NOVARTIS

Clinical Development

LMI070/Branaplam

LMI070C12203 / NCT05111249

A Randomized, Double-Blind, Placebo-Controlled Dose Range Finding Study with Open-Label Extension to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of LMI070/branaplam when Administered as Weekly Oral Doses in Participants with Early Manifest Huntington's Disease

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26-Oct-2023	*Prior to LPLV*	*Protocol amended*	*PK analysis is added.*	

Table of contents

Table of contents 3
List of tables 5
List of figures 5
List of abbreviations 6
1 Introduction 7
1.1 Study design 7
1.1.1 Primary estimand(s) 7
1.2 Study objectives and endpoints 7
2 Statistical methods 11
2.1 Data analysis general information 11
2.1.1 General definitions 11
2.2 Analysis sets 13
2.2.1 Subgroup of interest 13
2.3 Patient disposition, demographics and other baseline characteristics 14
2.3.1 Patient disposition 14
2.3.2 Demographics and other baseline characteristics 14
2.3.3 Medical history 15
2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance) 16
2.4.1 Study treatment / compliance 16
2.4.2 A listing showing exposure in doses and days. Prior, concomitant and post therapies 16
2.5 Analysis supporting primary objective(s) 16
2.5.1 Primary endpoint(s) 17
2.5.2 Statistical hypothesis, model, and method of analysis 17
2.5.3 Handling of intercurrent events 17
2.5.4 Handling of missing values not related to intercurrent event 17
2.6 Analysis supporting secondary objectives 17
2.6.1 Secondary endpoint(s) 17
2.6.2 Statistical hypothesis, model, and method of analysis 17
2.6.3 Handling of intercurrent events 21
2.6.4 Handling of missing values not related to intercurrent event 21
2.7 Safety analyses 22
2.7.1 Adverse events (AEs) 22
2.7.2 Deaths 24
2.7.3 Laboratory data 24

2.7.4 Other safety data 25
2.8 Pharmacokinetic endpoints 30
2.9 PD and PK/PD analyses 30
[redacted] 31
2.11 Biomarkers 31
2.11.1 NFL in serum and CSF 31
2.11.2 mHTT in CSF 32
[redacted] 32
[redacted] 33
2.13 Interim analysis (IA) 33
3 Sample size calculation 33
3.1 Primary endpoint(s) 33
3.2 Secondary endpoint(s) 34
4 Change to protocol specified analyses 34
5 Appendix 35
5.1 Imputation rules 35
5.1.1 Study drug 35
5.1.2 AE date imputation 35
5.1.3 Concomitant medication date imputation 36
5.1.4 Values below LLOQ 36
5.2 AEs coding/grading 36
5.3 Laboratory parameters derivations 36
5.4 Visit windows 36
5.5 Notable and abnormality criteria 41
5.6 Rule of exclusion criteria of analysis sets 44
6 Reference 45

List of tables

Table 1-1 Original objectives and related endpoints 8
Table 2-1 BSI measuring atrophy by region 18
Table 2-2 Plasma PK samples schedule for week 1 and week 17 20
Table 2-3 AEs indicative of neuro toxicity / peripheral neuropathy 22
Table 2-4 Example of consecutive worsening and recovery for Neuro Exam 28
Table 2-5 Nerve Conduction Safety Parameters 29
Table 3-1 Likelihood of Identifying AEs/SAEs with Hypothetical Incidence Rate 34
Table 5-1 Imputation of start dates 35
Table 5-2 Visit windows for Neurological Exams, nerve conduction studies, weight, urinalysis, C-SSRS, [redacted] 37
Table 5-3 Visit window for vital Signs, ECG, Hematology, chemistry, NTproBNP, Troponin 37
Table 5-4 Visit windows for echocardiogram 37
Table 5-5 Visit windows for ophthalmologic examination 38
Table 5-6 Visit windows for UHDRS scores (TFC, TMS, IS, [redacted]), [redacted] and brain MRI 39
[redacted] [redacted] 39
Table 5-8 Visit windows for biomarker collected via lumbar puncture ([redacted], Nfl[redacted]) 40
Table 5-9 Clinically notable criteria for vital signs 41
Table 5-10 Abnormal ranges for ECG 41
Table 5-11 Clinically notable criteria for selected hematology tests 42
Table 5-12 Clinically notable criteria for selected chemistry tests 42
Table 5-13 Clinically notable criteria for selected Other Lab parameters 42
Table 5-14 Clinically notable criteria for Echocardiogram with GLS 43
Table 5-15 Clinically notable liver function test values 43
Table 5-16 Subject Classification 44

List of figures

Figure 1-1 Study Design Overview 7

List of abbreviations

AE	Adverse Event
BE	Blinded extension
BL	Baseline
CRF	Case Report Form
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
DMS	Document Management System
DR	Dose response
DRF	Dose range finding
EoS	End of Study
FAS	Full Analysis Set
HD	Huntington's disease
HTT	Huntingtin
IA	Interim Analyses
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mHTT	Mutan huntingtin
MI	Multiple imputation
OLE	Open-label extension
PBO	Placebo
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
RAP	Reporting & Analysis Process
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard deviation
TFLs	Tables, Figures, Listings
UHDRS	Unified Huntington's Disease Rating Scales
Vol	Volumetric
WHO	World Health Organization

1 Introduction

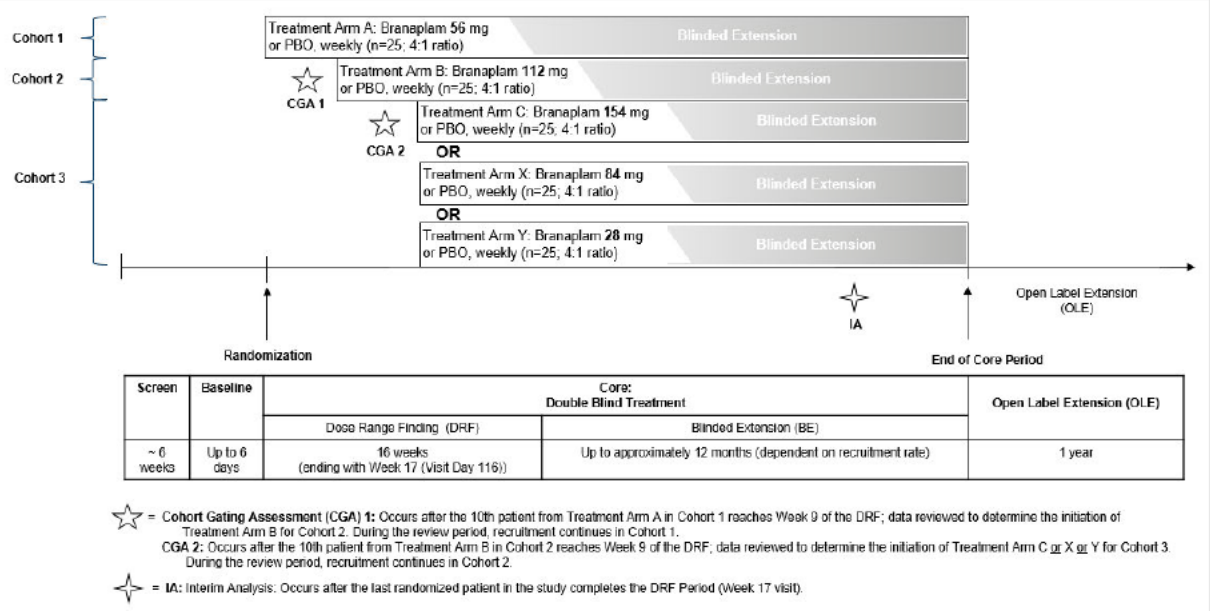
This document contains details of the statistical methods and the analysis strategy that will be used in the phase 2b study CLMI070C12203 based on protocol version 02 (30th -Jan 2023). As per the USM (6th-Dec-2022) and protocol version 02, study drug was permanently discontinued in all participants and no further cohorts will be initiated. Hence, only an abbreviated clinical study report (CSR) will be created for this study.

1.1 Study design

The original study design was a staggered cohort approach with three potential active treatment arms. However, due to safety concerns, an USM (6th-Dec-2022) was issued to early terminate the study drug. Therefore, only cohort 1 data is available for analysis:

Treatment Arm A: Branaplam 56 mg oral solution or matching PBO, once weekly

Figure 1-1 Study Design Overview



1.1.1 Primary estimand(s)

Not applicable due to early termination.

1.2 Study objectives and endpoints

As per the USM follow-up notification dated 06-Dec-2022, the original objectives are no longer applicable due to permanent discontinuation of study treatment. No statistical modelling will be done. Table 1-1 indicates the original planned objectives, endpoints and which of those will be summarized descriptively for the CSR.

Table 1-1 Original objectives and related endpoints

Original objective(s)	Original endpoint(s)	Will be reported in CSR
Primary objective(s)	**Endpoint(s) for primary objective(s)**	
• To assess the dose-response relationship of branaplam administered over 16 weeks on mHTT protein change from baseline in CSF	• Period: From baseline to Week 17 over the Dose Range Finding (DRF) • Reduction (%) of mHTT protein in CSF from baseline to Week 17. See Section 2.1 for Primary Estimand	• mHTT protein in CSF
• To evaluate the safety and tolerability of branaplam when administered for 16 weeks or longer in participants with HD.	• Safety and tolerability parameters/assessments including but not limited to adverse events, physical exam (including neurological examination), findings, clinical laboratory assessments, HTT lowering, etc.	• AEs • Neurological exams and nerve conduction studies • Labs, vital signs, ECG and etc (details in Section 2.7)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**	

• To assess the pharmacodynamics of branaplam in participants with HD on clinical, imaging, and biomarker endpoints relevant to HD.	• The following endpoints will be assessed over three periods:
	1. DRF: change from baseline to Week 17 compared to placebo
	2. Core: change from baseline to the end of Core compared to placebo
	3. Core + OLE: change from baseline and baseline-extension to week 53-extension
	  • Ventricular, Caudate and Total Brain Volume as measured by structural magnetic resonance imaging (MRI)
	  • Unified Huntington's Disease Rating Scale (UHDRS) Total Functional Capacity (TFC), UHDRS Total Motor Score (TMS), UHDRS Independence Scale (IS).
		• VolMRI ventricular, caudate and total brain volume
		• UHDRS TFC, TMS and IS

Original objective(s)	Original endpoint(s)	Will be reported in CSR
	• Concentrations of total HTT and mHTT protein in CSF and plasma	
• To assess pharmacokinetics of branaplam and its metabolite UFB112 in plasma and CSF	• PK parameters (e.g. area under the curve (AUC)last, AUCtau, maximum concentration (Cmax), Tmax) of branaplam and its metabolite UFB112 in plasma after first dosing and at the end of the DRF Ctrough of branaplam and UFB112 in plasma across the study duration Concentrations of branaplam and its metabolite UFB112 in CSF and concentration ratio CSF/plasma of the analytes	• PK concentration and parameters (details in Section 2.6)
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**	
[redacted]	[redacted]	[redacted]

Original objective(s)	Original endpoint(s)	Will be reported in CSR
[redacted]	[redacted]	
• To explore the effects of branaplam in patients with HD on pharmacodynamic biomarkers relevant to HD	• The following endpoints will be assessed over three periods: 1. DRF: change from baseline to Week 17 compared to placebo 2. Core: change from baseline to the end of Core compared to placebo 3. Core + OLE: change from baseline and baseline-extension to week 53-extension • NFL in serum and CSF [redacted]	• NFL in serum and CSF [redacted]
[redacted]	[redacted]	

Original objective(s)	Original endpoint(s)	Will be reported in CSR
[redacted]	[redacted]	
[redacted]	[redacted]	

2 Statistical methods

2.1 Data analysis general information

Due to early termination, the original planned analysis of primary, secondary and exploratory endpoints to demonstrate efficacy and dose range finding are no longer applicable. There was only one cohort (with one active dose of branaplam) initiated in the core study period and the open label extension (OLE) period is no longer applicable. Therefore, all analysis will be performed over one period and no analysis will be performed based on OLE.

Statistical analysis will be performed using SAS@ statistical software (SAS Institute, Cary, NC, USA.) version 9.4 or higher.

Unless specified differently, descriptive summary statistics for continuous variables include mean, median, standard deviation, Q1 (25th percentile), Q3 (75th percentile), minimum and maximum, and geometric mean (where appropriate), while for categorical variables frequencies and relative percentages will be reported.

2.1.1 General definitions

Treatment groups

Due to USM, only Cohort 1 was initiated. All analysis will be performed by treatment group within cohort 1:

- Cohort 1: LMI070 56 mg and Placebo

Study Day

Day 1 is defined as the date when the study treatment is started. Study day is defined as the number of days since the date of study treatment (Day 1). Therefore, for a particular date, study day will be calculated as follows:

- for dates on or after Day 1:

Study day = Assessment date – Day 1 + 1;

- for dates prior to Day 1:

  Study day = Assessment date – Day 1.

Baseline

The baseline value is defined as the last assessment performed prior to start of study treatment. In this study, baseline values will be the values obtained during screening, the week of Baseline or on Day 1. If the Baseline visit is missing or the assessment was not done at Baseline, the last assessment of an earlier visit (scheduled or unscheduled) which is the closest to the Baseline visit will be used as Baseline. In case an assessment is repeated at a later visit during the screening/baseline epoch, the latest one will be used as Baseline. Note: Assessments on the day of randomization are assumed to have been taken as per protocol, i.e. if the assessment should be performed before dosing, the assessment will be treated as pre-dose as per protocol. Practically, i.e. that the time part of the date/time entry will be ignored. Exception: In case there is a protocol deviation or a comment that specifically indicates that the assessment has been taken post-dose, the assessment will not be treated as pre-dose.

Post-baseline measurement

Post-baseline measurements are defined as those assessments after the first dose of treatment.

When change from baseline is of interest the following formula will be used for each scheduled visit and time-point where baseline and post-baseline values are both available **except** for volumetric (vol) MRI:

Change from baseline = post-baseline value – baseline value.

Percent (%) change from baseline= (post-baseline value – baseline value)/baseline value*100%.

Annualized change from baseline=365.25*change from baseline/ time interval (in days).

Annualized percent change from baseline=365.25*percent change from baseline/time interval (in days).

Time interval = (date of current assessment – date of baseline assessment + 1).

Note for MRI data, change is derived via BSI technique, the changes are already provided in source data (calculation of change and % change for MRI is available in Section 2.6.2.2).

Prior and Concomitant Medication

Prior medication will be defined as any non-study medication taken prior to the first dose of the study drug, irrespective of whether the medication continued into the treatment period.

Any non-study medication administered at least once between the day of first dose of study drug and end of the study will be a concomitant medication.

Therefore, some medications can be categorized as both, prior and concomitant medication.

Age at clinical HD diagnosis

It should be estimated from date of clinical HD diagnosis and age at screening as follows:

Age at screening+ rounded (down) difference in years between date of clinical HD diagnosis and screening date. If partial date is available for HD diagnosis, impute as follows:

- If only day is missing (year and month are available): impute as the first day of the month (01/MON/YYYY)
- If both day and month are missing (only year is available): impute as mid date of the year (01/JUL/YYYY)

In case HD diagnosis occurred in the same year as screening, the difference will be set to 0 (instead of rounding down).

On/off treatment

On treatment flag will be created for efficacy and safety endpoints including sNFL, volMRI, clinical endpoints, Nerve Conduction Studies (NCS), neuro exam, neuropathy symptoms [redacted] at visit level. An assessment is defined as on treatment if the collection date ≤ { last dosing date + 13}. An assessment is defined as off treatment if the collection date ≥ { last dosing date + 14}.

Visit windows

Visit-windows will be used for by visit summary tables. For any assessment, there are the protocol defined scheduled visits around which visit windows were created to cover the complete range of days within the study. When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows.

However, for figures that involves individual trajectory (NFL, volMRI, mHTT) and for reports related (regarding worsening and recovery) to Neuro exam or Neuropathy questionaire, an additional analysis visit based on actual analysis time (in weeks) instead of mapped windows will be used. This will be derived as ceiling of{ADY/7 }. ADY is study day defined in Section 2.1.1.

Details on calculation of visit windows based on the protocol will be provided in Section 5.4.

2.2 Analysis sets

The **Screened set** will consist of all screened participants.

The **Randomized Analysis Set (RAS)** will consist of all participants who received a randomization number, regardless of whether participants received study medication.

The **Full Analysis Set (FAS)** will consist of all randomized participants who received at least one dose of study drug.

The **Safety Set (SAF)** will consist of all participants who received at least one dose of study drug. All analysis will be conducted on SAF except PK related analysis.

The **PK analysis set** will consist of all participants with at least one evaluable concentration data sample. All PK analysis will be conducted on PK analysis set.

2.2.1 Subgroup of interest

Below participants will be flagged at participants level for various analyses:

- Participants with subdural hematoma. This will be used for volMRI analysis.
- AEs indicative of neuro toxicity/peripheral neuropathy. This will be used for recovery analysis.

2.3 Patient disposition, demographics and other baseline characteristics

Analyses for subject disposition, demographic characteristics, other baseline characteristics, will be summarized based on SAF by treatment group. Descriptive statistics of mean, standard deviation, minimum, median and maximum will be used for continuous variables. Frequency distributions will be used for categorical variables.

2.3.1 Patient disposition

Summary tables

- The number and proportion of participants, who completed the study will be presented by treatment group.
- The number and proportion of participants who discontinued the study prematurely along with the primary reason for discontinuation will be presented by treatment group.
- The number and proportion of participants who discontinued the study drug prematurely along with the reason for the study drug discontinuation will be summarized and presented by treatment group.
- The number and percentage of participants in each analysis set described above will also be presented. Reason for screen failure will be summarized for all screen-failed participants.
- The number and percentage of participants with protocol deviations will be summarized by treatment group and following category:
    - Selection criteria not met
    - Participants not withdrawn as per protocol
    - Treatment deviation
    - Prohibited concomitant medication
    - Other deviations (important deviations that do not fall in the above four categories)

Listings

Listing will be provided for primary reason for early discontinuation.

2.3.2 Demographics and other baseline characteristics

Summary tables

Patient demographics will be summarized with descriptive statistics for the SAF by treatment and overall. Parameters include:

- Age (at screening)

- Sex
- Race
- Ethnicity
- Height
- Weight
- BMI
- Educational level, years of education
- Smoking and alcohol history
- Country/region

Summary of HD history will include:

- CAG repeat length (larger allele from central lab)
- CAG age product (CAP) score defined as
    - Definition 1: CAP score = (length of CAG repeat – 35.0) × age at screening
    - Definition 2: CAP score = (length of CAG repeat – 30.0)/6.49 × age at screening
- Family history:
    - a Parent affected: (only) mother affected, (only) father affected, both parents affected, no parent affected, and unknown
- Age at clinical HD diagnosis (defined in Section 2.1.1)

Other baseline characteristics:

- Unified Huntington's Disease Rating Scales (UHDRS)
    - Total Function Capacity (TFC)
    - Total motor score (TMS)
    - Independence scale (IS)

[redacted]

- mHTT protein in CSF
- volMRI by region

2.3.3 Medical history

Medical history entered on the Medical History (MH) eCRF will be coded with the Medical Dictionary for Regulatory Activities terminology (MedDRA) using the most recent version at the time of reporting.

Summary tables

Relevant medical history and current medical condition will be summarized by primary system organ class (SOC), preferred term (PT) and treatment group using the SAF.

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

2.4.1 Study treatment / compliance

The SAF will be used for the below analyses.

Summary tables

- Duration of total follow-up time (including both on and off treatment period) will be summarized descriptively by number of weeks.
- Duration of exposure to study drug (only on treatment period) will be summarized descriptively by number of doses and in days.

The investigational drug is applied as a weekly dose. Exposure in days will be calculated by the number of doses taken × 7 days using category (≥ 1mos, ≥ 2 mos., ≥ 3 mos., ≥ 4 mos., ≥ 5 mos.. etc.).

Figures

- Follow-up time (in weeks) will be displayed graphically for each individual, color coded by treatment group and using different shades for on and off treatment.

Listings

2.4.2 A listing showing exposure in doses and days. Prior, concomitant and post therapies

Please refer to Section 2.1.1 for the definition of prior and concomitant medication.

Summary tables

- The number and percentage of participants receiving concomitant medications and significant non-drug therapy will be summarized using the SAF by ATC class and preferred term (according to the World Health Organization drug dictionary (WHO-DD), including Anatomical Therapeutic Chemical (ATC) classification code, using the most recent version at the time of reporting), by treatment group and overall.
- Prior medication and non-drug therapies will also be summarized in a similar way.

2.5 Analysis supporting primary objective(s)

Due to the early termination, the primary estimand and statistical modelling for dose-response relationship is no longer applicable. Primary endpoint of mHTT in CSF will be summarized descriptively. No sensitivity analysis or supplementary analysis will be performed.

The other primary endpoint safety and tolerability will be detailed the safety Section 2.7.

2.5.1 Primary endpoint(s)

2.5.2 Statistical hypothesis, model, and method of analysis

The efficacy primary endpoint is the % change from baseline of mHTT protein concentration in CSF at week 17, which is expressed as:

$$(mHTT_{wk17} - mHTT_{baseline})/ mHTT_{baseline} * 100\%$$

Summary tables

- Summary statistics of raw, change, % change and annualized % change by visit
- Difference between active and placebo for % change by visit
- Mean time (in days) from last dose to lumbar puncture (LP) for week 9 and 17 (protocol scheduled visit window will be used to derive week 9 and week 17)

  Days from last dose to LP = date of {LP} - date of {previous dosing date}

Note, if a dose is taken on the same day of LP performed, the previous dosing date should be used instead of the same day.

Figures

- Spaghetti plot of % change over time (using actual weeks)
- Mean % change over time (using scheduled weeks) and error bar (standard error) by treatment group (group average and N will be added on x-axis)

2.5.3 Handling of intercurrent events

Not applicable.

2.5.4 Handling of missing values not related to intercurrent event

The missing values will be treated as missing. Unless otherwise stated, missing data will not be inputed for the analysis.

2.6 Analysis supporting secondary objectives

2.6.1 Secondary endpoint(s)

The secondary objective is to assess

- The pharmacodynamics (PD) of branaplam in participants with HD on clinical, imaging and biomarker endpoints relevant to HD.
- The pharmacokinetics (PK) of branaplam and its metabolite UFB112 in plasma and CSF

2.6.2 Statistical hypothesis, model, and method of analysis

Secondary endpoints include:

- Clinical endpoints: Unified Huntington's Disease Rating Scale (UHDRS) Total Functional Capacity (TFC), UHDRS Total Motor Score (TMS), UHDRS Independence Scale (IS)

- Vol MRI: Ventricular, Caudate and Total Brain Volume
- PK: branaplam and its metabolite UFB112 in plasma and CSF.
- The biomarker secondary endpoints (total HTT in CSF, [redacted] plasma, and mHTT in [redacted] plasma) will NOT be reported due to assay issues with the vendor.

2.6.2.1 Clinical endpoints

Summary tables

- The clinical endpoints will be summarized with appropriate descriptive tables by visit, and treatment group.

Figures

- Average change from baseline with error bars (standard error) will be provided by group (group average and N will be added on x-axis)

2.6.2.2 Volumetric MRI

In order to assess atrophy rate, volMRI images from follow-up timepoints are compared to those from earlier timepoints using the boundary shift integral (BSI) technique in selected brain regions. The technique determines the total volume through which the boundaries of a given cerebral structure have moved, and hence, it aims at quantifying the amount of change in these selected brain regions. Absolute volume is provided using Medical Image Display and Analysis Software (MIDAS). BSI change is provided by vendor directly in the database, % change and annualized % change will be derived using BSI change and baseline from MIDAS. The output of the method is a change from BL in volume (atrophy). The direction of change (BSI) varies by region as illustrated in Table 2-1.

Table 2-1 BSI measuring atrophy by region

Region	Sign	direction of change
Whole brain	+	mean atrophy, ie volume reduction
Ventricles	+	ventricular expansion, ie volume increase
Caudate	+	mean atrophy, ie volume reduction

For all the volMRI analyses, the QC failures (QCGRADE= “Failed”) should always be excluded. For ADaM data, the sign will be unified for BSI such that “-“ always indicates atrophy (ie a volume reduction), and “+” always indicates an expansion (ie a volume increase) across regions.

Flags:

- on/off treatment flag will be derived at visit level
- Participants with subdural hematoma (from AE panel).

Summary tables

- Summary statistics of raw, change, % change and annualized % change by visit and by on/off trt and by brain region

- Repeat after excluding Participants with subdural hematoma

Figures

- Spaghetti plot of change, and % change over time (at actual weeks) and by treatment group and by brain region
- Mean % change from baseline with error bars (standard error) will be provided by group at scheduled timepoint (group average and N will be added on x-axis)
- Repeat after excluding Participants with subdural hematoma

2.6.2.3 Pharmacokinetic (PK) endpoints

Sample analysis have been executed using all PK samples available and reconciled by SGS. PK samples are only analyzed for participants on active treatment. Therefore, the population of this PK report is the active treatment participants whose PK samples were analyzed.

PK parameters will be estimated using actual times. All unscheduled samples will be reviewed and used for PK parameter analysis if they could be assigned to nominal collection times and are within the treatment period. Unscheduled samples collected outside of the treatment period will not be used for PK parameter assessment if the use cannot be not justified.

Only few samples have been collected at 12 h at week 1 and week 17. The concentrations at 12 h will be listed in the concentration listings and presented in the individual spaghetti plots. The consideration of the samples for PK parameter analysis will be tested in the PK parameter analysis and its use for PK parameter assessment will be decided after data review by the PK expert. Due to the limited number of samples for the 12 h time point compared to the other time points, both time points will not be used for descriptive statistics per timepoint, and not presented in the summary plots.

Outlier in terms of unexpected high or low concentrations will be identified and reviewed during PK parameter estimation. In case an outlier will be identified, the concentration will not be included into the descriptive summary statistics of the concentrations at the respective timepoint and will also not be used for PK parameter derivation. The justification of the exclusion will be added to the concentration data file. The identification of outliers and decision about exclusion of extreme concentration values will be handled by the pharmacokineticist of the study.

Descriptive statistics of branaplam and UFB112 concentrations

Summary tables

The following descriptive summary statistics of branaplam and UFB112 concentrations will be calculated in plasma and CSF for all available visits and timepoints: mean, geometric mean, SD, median, min, max, CV% mean, CV% geometric mean. Geometric mean and CV% will not be calculated in case any value is equal to 0.

Figures

For branaplam and UFB112 in plasma, spaghetti plots showing longitudinal data of all participants across the complete observation period (from first dosing 0 h, showing concentrations from all available time points and visits, up to the last available time point) will

be presented. In addition, for branaplam and UFB112 in plasma, similar spaghetti plots including only the data over the first week will be presented.

PK parameters in plasma

Summary tables

Ctrough will be presented for every visit (from week 2 to week 17). Accumulation ratios between Ctrough later than week 2 and Ctrough at week 2 will be calculated.

For branaplam in plasma, PK parameters including Tmax (h), Cmax (ng/mL), AUC0-168h (h*ng/mL), AUCinf (h*ng/mL) will be presented for week 1 and week 17. In addition, the accumulation ratio (the week 17/week 1 ratio of the parameter) will be calculated for Cmax and AUC0-168h.

Note that, at the week 17 visit, the PK sample is not collected at 168 h as per design. As illustrated in Table 2-2, the time 0 h (pre-dose) concentration value will be used as the concentration at 168h, which enables the estimation of the AUC0-168h.

Table 2-2 Plasma PK samples schedule for week 1 and week 17

Week 1

Day	Time point	PK sample #
1	0 h pre-dose	101
1	4 h postdose	102
1	7 h postdose	103
1	12 h post-dose	104
2	22 h post-dose	105
4	72 h post-dose	106
8	0 h pre-dose as well as 168 h post dose	107

Week 17

Day	Time point	PK sample #
113	0 h pre-dose	115
113	4 h postdose	116
113	7 h postdose	117
113	12 h post-dose	118
114	22 h post-dose	119

116	72 h post-dose	120
NA	168 h post dose will be imputed using 0 h pre-dose on day 113	NA

Figures

Spaghetti plots for Ctrough will be presented over time (from week 2 to week 17).

All above analysis will be repeated for UFB112 plasma. In addition, ratio of UFB112/branaplam will be calculated for the PK parameters (Cmax and AUClast at week 1 and 17) and summarized in tables. The UFB112/branaplam ratio will be calculated as follows:

metabolite ratio =
(PK_parameter_UFB112/PK_parameter_LMI070) * (molecular weight_LMI070/molecular weight_UFB112)

The molecular weights are 393.4 g/mol and 409.4 g/mol for branaplam and UFB112, respectively.

PK parameters in CSF

Summary tables

Branaplam concentrations (Ctrough) in CSF (ng/ml) and plasma (ng/ml) will be summarized at Week 9 and Week 17, as well as the mean concentration ratios: CSF/plasma and CSF/free plasma. The free plasma concentration will be calculated by multiplying the plasma concentration by the fraction unbound (fu: branaplam 0.349, fu UFB112: 0.0220, DMPK R1900562).

Figures

Scatter plots of Ctrough in CSF vs. plasma will be presented to explore the correlation (color coded by visit 9 and 17).

All above analysis will be repeated for UFB112.

Listings

Listings will be provided for all concentrations and PK plasma in both serum and CSF.

2.6.3 Handling of intercurrent events

Not applicable.

2.6.4 Handling of missing values not related to intercurrent event

The missing values will be treated as missing. Unless otherwise stated, missing data will not be inputted for the analysis.

2.7 Safety analyses

All safety analyses will be carried out based on the SAF. For some ECG, vital signs and lab assessments, if time is expected but missing at the end of study visit, will be imputed as 0 hour pre-dose as applicable.

2.7.1 Adverse events (AEs)

AEs will be considered as treatment-emergent (TEAE) if the event is starting after the start of double-blind treatment or the event is present prior to start of double-blind treatment but increased in severity after the start of treatment based on preferred term. This assumes the same AE with increased severity is properly entered as a separate record in the database with start date being the date when severity increases and that a second AE with same severity won't be entered before the same AE is resolved.

Adverse events will be coded using the MedDRA dictionary and presented by system organ class (SOC) and preferred term (PT). The MedDRA version used for reporting the study will be described in a footnote on AE related outputs.

Additionally, Participant with AEs indicative of neurotoxicity / peripheral neuropathy (listed in Table 2-3) will be flagged at participants level for recovery.

Table 2-3 AEs indicative of neuro toxicity / peripheral neuropathy

SOC	Preferred Term	Reported term
Nervous system disorders	Axonal and demyelinating polyneuropathy	SENSOMOTORIC AXONAL POLYNEUROPATHY
Nervous system disorders	Axonal neuropathy	AXONAL NERVE CONDUCTION CHANGE
Nervous system disorders	Coordination abnormal	HAND COORDINATION PROBLEM
Nervous system disorders	Electric shock sensation	PAIN LIKE ELECTRIC SHOCK RIGHT THIGH
Nervous system disorders	Hypogeusia	HYPOGEUSIA
Nervous system disorders	Hyporeflexia	DECREASE IN REFLEXES
Nervous system disorders	Loss of proprioception	PROPRIOCEPTIVE DIFFICULTY IN THE HANDS BILATERALLY
Nervous system disorders	Neuralgia	NEUROPATHIC PAIN
Nervous system disorders	Neuropathy peripheral	NEUROPATHIE
Nervous system disorders	Paraesthesia	TINGLING IN THE UPPER EXTREMITIES
Nervous system disorders	Paraesthesia	TINGLING IN THE LOWER EXTREMITIES
Nervous system disorders	Paraesthesia	PARESTHESIA
Nervous system disorders	Paraesthesia	PARESTHESIA (BILATERAL)

SOC	Preferred Term	Reported term
Nervous system disorders	Paraesthesia	TINGLING IN THE HANDS AND FEET
Nervous system disorders	Peripheral sensory neuropathy	SENSORY NEUROPATHY
Nervous system disorders	Polyneuropathy	POLYNEUROPATHY
Gastrointestinal disorders	Oral discomfort	BURNING MOUTH
		*THICK FIBER SENSORY POLYNEUROPATHY PREDOMINANTLY LOWER EXTREMITIES ENGLISH

* Reported term/SOC has not been coded and is subject to change

Summary tables

The number (and percentage) of participants with TEAE will be summarized by treatment group and presented by the SOCs in alphabetical order and the PTs in descending incidence in the total column. A patient with multiple AEs within a given category is only counted once for summary purposes. TEAEs, regardless of study drug relationship, will be summarized in the following ways:

- By treatment and PT
- By treatment and SOC
- By treatment, SOC and PT
- By treatment, SOC, PT and maximum severity

Separate summaries by SOC and PT will be provided for:

- TEAEs suspected to be study medication related
- TEAEs leading to treatment discontinuation
- TEAEs leading to dose interruptions and/or adjustments
- Serious treatment emergent AEs

Listings

Listing will be provided for all AEs and SAEs.

2.7.1.1 Adverse events of special interest / grouping of AEs

The Compound Case Retrieval Strategy (CRS) will be used to determine the MedDRA search criteria to be used to identify events of special interest. The most recent list of adverse events of special interest at the time of database lock will be used.

Summary tables

- The number (and percentage) of participants who reported treatment emergent adverse events of special interest will be summarized by risk name, PT, maximum severity and treatment group.

In the summary table, risk names will be sorted alphabetically and, within each risk name, the PTs will be sorted in descending order of frequency in the total column. If a patient reported more than one adverse event with the same PT, the AE will be counted only once. If a patient reported more than one AE within the same risk, the patient will be counted only once at that risk.

- SAEs of special interest will also be summarized by risk name, PT, maximum severity and treatment group.

2.7.2 Deaths

Summary tables

Deaths regardless of relationship to study drug by SOC and PT will be summarized on the SAF.

Listings

Deaths will be listed by treatment including the start date of the study treatment, the last date on study treatment, the death date and the primary cause (and contributing cause if any) for death.

2.7.3 Laboratory data

Only central lab parameters will be included in reporting. The summary of laboratory evaluations will be presented for six groups of laboratory tests: Chemistry, Hematology, Urinalysis, Coagulation, Pregnancy Test and additional tests. On presenting abnormalities laboratory data will be grouped and displayed in an alphabetical order within each of the six groups.

Summary tables

- Absolute values and change from baseline will be summarized for continuous laboratory parameters by visit.
- For selected laboratory tests, the number and percentage of participants with newly occurring or worsening laboratory/liver enzyme abnormalities meeting the clinically notable criteria at any time post baseline will be summarized. Clinically notable criteria are defined in Appendix 5.5.

For a participant to meet the criterion of a newly occurring clinically notable value, the participant needs to have a baseline value that is not clinically notable for that parameter. For a participant to meet the criterion of a worsening clinically notable value, the participant needs to have a baseline value that is clinically notable and also have a worse post-baseline value. For participants with missing baseline value, any post-baseline notable value will be considered as newly occurring.

For each participant, all applicable post-baseline values (including unscheduled or unplanned visits) will be checked against the respective criteria. If at least one of the results, for a particular parameter, exceeds the criteria, the participant will be considered as clinically notable abnormal for that parameter. A participant can be counted in both low and high categories. If multiple

abnormality occurrences exist for the same lab parameter, the worst case within a lab parameter will be used to categorize the abnormality.

Figures

- Box-plots for lab parameters will be provided over time by treatment group.

Listings

- Laboratory data of participants with at least one clinically notable value will be listed.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

ECG

Triplicate ECGs (3 ECGs are collected) are performed at week 1 and week 9. Regular ECGs are performed for the rest of scheduled visits. ECG clinically significant abnormalities will be recorded on the eCRF as either medical history/current medical conditions or AEs as appropriate. For the analysis of continuous ECG parameter, for triplicate ECG, the mean value of the 3 ECG measurements will be used, for ECG interpretation, all findings of the 3 ECGs will be considered. ECG parameters include heart rate, PR duration, QT duration, QRS duration, QTcF (QT corrected using Fridericia's correction formula).

Summary tables

- Absolute values and change from baseline will be summarized for ECG parameters by visit and time point.
- The number and percentage of participants with newly occurring or worsening ECG abnormalities at any post-baseline visits will be summarized.

For derivation of notable values of triplicate ECG, the mean of the triplicate ECGs will be used. Notable criteria are defined in Appendix 5.5.

Listings

ECG data of participants with at least one abnormal value will be listed.

Echocardiogram with Global Longitudinal Strain (GLS)

Two dimensional echocardiography measurements will be assessed during the study. Central assessment results will be used for reporting.

Summary tables

Descriptive statistics will be summarized for the following parameters by visit:

- Left ventricular ejection fraction (LVEF)
- Left Ventricular Global Longitudinal Strain (LVGLS)

The number and percentage of participants with clinically notable values at any post baseline visits will be summarized by period, parameters. The clinically notable are defined in Appendix 5.5.

Listings

Echocardiogram data will be listed for the participants with clinically notable values.

2.7.4.2 Vital signs

Vital signs includes temperature, blood pressure (sitting systolic and diastolic) and pulse.

Summary tables

- Absolute values and change from baseline will be summarized for vital signs parameters by visit.
- The number and percentage of participants with newly occurring or worsening clinically notable vital sign values at any time post baseline will be summarized. Clinically notable changes are defined in Appendix 5.5. All applicable post-baseline values (including unscheduled or unplanned visits) will be checked against the respective criteria.

Figures

- Box-plots for vital signs parameters will be provided over time by treatment group.

Listings

- Vital signs data of participants with at least one clinically notable value will be listed.

2.7.4.3 Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire that prospectively assesses suicidal ideation and suicidal behavior. The C-SSRS must be administered at each visit, including unplanned visits. At the first study visit, the “baseline/screening” version of the C-SSRS will be administered. This version assesses suicidal ideation and suicidal behavior during the participant's lifetime and during a predefined period. At subsequent visits, the “since last visit” version will be administered. AE and SAE will be reported respectively for events of “Non-Suicidal Self-Injurious Behavior” and life-threatening events.

Summary tables

- Summary showing numbers and percentages of participants who have an answer “yes” to a suicidal behavior or ideation category at any post-baseline visit.
- The number and percentage of participants who have an answer “yes” to a suicidal behavior or ideation category for the lifetime assessment at screening will be included.

Listings

- All data of participants with any “Yes” on item 4 or item 5 of the Suicidal Ideation section of the CSSRS or any “Yes” on any item on the suicidal behavior section will be listed.

2.7.4.4 Neurological Exam

Neurological examinations are conducted at each visit to monitor for any clinically significant abnormalities. The exam has three subcategories: Motor function, Deep tendon reflexes and Sensory system. Each subcategory includes multiple exams on various body locations. AE and SAE will be reported respectively in case of clinically significant findings.

A worsening at post BL is defined as: a decrease from baseline and the score is **NOT** normal. In order to systematically summarize the worsening from baseline, the following flags will be created to capture different degrees of worsening and recovery:

Flags by visit and by parameter level:

- By visit flag 1 (worsening): reduced grade (decrease) in at least 2 consecutive visits post BL (same worsening at the same parameter/location/laterality). Flag the last visits with worsening.
- By visit flag 2 (recovery): For participants who met the criterion for 2 consecutive visits, flag visits after **last** visit with worsening (this worsening stands for any worsening and don't have to be consecutive) that the grade is back to baseline

Flags by participant level and by three **subcategories** based on the above visit-based:

- participant level flag 1: Participant without any worsening at 2 consecutive visits by Motor function, DTR, and Sensory
- participant level flag 1.5: Participant without any worsening at 2 consecutive visits in any subcategory
- participant level flag 2 (worsening): Participant with any worsening at 2 consecutive visits by Motor function, DTR and Sensory
- participant level flag 3 (recovery): Participant with any worsening at 2 consecutive visits followed by recovery (worsening no longer present in all parameters within the category) by Motor function, DTR and Sensory
- participant level flag 4 (partial recovery): Participant with any worsening at 2 consecutive visits followed by partial recovery (worsening no longer present in at least one of the parameters within the category) by Motor function, DTR and Sensory
- participant level flag 5 (overall worsening): Participant with worsening at 2 consecutive visits in any subcategory
- participant level flag 6 (overall recovery): Participant with worsening at 2 consecutive visits in any subcategory followed by recovery (recovered in all parameters)
- participant level flag 7 (overall partial recovery): Participant with worsening at 2 consecutive visits in any subcategory followed by partial recovery (worsening no longer present in at least one of the parameters)

Note that flags will be created based on weekly basis window instead of protocol scheduled visit window.

Tables

- Summary tables showing number and frequencies of participants for the following categories: no consecutive worsening; consecutive worsening; partial recovery; full recovery by category Motor function, DTR and Sensory and overall

Table 2-4 Example of consecutive worsening and recovery for Neuro Exam

Visit	**Scenario 1** **No** consecutive worsening	**Scenario 2** consecutive worsening followed by recovery	**Scenario 3** consecutive worsening **NOT** followed by recovery
Baseline	normal	normal	normal
Wk1	normal	normal	normal
Wk2	decrease	decrease	normal
Wk3	normal	decrease	decrease
Wk5	decrease	normal	decrease
Wk9	normal	decrease	normal
Wk13	decrease	normal	decrease
…			

2.7.4.5 Neuropathy questionnaire

For neuropathy symptoms: worsening is defined for participants with a change in answer from "No" at baseline to "Yes" at post BL.

Flags by visit and by parameter level:

- By visit flag 1: adverse change indicated by a "YES" response to the same question in the questionnaire in at least 2 consecutive visits. flag the last visit with finding
- By visit flag 2: adverse change indicated by a "YES" response to a question in the questionnaire at any post baseline visit
- By visit flag 3 (recovery): Flag visits after **last** visit with finding (this finding stands for any worsening and don't have to be consecutive) that the answer is back to baseline

Flags by participant level based on the above visit-based:

- Participant level flag 1: Participant without any finding at 2 consecutive visits
- Participant level flag 2: participants with any finding at 2 consecutive visits

- Participant level flag 3 (recovery): participants with any finding at 2 consecutive visits and followed by recovery (finding no longer present in all worsened questionnaire)
- Participant level flag 4 (partial recovery): participants with any finding at 2 consecutive visits and followed by partial recovery (finding no longer present in at least one of the worsened questionnaire)
- Participant level flag 4: Participant without any finding at any visit
- Participant level flag 5: participants with any finding at any visit
- Participant level flag 6 (recovery): participants with any finding and followed by recovery (finding no longer present in all worsened questionnaire)

Participant level flag 6.5 (partial recovery): participants with any finding and followed by partial recovery (finding no longer present in at least one of the worsened questionnaire)Note that, flags will be created based on weekly basis window instead of protocol scheduled visit window.

Tables

- Summary tables showing number and frequencies of participants with at least 2 consecutive worsening change, recovery and partial recovery
- Summary tables showing number and frequencies of participants with any worsening change recovery and partial recovery

Listings

- Listing will be provided for participants with consecutive findings.

2.7.4.6 Nerve conduction study (NCS)

NCS are conducted at baseline and repeated in every patient as per USM.

Table 2-5 Nerve Conduction Safety Parameters

Maximum of 3 measures performed per nerve
1a Sural SNAP Measurement #1 #2 #3
1b Sural Sensory NCV measurement #1 #2 #3
2a Tibial CMAP measurement #1 #2 #3
3b Tibial Motor NCV measurement #1 #2 #3

Numbers with a/b refer to the fact that these measurements are yielded from one and the same stimulation.

There are four parameters included in NCS indicated in Table 2-5, each will be measured three times on either laterality or both. For each parameter, per visit, the max value will be derived to calculate change from baseline:

Change = max (post-BL measurement #1, #2, #3) - max (BL measurement #1, #2, #3)

Note that, if a measurement is not repeated three times, max will be derived using available measurements (maybe less than three times).

The following flags and analyses will be created to capture worsening and recovery for each parameter by laterality: SNAP, sural NVC, tibial NCV and CMAP:

Flags by visit level:

- By visit flag 1: ≥50% reduction
- By visit flag 2 (recovery): For participants who met the criterion flag1 reduction ≥ 50%: Flag the visits after last visit with reduction ≥50% that the criteria (reduction ≥50%) is no longer met

Flags by participant level for each parameter SNAP, sural NVC, tibial NCV and CMAP based on the above visit-based:

- Participant level flag 1: participants without any reduction ≥50% at any visit on any side
- Participant level flag 2: participants with a reduction of ≥ 50% at any visit on any side
- Participant level flag 3: participants with reduction of ≥ 50% at any visit and followed by recovery for all the side(s) that had worsening

Tables

- For each parameter, summary tables showing number and frequencies of participants with reduction of ≥ 50% at any visit, and followed by recovery and partial recovery

Listings

Listing will be provided for participants and parameters with findings.

2.7.4.7 Overall safety findings and recovery

Results from Neuro findings including: NCS, neuro exam, symptoms (AEs and neuro questionnaire) will be summarized in one table for participants on active to show number (%) of participants with finding together with the information about recovery (yes/no) at the end of observation.

2.7.4.8 Ophthalmologic Examination

New findings/changes in ophthalmologic examination, compared to baseline or previous assessment considered clinically significant will be documented and reported as AE.

Summary tables

Frequency table will be provided for any retinal atrophy by visit.

Listings

Listing will be provided for participants with retinal atrophy.

2.8 Pharmacokinetic endpoints

PK as secondary endpoint analysis is described in Section 2.6.

2.9 PD and PK/PD analyses

Not applicable

[redacted]

2.11 Biomarkers

2.11.1 NFL in serum and CSF

Serum and CSF NFL levels are used to monitor neurotoxicity.

Visit level Flags:

- on/off treatment (serum only)
- sNFL > 100 pg/mL
- sNFL > 2 x BL sNFL
- sNFL: > 100 pg/mL or > 2 x BL
- sNFL recovery: for participants who met the criterion for any increase of sNfL (sNFL > 100 pg/mL or sNFL > 2 x BL sNFL) at any visit: Flag the visits after last visit with increase that criteria are no longer met (sNFL ≤ 100 pg/mL and sNFL ≤ 2 x BL sNFL)
- CSF NfL > 10000 pg/ml
- CSF NfL > 2 x BL CSF NfL
- CSF NfL > 2 x CSF NfL of the previous assessment
- CSF NfL > 2 x BL CSF NfL or CSF NfL > 2 x CSF NfL of the previous assessment
- CSF NfL > 10000 pg/ml or CSF NfL > 2 x BL CSF NfL or CSF NfL > 2 x CSF NfL of the previous assessment
- CSF NfL recovery: for participants who met the criterion for any increase of CSF NfL at any visit: Flag the visits after last visit with increase that criteria are no longer met (CSF NfL ≤ 10000 pg/ml and CSF NfL ≤ 2 x BL CSF NfL and CSF NfL ≤ 2 x CSF NfL of the previous assessment)

Participant level flag:

- Participant without any increase in sNfL
- participants with any increase in sNfL
- participants with any increase in sNfL followed by recovery (sNFL ≤ 100 pg/mL and sNFL ≤ 2 x BL sNFL)
- Participant without any increase in CSF NfL;
- participants with any increase in CSF NfL;
- participants with any increase in CSF NfL followed by recovery (CSF NfL ≤ 10000 pg/ml and CSF NfL ≤ 2 x BL CSF NfL and CSF NfL ≤ 2 x CSF NfL of the previous assessment)

Note that, flags will be created based on weekly basis window instead of protocol scheduled visit window.

Summary tables

- Summary statistics of raw values and change from BL by visit and by on/off trt (serum only)
- Frequency table for participants who had any increase together with the information about recovery (yes/no) at the end of observation.
- Repeat for subgroup of participants with at least 9 weeks of treatment

Figures

- sNFL: spaghetti plot of raw values (log scale for sNFL) over time (in weeks) and by treatment group using color coding to show on/off treatment (line changing color) and add dot color to represent criteria
- CSF: spaghetti plot of raw values over time (in weeks) and by treatment group with colored dots highlighting values meeting criteria

2.11.2 mHTT in CSF

Summary tables

- Summary statistics of raw, change, % change and annualized % change by visit
- Difference between active and placebo for % change by visit
- Mean time (in days) from last dose to LP for week 9 and 17 (protocol scheduled visit window will be used to derive week 9 and week 17)

Days from last dose to LP = date of {LP} - date of {previous dosing date}

Note, if a dose is taken on the same day of LP performed, the previous dosing date should be used instead of the same day dosing.

Figures

- Spaghetti plot of % change over time (at actual weeks) and by treatment group
- Average % change from baseline with error bars will be provided by group (at scheduled timepoint, summary statistics and N will be added on x-axis)

[redacted]

[redacted]

2.13 Interim analysis (IA)

IA was performed in April 2023 to share information about the Phase IIb study with broader HD community at HDTC (Huntington's Disease Therapeutics Conference). Analysis plan for IA can be found in SubWay.

3 Sample size calculation

Sample size is determined by feasibility and is evaluated using the primary endpoint mHTT reduction in CSF from baseline to Week 17.

3.1 Primary endpoint(s)

In the analysis, all participants assigned to matching placebo in different treatment arms will be pooled together as one placebo group.

The Multiple Comparison Procedure – Modelling (MCP-Mod) methodology (Bretz et al 2005 and Pinheiro et al 2014) will be employed to test for an overall dose response (DR) signal and to estimate the DR curve. Five candidate sigmoidal Emax models will be used for the testing step with parameter (ED50, h) being (5, 1), (20, 2), (50, 1), (50, 3), and (90, 6).

For the primary endpoint of mHTT reduction in CSF, the planned minimum sample size of N = 75 for 3 dose arms (3 active treatment groups with n = 20 each and a placebo group with n = 15) will be sufficient to reach > 80% power on average for detecting DR signal using MCP-Mod methodology (under the MCP step) with one-sided significance level of 5%. Power will be higher if Cohort 3 and/or Cohort 4 are initiated (N=80 and 100 respectively). The calculations are based on assumption of 40% mHTT lowering in CSF (for the highest dose) and 0% mHTT lowering for placebo. The assumptions on SD were based on Tabrizi et al 2019. An inflation factor of 50% has been applied to the SD of both the active groups (SD = 0.195) and placebo group (SD = 0.471) in order to be conservative leading to an overall treatment effect size of 1. The sample size calculation is performed in RStudio 3.6.1 using package "DoseFinding".

For the safety endpoint, no formal sample size calculation is performed. In general, AEs/SAEs with higher incidence rate will be identified more likely. Low incidence AEs/SAEs are less likely to be observed until later in the study when there are more participants recruited. Table 3-1 presents the likelihood to identify AEs/SAEs at different timing of the cohort gating assessments and interim analysis.

Table 3-1 Likelihood of Identifying AEs/SAEs with Hypothetical Incidence Rate

Time of Assessment	# in active group	Incidence rate	Likelihood to observe at least one AE/SAE
Cohort Gating Assessment 1	16	1%	15%
	5%	56%	
	10%	81%	
Cohort Gating Assessment 2	24	1%	21%
	5%	71%	
	10%	92%	
Cohort Gating Assessment 3	32	1%	28%
	5%	81%	
	10%	97%	
Interim analysis	Minimum 60	1%	45%
	5%	95%	
	10%	99%	

3.2 Secondary endpoint(s)

The study is not powered for secondary endpoint.

4 Change to protocol specified analyses

See above.

5 Appendix

5.1 Imputation rules

If the visit date(s) is missing, no imputation will be implemented.

5.1.1 Study drug

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

5.1.2 AE date imputation

To decide whether the event was prior or post-dosing is carried out as follows:

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

Table 5-1 Imputation of start dates

Missing elements	Rule
Day, month, and year	The date uncertainty is too high to impute a rational date. Therefore, if the year value is missing, the imputed start date is set to NULL.
Day and month	• If available year = year of study treatment start date then – If end date contains a full date and end date is earlier than study treatment start date then set start date = 01JanYYYY – Else set start date = study treatment start date. • If available year > year of study treatment start date then 01JanYYYY • If available year < year of study treatment start date then 01JulYYYY
Day	• If available month and year = month and year of study treatment start date then – If end date contains a full date and end date is earlier than study treatment start date then set start date= 01MONYYYY. – Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY

	• If available month and year < month year of study treatment start date then 15MONYYYY

5.1.3 Concomitant medication date imputation

The same rule as AE imputation will be applied.

5.1.4 Values below LLOQ

For biomarker parameters, values below the lower limit of quantification (LLOQ) will be set to LLOQ/2 for statistical analysis. LLOQ value may differ across samples. For statistical analysis, the sample specific LLOQ and ULOQ value should be used.

5.2 AEs coding/grading

AEs are coded using the MedDRA terminology. The latest version of MedDRA will be used and will be specified in the footnote of relevant output.

AEs grade are assessed by investigators and captured on the AE CRF based on three levels: mild, moderate, and severe.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Visit windows

In general, if two consecutive visits Vt and Vs are x days apart, the upper limit of the visit window for Vt will be Vt+x/2 and the lower limit for the visit Vs will be Vs-x/2 +1 (if x is even). The algorithm needs to ensure that visit windows are not overlapping and that there are no gaps, such that each assessment can be uniquely allocated to one visit window.

Both scheduled and unscheduled assessments will be considered.

In case of competing assessments within a visit window:

- For efficacy parameters: the assessment value closest to the scheduled visit day will be used. In case of equal distances, the earliest assessment value will be used.
- For safety parameters: the worst assessment value within the visit window will be used (see Section 5.4). If more than one assessments are equally worst, the one closer to visit window will be used.

Note that NFL (both serum and CSF) will be considered as safety parameters (the higher the worse).

For tables displaying the worst-case scenario for safety assessment, all assessments within a visit window will be used to identify the worst.

Listings will include all assessments, sorted by date of assessment, flagging unscheduled visits. The listings will flag to indicate the assessment's inclusion in the analysis.

In the below tables, the end of Core period is defined as the day of last assessment for Core period and the end of OLE is defined as the day of last assessment for OLE.

Table 5-2 Visit windows for Neurological Exams, nerve conduction studies, weight, urinalysis, C-SSRS[redacted]

Label	Start day	Target day	End day
Baseline	See baseline assessment of the Study (Section 2.1.1, baseline definition)		
Wk 1			
Wk 2	2	8	11
Wk 3	12	15	22
Wk 5	23	29	43
Wk 9	44	57	71
Wk 13	72	85	99
Wk 17	100	113	127
Wk 21	128	141	155
Wk 25	156	169	183
Wk 29	184	197	211
Wk 33	212	225	239
Wk 37	240	253	267
Wk 41	268	281	295
Wk 45	296	309	323
Wk 49	324	337	351
Wk 53	352	365	421
Wk 69	422	477	until end of study

Table 5-3 Visit window for vital Signs, ECG, Hematology, chemistry, NTproBNP, Troponin

Same as Table 5-2 except the beginning phase:

Label	Start day	Target day	End day
Baseline	See baseline assessment of the Study (Section 2.1.1, baseline definition)		
Wk 1	1 (planned post-dose)	1	4
Wk 2	5	8	11
Wk 3	12	15	22
....			

Table 5-4 Visit windows for echocardiogram

Label	Start day	Target day	End day
Baseline	See baseline assessment of the Study (Section 2.1.1, baseline definition)		
Wk 2			
Wk 3			
Wk 5	2	29	57
Wk 9			
Wk 13	58	85	113
Wk 17			
Wk 21	114	141	169
Wk 25			
Wk 29	170	197	225
Wk 33			
Wk 37			
Wk 41			
Wk 45			
Wk 49			
Wk 53	338	365	393
Wk 57			
Wk 61			
Wk 65			
Wk 69			

Table 5-5 Visit windows for ophthalmologic examination

Label	Start day	Target day	End day
Baseline	See baseline assessment of the Study (Section 2.1.1, baseline definition)		
Wk 2			
Wk 3			
Wk 5			
Wk 9			
Wk 13	2	85	169
Wk 17			
Wk 21			
Wk 25			
Wk 29			
Wk 33			
Wk 37	170	253	309
Wk 41			
Wk 45			
Wk 49			
Wk 53	310	365	449

Label	Start day	Target day	End day
Wk 57			
Wk 61			
Wk 65			
Wk 69			

Table 5-6 Visit windows for UHDRS scores (TFC, TMS, IS, [redacted]), [redacted] and brain MRI

Label	Start day	Target day	End day
Baseline	See baseline assessment of the Study (Section 2.1.1, baseline definition)		
Wk 2			
Wk 3			
Wk 5			
Wk 9			
Wk 13			
Wk 17	2	113	169
Wk 21			
Wk 25			
Wk 29			
Wk 33	170	225	295
Wk 37			
Wk 41			
Wk 45			
Wk 49			
Wk 53	296	365	421
Wk 57			
Wk 61			
Wk 65			
Wk 69	422	477	until end of study

[redacted]

[redacted]

Table 5-8 Visit windows for biomarker collected via lumbar puncture ([redacted] Nfl[redacted])

Label	Start day	Target day	End day
Baseline	See baseline assessment of the Study (Section 2.1.1, baseline definition)		
Wk 1			
Wk 2			
Wk 3			
Wk 5			
Wk 9	2	57	85
Wk 13			
Wk 17	86	113	169
Wk 21			
Wk 25			
Wk 29			
Wk 33	170	225	295
Wk 37			
Wk 41			
Wk 45			
Wk 49			
Wk 53	296	365	421
Wk 57			
Wk 61			
Wk 65			

Label	Start day	Target day	End day
Wk 69	422	477	until end of study

5.5 Notable and abnormality criteria

Please notice that in the below tables, we always used 'baseline' for clarity. For the OLE summaries, please replace by Baseline-Ext, as appropriate.

Table 5-9 Clinically notable criteria for vital signs

Vital Sign Variable	Notable Criteria
Pulse Rate (beats/min)	> 120bpm or Increase of ≥15 bpm from baseline or < 50bpm or Decrease of ≥15 bpm from baseline
Systolic BP (mmHg)	>180 mm Hg or Increase of ≥20 mm Hg from baseline Or < 90 mm Hg or Decrease of ≥ 20 mm Hg from baseline
Diastolic BP (mmHg)	> 105 mmHg or Increase of ≥ 15 mm Hg from baseline Or < 50 mmHg or Decrease of ≥ 15 mm Hg from baseline
Body weight (kg)	Decrease ≥ 7% from baseline weight Increase ≥ 7% from baseline weight
Body Temperature (°C)	High: >=38 °C

Table 5-10 Abnormal ranges for ECG

ECG Parameter	Abnormality Flags	
	Lower bound	Upper bound
Notable value		
HR	<50 bpm or <= -15 bpm change from baseline	>120 bpm or >= 15 bpm change from baseline
RR Interval	< 600 msec	> 1200 msec
PR interval	< 120 msec	> 200 msec
QRS Interval	< 60 msec	> 109 msec
QT Interval	< 320 msec	> 450 msec
QTcF Interval (Fridericia's correction)	< 320 msec	> 450 msec
Notable relative change from previous visit		
QTcF Interval (Fridericia's correction)	≤ -20%;	≥ 20%

Table 5-11 Clinically notable criteria for selected hematology tests

	US or Other unit		SI unit	
Laboratory parameter	Lower bound	Upper bound	Lower bound	Upper bound
Notable value				
Hemoglobin	8(g/dL)	20 (g/dL)	80 (g/L)	200 (g/L)
Hematocrit	24%	60%	0.24 (v/v)	0.6 (v/v)
White blood cells	2 (x103/uL)	35 (x103/uL)	2 (x10E9/L)	35 (x10E9/L)
Platelets	50 (x103/uL)	1000 (x103/uL)	50 (x10E9/L)	1000 (x10E9/L)
Neutrophils	10 (x103/uL)		10 (x10E9/L)	

Table 5-12 Clinically notable criteria for selected chemistry tests

	US or Other unit		SI unit	
Laboratory parameter	Lower bound	Upper bound	Lower bound	Upper bound
Notable value				
Sodium	120 (mmol/L)	160 (mmol/L)	120 (mmol/L)	160 (mmol/L)
Potassium	3 (mmol/L)	6 (mmol/L)	3 (mmol/L)	6 (mmol/L)
Magnesium	1 (mg/dL)	6.1(mg/dL)	0.4 (mmol/L)	2.5 (mmol/L)
Albumin	25 (g/L)		25 (g/L)	
Gamma-glutamyl-transferase (GGT)		3 X ULN		3 X ULN
estimated Glomerular filtration rate (eGFR)	<=30 (mL/min)		<=30 (mL/min)	
Lipase		1.5 x ULN		1.5 x ULN
Amylase		1.5 x ULN		1.5 x ULN
Notable relative change from baseline				
Creatinine*		>50%		>50%
* Baseline Creatinine is calculated as the average of screening and baseline (if either one is missing, the non-missing one will be used as baseline, if multiple screening assessments is available, average screening assessments first and then average with baseline)				

Table 5-13 Clinically notable criteria for selected Other Lab parameters

	US or Other unit		SI unit	
Laboratory parameter	Lower bound	Upper bound	Lower bound	Upper bound

Notable value				
Dipstick proteinuria		≥ 3^+		≥ 3^+
FSH (male only)		> 5 (mIU/mL)		> 5 (U/L)
Troponin T		>= 14.0 (ng/L)		>= 0.014 (ug/L)
NTproBNP		>125 pg/mL		> 14.75 pmol/L
Dipstick Hematuria		≥ 3^+ on		≥ 3^+
Combined rules				
Urine protein-creatinine ratio		Dipstick proteinuria ≥ 3^+ OR PCR ≥ 1g/g (or ≥ 113 mg/mmol equivalent as converted by the measuring laboratory)		Dipstick proteinuria ≥ 3^+ OR PCR ≥ 1g/g (or ≥ 113 mg/mmol equivalent as converted by the measuring laboratory)
Notable relative change from baseline				
FSH (male only)		double from baseline and value> 5 mIU/mL		double from baseline and value> 5 (U/L)

Table 5-14 Clinically notable criteria for Echocardiogram with GLS

Parameter	Lower bound	Upper bound
Notable value		
Left Ventricular Ejection Fraction (LVEF)	< -50%	

Table 5-15 Clinically notable liver function test values

Criterion

ALT > 3 x the upper limit of normal range (ULN) ALT > 5 x ULN ALT > 8 x ULN ALT > 10 x ULN ALT > 20 x ULN
ALT or AST > 3 x ULN ALT or AST > 5 x ULN ALT or AST > 8 x ULN ALT or AST > 10 x ULN ALT or AST > 20 x ULN
Total bilirubin (BILI) > 1 x ULN Total bilirubin (BILI) > 1.5 x ULN Total bilirubin (BILI) > 2 x ULN
ALP > 1.5 x ULN ALP > 2 x ULN ALP > 3 x ULN ALP > 5 x ULN
ALT or AST > 3 x ULN and total bilirubin > 1.5 x ULN ALT or AST > 3 x ULN and total bilirubin > 2 x ULN ALT or AST > 5 x ULN and total bilirubin > 2 x ULN ALT or AST > 8 x ULN and total bilirubin > 2 x ULN ALT or AST > 10 x ULN and total bilirubin > 2 x ULN ALT or AST > 20 x ULN and total bilirubin > 2 x ULN
ALP > 3 x ULN and total bilirubin > 2 x ULN ALP > 5 x ULN and total bilirubin > 2 x ULN
ALT or AST > 3 x ULN and Total Bilirubin > 2 x ULN and ALP < 2 x ULN (Hy's law)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALP = alkaline phosphatase

When a criterion contains multiple laboratory parameters, the criterion will only be considered to have been met when all conditions occur within a 3-day window. A case where all criteria are met at a post-baseline time point will be considered as newly occurring if the criteria are not met at baseline and will be considered as worsening if the criteria are met at baseline and at least one component is worsening from baseline irrespective of whether the other(s) are better. Rule of exclusion criteria of analysis sets.

5.6 Rule of exclusion criteria of analysis sets

Table 5-16 Subject Classification

Analysis Set	PD ID that cause participants to be excluded	Non-PD criteria that cause participants to be excluded
All analysis sets	NA	Not having informed consent
RAS/FAS/SAF/	NA	Not randomized

Analysis Set	PD ID that cause participants to be excluded	Non-PD criteria that cause participants to be excluded
FAS/SAF/	NA	No double-blind study drug taken

6 Reference

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