}$, $AUC_{last}$, $AUC_{inf}$, T1/2, Vz/F and CL/F from the plasma concentration-time data.

The linear trapezoidal rule will be used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of T1/2 will include at least 3 data points after Cmax. If the adjusted $R^2$ value of the regression analysis of the terminal phase will be less than 0.75, no values will be reported for T1/2, AUCinf, Vz/F, and CL/F.

#### Part 3

The following pharmacokinetic parameters will be determined for branaplam using the actual recorded sampling times with Phoenix WinNonlin (Version 8 or higher): $C_{trough}$ and $C_{4h}$. Summary statistics will be calculated for these parameters.

[redacted]

[redacted]

### 7.5.3 RNA

The intermediate products of gene expression, such as mRNA and miRNA will be used to examine expression in whole blood using concurrent nucleic acid analytical technologies, such as expression microarrays, PCR, Nanostring, Next Generation Sequencing techniques, or others.

[redacted]

### 7.5.4 Acceptability and Palatability Questionnaire

The Acceptability and Palatability Questionnaire should be completed at time points specified in Table 7-2 and in Table 7-3. This questionnaire will assess the investigational drug with respect to:

- Ease of administration/ acceptability/ tolerability
- Palatability (taste)

### 7.5.5 Speech and motor performance (milestones)

Speech and motor performance (milestones) that are not captured with the CHOP INTEND nor the HINE-2 will be captured in the eCRF page called Motor and Speech Domains. The following domains including the date of the assessment can be entered into the database:

- Voluntary Grasp
- Upper extremity function
- Hip strength
- Speech

[redacted]

The assessment has to be performed as specified in the assessment schedules in Section 7. Further details are provided in the study operation manual (SOM).

### 7.5.6 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population.

# 8 Discontinuation and completion

## 8.1 Discontinuation from study treatment and from study

### 8.1.1 Discontinuation of study treatment (applicable for participants following the Extended Schedule of Assessment Part 1 and participants enrolled in Part 2 and in Part 3)

A patient's parent or guardian may request discontinuation of study treatment for any reason at any time.

The investigator must discontinue study treatment for a given participant if he/she believes that continuation would negatively impact the participant's well-being.

Discontinuation from study treatment is required under the following circumstances:

- Participant's parent/guardian withdraws consent
- Clinical judgement of site investigator in consultation with Sponsor and independent DMC that incurred risks outweigh any potential clinical benefits
- Any adverse event, toxicity and laboratory abnormality as per Table 5-7
- Participant has unresolved adverse events that require 2 dose de-escalations
- Use of prohibited treatment as per Section 5.3 if the potential risk associated with the use of the medication outweighs any potential clinical benefits. If a prohibited medication is inadvertently administered to a participant, the investigator should contact Novartis providing as many details as possible on the co-administered drug (dose and dose regimen, duration of treatment, PK data if available) to discuss further steps.
- Use of other approved SMA therapies as per Section 5.3
- Participants SMA disease course progresses without clear evidence of improvement or stabilization of motor function over 6 months.
- Participants SMA disease trajectory is unfavorable and tracking towards late- or end-stage of type I SMA e.g. impaired respiratory function requiring a tracheostomy or permanent ventilation defined as > 21 days for > 16 hours/day of ventilation as adjudicated by the independent DMC.
- Any protocol deviation that results in a significant risk to the participant's safety
- If there is perceived clinical benefit, after discussion with Novartis, the investigator and the independent DMC, continuation of study treatment may be considered

**Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they**

**withdraw their consent (see Section 8.1.3).** Where possible, they should return for the assessments indicated in the Assessment table. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, and letter) should be made to contact them as specified in Section 8.2.

If discontinuation from study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's discontinuation from study treatment and record this information.

Participants who discontinue from study treatment agree to return for the end of treatment and follow-up visits indicated in the Assessment Schedule (refer to Section 7).

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant's parent/guardian. This telephone contact should preferably be done according to the study visit schedule.

### 8.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant's parent/guardian agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 7).

### 8.1.3 Withdrawal of informed consent/Opposition to use data/biological samples

A patient's parent or guardian may voluntarily withdraw consent for their child to participate in the study for any reason at any time. Withdrawal of consent/opposition to use data/biological samples occurs when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be in writing (depending on local regulations) and recorded in the source documentation.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw his/her consent/opposition to use data/biological samples and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

[redacted]

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the participant's study withdrawal should be made as detailed in the Assessment Schedule (Section 7).

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

For US: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

### 8.1.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be formally considered lost to follow-up until due diligence has been completed or until the end of the study.

### 8.1.5 Early study termination by the sponsor

The study will be reviewed on an on-going basis by the sponsor, the study investigators, and the independent DMC.

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to patients enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider patient welfare and safety. Should early termination be necessary, patients must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

[redacted]

## 8.2 Study completion and post-study treatment

Study completion is defined as when the last patient finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or, in the event of an early study termination decision, the date of that decision

Each patient enrolled into the study will be followed up until disease progression, death, lost to follow up, withdrawal or until end of the study. Study completion is defined as when the last patient completes their End of Study visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

End of Study visit will happen 30 days after the last administration.

If patient is discontinued early, the investigator must provide standard follow-up medical care, or must refer them for appropriate ongoing care. If Novartis decides to terminate the study for reasons other than safety, the ongoing patients will be offered alternative treatment.

# 9 Safety monitoring, reporting and committees

## 9.1 Definition of adverse events and reporting requirements

### 9.1.1 Adverse events

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 patient or clinical investigation patient *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of adverse events should be sought by non-directive questioning of the patient parent(s)/guardian(s) at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for liver related events are included in Table 5-6 and Table 5-7.

[redacted]

Adverse events must be recorded on the Adverse Events CRF for patients that pass screening and enter into the study. The adverse events should be reported according to the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. The Common Toxicity Criteria (CTC) AE grade (most current version)
   If CTC-AE grading does not exist for an adverse event, use:
   - 1=mild,
   - 2=moderate,
   - 3=severe
   - 4=life threatening.

   CTC-AE grade 5 (death) is not used, but is collected in other CRFs (e.g. Study Completion, Death/Survival).
2. Its relationship to the study treatment (no/yes), or investigational treatment (no/yes), or other study treatment (non-investigational) (no/yes), or both or indistinguishable,
3. Its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
4. Whether it constitutes a serious adverse event (SAE). See Section 9.1 for definition of SAE.
5. Action taken regarding [study/investigational] treatment (select as appropriate).
   All adverse events should be treated appropriately. Treatment may include one or more of the following:
   - no action taken (i.e. further observation only)
   - study treatment dosage adjusted/temporarily interrupted
   - study treatment permanently discontinued due to this adverse event
   - concomitant medication given
   - non-drug therapy given
   - patient hospitalized/patient's hospitalization prolonged
6. Its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about expected side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient parents/guardians during the study as needed.

The investigator should also instruct each patient parent/guardian to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be

[redacted]

recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

### 9.1.2 Serious adverse events

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency out-patient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

If all AEs (serious and non-serious) are captured on the CRF, SAEs are monitored continuously and have also special reporting requirements; see section below.

[redacted]

### 9.1.3 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patients parents/guardians have provided informed consent and until 30 days after the last study visit must be reported to Novartis safety immediately, without undue delay, under no circumstances later than 24 hours of learning of its occurrence as described below. Any SAEs experienced after this should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow up information*)* is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship to each specific component of study treatment (if study treatment consists of several drugs) complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department, notifying the Clinical Trial Leader. Contact information is listed in the Site Operations Manual.

The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the source documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

### 9.1.4 Pregnancy reporting

Not required for this patient population.

[redacted]

### 9.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

**Table 9-1 Guidance for capturing the study treatment errors including misuse/abuse**

| Treatment error type | Document in Dosing CRF (Yes/No) | Document in AE eCRF | Complete SAE form |
|---|---|---|---|
| Unintentional study treatment error | Yes | Only if associated with an AE | Only if associated with an SAE |
| Misuse/Abuse | Yes | Yes | Yes, even if not associated with a SAE |

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

## 9.2 Additional Safety Monitoring

### 9.2.1 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

[redacted]

### 9.2.2 Data Monitoring Committee

An independent DMC is instituted for this open label study with focus on safety. The DMC will periodically review the safety information throughout the study to monitor for unexpected toxicity.

The mission of the DMC will be to independently review and evaluate the safety, PD and efficacy data generated during the study as defined in this protocol. The DMC must also ensure that study patients are not exposed to unnecessary or unreasonable risks and that the study is conducted with high scientific and ethical standards. Finally, the DMC must make recommendations to the Sponsor on the actions to be taken on the study, which may include but not limited to the following:

- Continuation of individual patient treatment based on demonstrated tolerability and clinical benefit with agreement with the sponsor and investigator
- Initiation of Part 2 of study based on data collected in Part 1
- Discontinuation of the study
- Suggested modifications to the study protocol and/or the informed consent document
- Continuation of the study according to the protocol and the relevant amendments

The DMC is accountable to the Sponsor for appropriate monitoring of the study data.

Although the DMC may make recommendations to the Sponsor about changes in the conduct of the study, final decisions will be made by Novartis. In the case of early termination, consultation with Health Authorities may be required.

The frequency of the DMC meetings will be determined by the members and ratified in the DMC Charter.

### 9.2.3 Steering Committee

Not applicable to this study

### 9.2.4 Adjudication Committee

Not applicable to this study

# 10 Data collection and database management

## 10.1 Data collection

Data not requiring a separate written record will be defined in the Site Operations Manual and Assessment Schedule and can be recorded directly on the CRFs. All other data captured for this study will have an independent originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

[redacted]

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data EDC. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM of the patient data for archiving at the investigational site.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

## 10.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and *made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician.* Any changes to the database after that time can only be made after written agreement by Novartis development management.

# 11 Data analysis and statistical methods

## 11.1 Analysis sets

As a general principle, all tabulations and analyses will be done by the treatment received in the initial treatment period. For some inferential analyses on patients who receive multiple different doses over time, the actual dose received may be used. In the text below “treatment group” refers to the dose administered in the initial treatment period.

The following populations will be used for the statistical analyses:

[redacted]

The Enrolled Set (ENR) will consist of all patients who signed informed consent and were assigned to a treatment arm.

The Full Analysis Set (FAS) will consist of all patients in the Enrolled Set who received at least one dose of study drug.

The Safety Analysis Set (SAF) will consist of all patients in the Enrolled Set who received at least one dose of study drug. The safety population will be used for the analyses of safety variables

For Part 1 only: The Dose Determining Set (DDS) consists of all patients 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. Patients 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.

For Parts 1 and 2, the PK analysis set will include all patients that received at least one dose of branaplam with available PK data and no protocol deviations with relevant impact on PK data.

The PD analysis set will include all patients that received at least one dose of branaplam with available PD data and no protocol deviations with relevant impact on PD data.

## 11.2 Patient demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and patient. Summary statistics will be provided by treatment group. Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and patient.

## 11.3 Treatments

Data for study drug administration (rescue medication) and concomitant therapies will be listed by part, treatment group, and patient.

## 11.4 Analysis supporting primary objectives

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 patients 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).

The primary objective of Part 2 is to evaluate the safety and tolerability of multiple dose regimens of branaplam for 52 weeks in patients with Type 1 SMA.

The primary objective of 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.

[redacted]

All information obtained on adverse events will be displayed by initial and administered dose and patient. Additional interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general or in case of any safety concerns. Internal analysis of Part 2 will be conducted once all Part 2 patients completed 52 weeks of treatment. After all patients have transitioned from Part 1 and 2 of the study in the Part 3, additional interim analysis might be conducted.

### 11.4.1 Definition of primary endpoint(s)

The primary endpoint is the incidence of dose limiting toxicity (DLTs) in the first 2 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 11.4.2.

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

#### 11.4.2.1 Rules for Dose escalation in Part 1

An adaptive, 2 parameter Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle, will be used to make dose recommendations and estimate the MTD during the escalation part of the study. 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$^2$. 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 Bayesian approach requires the specification of prior distributions for the model parameters. The prior distributions and the process of their derivation are provided in the statistical appendix (Appendix 1).

#### 11.4.2.2 Dose recommendation

After each cohort is completed the posterior distributions for the probabilities of DLT at different dose levels are obtained. The results of this analysis are 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 patients the recommended dose is 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 25% or higher. In addition, the maximum dose escalation is limited to 100% of the previous dose.

[redacted]

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.

Details of the criteria for dose escalation and the determination of the MTD are provided in Section 5.4.

#### 11.4.2.3 Analysis of the primary variable

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

#### 11.4.2.4 Listing/summary of DLTs

DLTs will be listed and their incidence summarized by primary system organ class, worst grade based on the CTCAE version 5.0, type of adverse event, and by treatment. The DDS will be used for these summaries.

### 11.4.3 Handling of missing values/censoring/discontinuations

In Part 1, patients who are ineligible for the dose-determining set (DDS) may be replaced if necessary. In Part 2, patients lost to follow up and are unable to provide week 12 data due to non-treatment related reason may be replaced if necessary.

In the inferential analyses of secondary [redacted] variables, missing observations will be assumed to be missing at random (MAR).

## 11.5 Analysis supporting secondary objectives

### 11.5.1 Efficacy and/or Pharmacodynamics endpoint(s)

Secondary endpoints including growth measurements, respiratory function assessments, and CHOP INTEND infant motor scale, as well as their difference from baseline where a baseline is present, will be summarized at different time points for Parts 1&3 and Parts 2&3 separately.

Measurements which fall on a close to continuous scale (such as CHOP-INTEND and), the change from baseline will be analyzed by a mixed model for repeated measurements (MMRM) for study parts 2 and 3, with terms for treatment group, baseline value, baseline age category (<= 4 months/> 4 months), visit, treatment group*visit interaction, and baseline value*visit interaction.

Kaplan Meier plots for time to death or permanent ventilation will be provided with 95% confidence intervals.

[redacted]

### 11.5.2 Safety endpoints

#### Adverse events

All information obtained on adverse events will be displayed by initial and administered dose and patient. 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. TEAEs will be summarized in appropriate summary tables and in Parts 2 & 3, also displayed in stacked bar charts. All adverse events will be presented in listings.

#### Vital signs

All vital signs data will be listed by treatment, patient, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by scheduled visit, part, and treatment where appropriate. Individual blood pressure and pulse will be displayed in panel plots, while individual length and weight data will be displayed in spaghetti plots with US Center for Disease Control and Prevention (CDC) percentiles relative to age at evaluations (in months).

#### ECG evaluations

All ECG data will be listed by treatment, patient and visit/time, abnormalities will be flagged. Summary statistics will be provided by scheduled visit, part, and treatment where appropriate. Individual ECG data will be displayed in panel plots.

#### Clinical laboratory evaluations

All laboratory data will be listed by treatment, patient, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by scheduled visit, part and treatment where appropriate.

In addition, shift tables will be provided for all parameters to compare a patient's baseline laboratory evaluation relative to the post-baseline values. Liver enzyme data will be summarized according to newly occurring abnormality criteria, as well as some standard graphs for this data.

### 11.5.3 Pharmacokinetics

Branaplam plasma concentration data will be listed by protocol part, dose, patient, and sampling time point. Descriptive summary statistics will be provided by dose and sampling time point, including concentrations below the LLOQ reported as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported

[redacted]

if the dataset includes zero values. Pharmacokinetic parameters will be calculated as described in Section 7.5.1 and will be listed by protocol part, dose and patient.

### 11.5.4 DNA

SMN2 copy number could be listed by patient.

### 11.5.5 Pharmacokinetic / Pharmacodynamic relationships

If possible and depending on the data a PK/PD model will be developed relating PK to SMN blood protein levels. The model may be used for guiding the dose frequency decision in Part 2 of the protocol.

[redacted]

## 11.7 Interim analyses

After each cohort of patients 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 patients. 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,

[redacted]

respiratory function assessments and CHOP INTEND infant motor scale will be summarized at different time points and compared to baseline.

Additional interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general or in case of any safety concerns. Internal analysis of Part 2 will be conducted once all Part 2 patients completed 52 weeks of treatment. After all patients have transitioned from Part 1 and 2 of the study in the Part 3, additional interim analysis might be conducted.

Additional interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general or in case of any safety concerns.

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.

## 11.8 Sample size calculation

### 11.8.1 Part 1

The sample size for Part 1 is driven by feasibility. In part 1, cohorts of at least 2 patients 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. Thirteen patients were enrolled and treated, to test 5 dose levels. At least 2 patients 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 patients present simultaneously for the study, additional patient(s) may be dosed in a cohort to avoid unnecessary delays in treatment of this life-threatening disease.

### 11.8.2 Part 2

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

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 patient's variance components). The table below (Table 11-1) 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

[redacted]

### 11.8.3 Part 3

The sample size of Part 3 depends on the number of patients enrolled in Parts 1 and 2. All patients who complete at least 52 weeks of treatment in either Part 1 or Part 2 are eligible to enroll in Part 3.

**Table 11-1 Power to detect a difference in CHOP INTEND score between two adjacent dose groups (by one-sided t test at nominal significance level 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% |

# 12 Ethical considerations and administrative procedures

## 12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

## 12.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g. advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Novartis around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

## 12.3 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

[redacted]

## 12.4 Quality Control and Quality Assurance

Novartis/sponsor maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes

# 13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study patients. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators must apply due diligence to avoid protocol deviations. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the clinical study report (CSR).

## 13.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented, provided the Health Authorities and the reviewing IRB/IEC are subsequently notified by protocol amendment.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the CTL should be informed and (serious) adverse event reporting requirements (Section 9) followed as appropriate.

[redacted]

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# 15 Appendices

## 15.1 Appendix 1 Prior calibration of the Bayesian logistic regression model

### Introduction

An adaptive Bayesian logistic regression model (with 2 parameters) guided by the escalation with overdose control principle will be used to make dose recommendations and estimate the MTD during Part 1 of the study. The use of Bayesian response adaptive models for Phase I studies has been advocated by the EMEA guideline on small populations (2006) and by Rogatko and Tighiouart (2007) and is one of the key elements of the FDA's Critical Path Initiative.

The dose-toxicity (DLT) relationship in the escalation part of the study 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. Doses are rescaled as d/d* with reference dose 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.

### Prior specification

A vague bivariate normal prior for the model parameters ($\log(\alpha)$,$\log(\beta)$) is derived by assuming that the median DLT rate at reference dose d*= 40 mg/m$^2$ equals the targeted toxicity 25%, and that for the remaining doses, median DLT rates *a priori* are linear in logit-scale as a function of log-dose (Neuenschwander et al 2008).

The information to derive the prior distribution of model parameters is provided in Table 15-1. Table 15-2 summarizes the associated prior distribution of the DLT rates. The doses not meeting the overdose criteria under the prior are bold in the table, i.e. doses not eligible at the start of the study.

**Table 15-1 Prior parameters for bivariate normal distribution of model parameters**

| Parameters | Means | Standard deviations | Correlation |
|---|---|---|---|
| $\log(\alpha)$, $\log(\beta)$ | (-1.099, 0) | (3.2, 1) | 0 |

[redacted]

**Table 15-2 Summary of prior distribution of DLT rates derived from the prior in Table 15-1**

| branaplam (mg/m$^2$) | Prior probabilities that Pr(DLT) is in interval: | | | Mean | SD | Quantiles | | |
|---|---|---|---|---|---|---|---|---|
| | [0, 0.1) | [0.1, 0.25) | [0.25, 1] | | | 2.5% | 50% | 97.5% |
| 1 | 0.771 | 0.072 | 0.157 | 0.119 | 0.244 | <0.001 | 0.004 | 0.927 |
| 3 | 0.705 | 0.089 | 0.206 | 0.156 | 0.274 | <0.001 | 0.012 | 0.956 |
| 6 | 0.648 | 0.101 | 0.251 | 0.190 | 0.296 | <0.001 | 0.026 | 0.970 |
| 12 | 0.570 | 0.117 | 0.313 | 0.236 | 0.320 | <0.001 | 0.056 | 0.981 |
| 24 | 0.464 | 0.132 | 0.404 | 0.306 | 0.345 | <0.001 | 0.130 | 0.989 |
| 40 | 0.367 | 0.134 | 0.499 | 0.381 | 0.363 | 0.001 | 0.248 | 0.994 |
| 48 | 0.333 | 0.132 | 0.535 | 0.413 | 0.370 | 0.001 | 0.308 | 0.996 |
| 60 | 0.299 | 0.125 | 0.576 | 0.451 | 0.376 | 0.001 | 0.385 | 0.998 |

Note: bold values indicate doses not meeting the overdosing criterion (more than 25% chance of excessive toxicity) with the prior information only.

[redacted]

## 15.2 Appendix 2 - Administration of branaplam by caregivers- Instruction for study site staff and caregivers

Only caregivers holding legal responsibilities of the patient will be allowed to administer the study medication to the patients at home. Branaplam (IMP) will be administrated weekly at home.

If any mild or moderate adverse events are ongoing at the time of the planned dose administration, the investigator will decide whether the patient must visit the study site and receive study medication at the study site.

### Principles:

The investigator holds the responsibility to explain to the caregivers the procedure of IMP maintenance and administration at home, including IMP administration, handling, storage and accountability of the IMP at home. Two caregivers or legal representatives must be identified and trained on IMP administration. The process of training for IMP maintenance and administration at home must be documented in medical records.

**Before IMP is dispensed to caregivers investigator or delegate will:**

- Explain to caregivers the Administration of branaplam for phase I/II by the caregivers document
- Train caregivers basing on Instruction for administration of LMI/branaplam for phase I/II investigational human use
- Explain and dispense Administration of branaplam by caregivers at home- Drug accountability log (Patient Diary)
- Explain and dispense Acceptability and palatability questionnaire
- If available demonstrate Study drug training kits containing water and ensure full understanding of the procedure, the risks and benefit and all the documents

### Training and instruction for the first dose of administration of branaplam by caregivers at the study site:

- The Principal investigator will present, explain and dispense the Instruction for administration of LMI/branaplam for phase I/II investigational human use document- including the safety instruction, disposal instruction and storage conditions, use instructions- important usage information.
- The dose volume calculation will not be presented as the responsibility will remain with the PI. However the PI will explain that the dose is calculated based upon the weight of the child and must assure that caregivers are given the appropriate syringes size, according to Pharmacy Manual.
- When available the dose/volume preparation, dose administration, disposal will be presented supported by training kits available at site. The training kits contains water. The nurse in presence of the principal investigator or delegate as documented in the delegation log at site will choose a volume and demonstrate the preparation of the syringe using a training kit. Each caregivers will be asked to prepare the same dose. The caregiver repeats

[redacted]

the test as many times as necessary or wished and all attempts are documented in the medical file. Once the study team decides that the caregivers are ready, the caregivers will be ask to prepare the actual dose of the visit and administer to their child under the study nurse supervision. All events must be documented in the source notes. In case training kits are not available the site can use local available materials to demonstrate how the accurate volume should be taken.

- Caregivers will prepare the syringe and administer the medication at the site. This will serve as a control and enable the study team to identify issues or need for re-training.

### Instruction for administration of branaplam by caregivers at home:

The caregivers will be given Patient Diary prefilled with planned date for study medication administration, number of vials, syringes and extenders handed over, planned number of vials per visit, study medication kits number (6 digit number).

For Part 1 and Part 2: Weight will be taken every month at the onsite visits.

For Part 3: Weight will be measured every month at the onsite visit. In case patient will not be able to visit the site for the visit a home nurse visit can be performed or telephone call will be done by the site. If during Home Visit or Telephone Interview the weight change has been reported the site will calculate new volume, record in the source note and inform the caregiver of the new volume in mL to administer. The caregiver must report in the Patient's Diary the volume and the day of administration. The weight at home will be measured according to local standards. In special circumstances Sponsor can provide to the patients the balance device. **Note**: the branaplam dose will always be calculated by the site staff (study nurse, pharmacist investigator), reviewed and approved by principal investigator or delegate and communicated to caregiver by study nurse, principal investigator at the site or by phone.

The caregiver completes on the same day as the dose administration the Acceptability and Palatability questionnaire when required.

Instruction for administration of LMI/branaplam for phase I/II investigational human will be dispensed to patient.

### What should the caregivers do in case of vomiting?

The administration of the dose should be immediately repeated in case if the child vomits or regurgitates within 10 minutes of dose administration. If vomiting or regurgitation occurs more than 10 minutes after dosing, no dose re-administration should occur.

The caregivers will document this event in Patient’s Diary.

### At which visits branaplam can be administered at home by the caregivers?

Home dosing can be implemented as soon as caregivers/legal representatives were trained by investigator according to Administration of branaplam by caregivers- Instruction for study site staff and caregivers.

The IMP will be dispensed and returned according to Pharmacy Manual.

[redacted]

### What will the caregivers be provided with?

- IMP kits and syringes

Depending on the weight of the child 1 or more vials will be used. 1 package of study treatment contains 4 vials with the same drug ID number.

The number of kits given to the caregivers, and syringes will depend upon the weight of the child and planned estimated volume and it will include back up kits. The number of dispensed kits will depend on the time till next onsite visit.

The investigator is responsible and must ensure that the medication expiry date won't be exceeded during home dosing period before next site visit. In case caregivers spot the IMP has expired or is to expire shortly, he or she must immediately contact the site in order to return affected IMP kits and receive new ones. Expired IMP must not be administrated.

- Patient Diary
- Instruction for administration of LMI/branaplam for phase I/II investigational human
- Acceptability and Palatability questionnaires

### What the caregivers should do in case of dosage error?

The caregivers must report immediately to the site staff any error in the preparation of the study medication leading to an under or over- dosage. This must also be documented in the Patient's Diary.

### What is a Patient's Diary to complete?

The document is used to document all the information related to the branaplam administration at home: date, dose, by who, kits number as well as patient's weight change, new symptoms, new medications including supplements. The site staff must prefilled the Patient's Diary with planned date for study medication administrations and study medication kits number (6 digit number), quantities of bottle, number of syringes and extender given to the caregivers. The caregivers must complete this document precisely, before and after each administration and bring it back to review and discuss with the principal investigator at the next planned visit at the study site. The caregivers must save all used vials and bring it back at the next planned visit at the study site.

[redacted]