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Novartis Research and Development

LMI070/branaplam

Clinical Trial Protocol CLMI070C12203 / 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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List of abbreviations

ADME	absorption, distribution, metabolism and excretion
AE	Adverse Event
[redacted]	[redacted]
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASO	AntiSense Oligonucleotide
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
AUCinf	Represents the total drug exposure across time
AUClast	Area under the plasma concentration-time curve from time zero to time of last measurable concentration
AUCtau	To the end of the dosing period
AV	atrioventricular
BE	Blinded extension
BL	Baseline
BUN	Blood Urea Nitrogen
C-SSRS	Columbia Suicide Severity Rating Scale
CABG	coronary artery bypass graft
CAG	cytosine-adenine-guanine
CAP	CAG age product
CDT	carbohydrate deficient transferrin
CFR	Code of Federal Regulation
CGA	Cohort Gating Assessment
[redacted]	[redacted]
CHDI	Child Health and Development Institute
CK	Creatine Kinase
CL/F	Apparent total clearance of the drug from plasma in oral administration
ClinRO	Clinician Reported Outcomes
CMAP	compound motor action potential
Cmax	Maximum concentration
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
COA	Clinical Outcome Assessment
COVID-19	Coronavirus 19
CPK	Creatine phosphokinase
CRA	Clinical research associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computerized tomography

Ctrough	The drug concentration observed at the last planned timepoint prior to dosing.
CTP	Clinical Trial protocol
CTT	Clinical Trial Team
[redacted]	[redacted]
CV	coefficient of variation
CYP3A4	Human Cytochrome P450 3A4
DBP	Diastolic Blood Pressure
DCL	diagnostic confidence level
DDI	Drug-Drug Interaction
DILI	Drug Induced Liver Injury
DIN	Drug-induced nephrotoxicity
DLT	Dose limiting toxicities
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DRF	Dose range finding
DSM-V	Diagnostic and Statistical Manual of Mental Disorders Fifth Text revision
DTI	diffusion tensor imaging
DTRs	Deep tendon reflexes
EC	Ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	electronic Case Report Forms
ED50	median effective dose
EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
Emax	maximum effect
EOS	End of study
EOT	End of treatment
EQ VAS	EQ Visual Analog Scale
[redacted]	[redacted]
ERCP	Endoscopic retrograde cholangiopancreatography
EU	European Union
EXT	Extension
[redacted]	[redacted]
FDA	Food and Drug Administration
fMRI	Functional MRI
FSH	Follicle Stimulating Hormone
FU	Follow up
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GI	gastrointestinal
GLDH	Glutamate dehydrogenase
GLS	Global longitudinal strain

g/L	grams per liter
h	Hour
[redacted]	[redacted]
HBsAg	Hepatitis B virus surface antigen
HSVab	Hepatitis C antibody test
HD	Huntington’s disease
HDL	High density lipoproteins
HbA1c	glycated hemoglobin
hERG	human Ether-à-go-go-Related Gene
HIV	human immunodeficiency virus
HSG	Huntington's Study Group
HTT	Huntingtin
IA	Interim analysis
IB	Investigator's Brochure
IBS	irritable bowel syndrome
ICF	Informed Consent Form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICV	Intracerebroventricular
iDBL	Interim Database Lock
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IS	Independence Scale
IUD	intrauterine device
IUS	Intrauterine system
L	Liter
LDH	lactate dehydrogenase
LDL	Low density lipoproteins
LFT	Liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
LP	Lumbar puncture
LPLV	Last Participant Last Visit
LVEF	Left ventricular ejection fraction
MAR	missing at random
MATE2-k	Multiple Comparisons Procedure - Modelling
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCP-1	Monocyte chemoattractant protein-*1*
MCS	mental component summary
MCV	Mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities

mg	milligram(s)
mHTT	mutant huntingtin protein
MI	multiple imputation
mL	milliliter(s)
MMRM	mixed model repeated measures
MoA	mechanism of action
[redacted]	[redacted]
MPV	mean platelet volume
MRI	magnetic resonance imaging
mRNA	Messenger RNA
MCP-Mod	Multiple Comparison Procedures-Modelling
NCS	Nerve Conduction Study
NCV	nerve conduction velocity
NfL	neurofilament light chain
ng	nanogram(s)
NSAIDs	Nonsteroidal anti-inflammatory drugs
NTproBNP	N-terminal (NT)-pro hormone pro B-type natriuretic peptide
OCT	optical coherence tomography
OLE	open label extension
OLS	ordinary least squares
OLSAF	Open label Safety Analysis Set
[redacted]	[redacted]
PBO	placebo
PCR	protein-creatinine ratio
PCS	physical component summary
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PLTs	platelet(s)
PRO	Patient Reported Outcomes
PT	prothrombin time
PT/INR	prothrombin time/international normalized ratio
QC	Quality control
QMS	quality management system
QTcB	QT interval corrected by Bazett's formula
QTcF	QT interval corrected by Fridericia's formula
RAS	Randomized analysis set
RBC	red blood cell
ROI	Regions of interest
RNA	ribonucleic acid
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAF	Safety set
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome–related coronavirus 2
SBP	Systolic Blood Pressure

SC	Steering Committee
SD	standard deviation
[redacted]	[redacted]
[redacted]	[redacted]
SMA	Spinal Muscular atrophy
SMN	survival motor neuron
SMQ	Standardised MedDRA Queries
SNAP	sensory nerve action potential
SOP	standard operating procedures
SUSAR	Suspected Unexpected Serious Adverse Reactions
[redacted]	[redacted]
T1/2	Elimination half-life
T3	Triiodothyronine
T4	Thyroxine
TBL	total bilirubin
TdP	Torsades de pointes
TEAE	Treatment emergent adverse events
TFC	total functional capacity
THC	Tetrahydrocannabinol
Tmax	time takes to reach Cmax
TMS	Total Motor Scale
TSH	thyroid stimulating hormone
UHDRS	Unified Huntington's Disease Rating Scale
ULN	upper limit of normal
US CFR	United States Code of Federal Regulations
USM	Urgent Safety Measure
UTI	Urinary tract infection
VES	Visit Evaluation Schedule
vMRI	Volumetric MRI
Vz/F	Apparent volume of distribution during terminal phase after non-intravenous administration
WHO	World Health Organization
WK	Week
WOCB	Women of childbearing potential
[redacted]	[redacted]
ZFP	Zinc Finger Proteins

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A specific group of participants fulfilling certain criteria
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.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. 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 milligrams (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 source data/documents 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
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Estimand	As defined in the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an Interactive Response Technology (IRT) system.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study or the participant allocated to an invalid stratification factor
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.

Off-site healthcare Professional (OHP)	A qualified healthcare professional, such as include those used in the study e.g. Nurse, Phlebotomist, Physician, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
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 participant with the condition of interest
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-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
Period	A single component of a study which contains different objectives or populations within that single study.
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant, corresponding to a specific treatment arm assignment
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
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 is screened but is not treated or randomized
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 drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
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.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed participant, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
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.

Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or 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. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.

Amendment 02 (30-Jan-2023)

Amendment rationale

This amendment documents the changes regarding follow-up of participants after the Urgent Safety Measure (USM) Investigator Notifications (IN) distributed on 05-Aug-2022 and 06-Dec-2022, addressing temporary and then permanent study treatment discontinuation, respectively.

The USM Investigator Notification (IN) (05-Aug-2022) was issued by Novartis to immediately and temporarily suspend study treatment for all participants in the study. This was based on the recommendation from the independent Data Monitoring Committee (DMC) and endorsement from the VIBRANT-HD Steering Committee (SC). This decision followed a planned data review by the DMC on 28-Jul-2022 which assessed unblinded data from the study. The DMC did not recommend terminating the study at that time and requested to review follow-up data after study treatment interruption.

The DMC noted several findings suggestive of branaplam-induced neurotoxicity (peripheral neuropathy) in some participants, including:

- Changes in the neurological exam, predominantly new hypoactive and/or absent deep tendon reflexes (DTRs) observed in approximately 1/3 of participants after 13 weeks on treatment
- Increased serum neurofilament light chain (sNfL) levels observed in more than half of the participants after 9 weeks on treatment
- Decreased amplitude in the sural nerve (SNAP) compared to baseline in the 3 participants with both an increase in sNfL and decreased or absent DTRs
- Paresthesia in the lower extremities was reported by two participants. One resolved on treatment within 5 days and one led to early treatment discontinuation and subsequently resolved.

In this communication:

Participants that were actively taking study treatment at the time were instructed to stop the study treatment immediately and to return to the site for an on-site visit no later than 7 business days after being informed of the USM. The USM letter provided details on the assessments to be conducted during that visit. Subsequent to this on-site visit participants were to continue to adhere to their monthly visit evaluation schedule for on-site visits as per protocol (e.g., Week 9, 13, 17, 21, 25 etc.) until further notice. During these visits, all scheduled assessments were to be performed as per protocol with the following exceptions:

- Study drug should no longer be taken by participants
- PK [redacted] including mHTT/HTT (plasma [redacted]) [redacted] should only be collected up to 6 weeks after the last dose of study drug. The 0-Hour timepoint (pre-dose in the protocol pre-USM) is the only required timepoint for collection.
- No additional lumbar puncture will be scheduled thereafter unless deemed necessary by the investigator.
- Follow-up Nerve Conduction Study (NCS) evaluation may be required on a case-by-case basis, in consultation with the DMC.

Participants that had already permanently discontinued study treatment and had scheduled an End of Treatment (EOT) and/or follow up assessments at the time of this USM were to continue the previously agreed upon schedule of assessments as per discussions between investigator and Sponsor.

Subsequently **a Follow-up IN (24-Oct-2022)** was sent to sites to provide an update on activities related to the ongoing study following the initial communication on 05-Aug-2022. No new changes were implemented as the purpose was to remind of the above schedule of assessments exceptions.

The USM Follow-up IN (06-Dec-2022) was issued by Novartis to inform investigators that Novartis has decided to discontinue development of branaplam as a potential treatment for people with Huntington's disease. The decision followed a review of unblinded data from VIBRANT-HD indicating that the benefit:risk of branaplam in Huntington's disease is not positive. This decision was endorsed by the independent Data Monitoring Committee (DMC) as well as the VIBRANT-HD SC.

Key findings from this review included:

- Increased NfL levels in serum and/or cerebrospinal fluid (CSF) observed in the majority of the participants in active arm.
- Changes in the neurological exam on two consecutive visits, predominantly new hypoactive and/or absent DTRs, observed in more than half of participants in the active arm and the majority of participants with 12 weeks or more of treatment.
- Almost half of the participants in the active arm reported symptoms of peripheral neuropathy, either through the neuropathy questionnaire or as an adverse event report.
- Decreased amplitude (50%) in the sural nerve (SNAP) compared to baseline was observed in 7 participants in active arm.
- Preliminary magnetic resonance imaging (MRI) findings suggestive of an increased volume of the lateral ventricles were seen in majority of patients in active arm.
- Steady state mutant HTT lowering in CSF estimated to be approximately 30% with weekly doses of 56 mg branaplam.

Given the high incidence of signs/symptoms of neurotoxicity at the current dose of branaplam, it is considered highly unlikely that lower doses or different dose regimens can be identified that would be safe and provide clinically meaningful benefit.

With the **USM (06-Dec-2022)** letter, study drug is now permanently discontinued in the VIBRANT-HD study and no further cohorts will be initiated. Both the DMC and the SC recommended that all participants who received active treatment (branaplam) remain in the study for follow-up for approximately one year following initial treatment discontinuation, specifically to continue to assess signs and symptoms of peripheral neuropathy as well as to collect additional MRI data.

Additionally, the allocation to treatment (branaplam or placebo) for each of the participants at the sites was provided to investigators in separate communications.

The following actions were to be taken by sites as part of the update to the USM in the VIBRANT-HD study:

- Upon receipt of the communication, the sites were to contact participants as soon as possible informing them of the following and documenting the conversation in the source medical records:
  - Development of branaplam in HD has been terminated due to the high incidence of signals of neurotoxicity at the current dose of branaplam and the low likelihood that lower doses or different dose regimens can be identified that would be safe and provide clinically meaningful benefit. All topics in the Talking Points in the USM must be included in the discussion with the participants; these points explain the safety findings observed in VIBRANT-HD, the rationale for not resuming treatment, and the importance for participants in the active arm to continue study visits.
  - Dosing in the VIBRANT-HD study is permanently discontinued, and no further cohorts will be started.
  - The treatment arm to which they were randomized. Allocation to treatment may be shared with participants either during an upcoming visit or over the phone.
  - Participants randomized to placebo do not require additional safety assessments and can be discontinued from the study at their upcoming Week 33 visit or immediately if this visit has already been completed. The EOT and End of Study (EOS) dispositions can be declared.
  - Participants randomized to branaplam are requested to continue assessments for approximately one year from last dose (as defined below).
  - Novartis has prepared a separate letter for the trial participants that will be sent to them, in local language, if required as per local law and regulation.

With respect to the follow up schedule of assessments per USM, refer to Table 8-5.

Upon completion of the final Week 69 visit, the EOT and the End of Study dispositions (EOS) can be declared for each participant.

Participants that had already permanently discontinued study treatment and had scheduled an EOT and/or follow up assessments at the time of the USM dated 05-Aug-2022 should continue the previously agreed upon schedule of assessments as per discussions between Investigator and Sponsor.

These actions were to be implemented immediately, prior to Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or Health Authority (HA) approval. Last Patient Last Treatment (LPLT) in the VIBRANT-HD trial occurred 08-Aug-2022.

Changes to the protocol:

This protocol amendment documents the final set **of cumulative modifications** after the **USM (06-Dec-2022)** letter.

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 underline for insertions.

A revised Visit Evaluation Schedule (VES) for weeks 33, 53, 69 and EOS is included in Section 8 Visit schedule and assessments.

Additionally, several clarifications have been included in other protocol sections that are impacted by the early program termination (e.g., Data Analysis: all changes to analyses will be documented in the statistical analysis plan).

In addition, clarifications and corrections were made to the protocol summary and the protocol body to improve consistency and understanding.

IRBs/IECs

This amended protocol will be sent to the (IRBs)/ (IECs) and HAs as a substantial amendment following the USM.

The changes described above as part of the USM dated 05-Aug-2022 and Follow-up Notification to Investigators of 06-Dec-2022 were required to enhance monitoring of participant safety (i.e., necessary to eliminate immediate hazards to the trial subjects International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) 3.3.8).

The changes described as part of the Follow-up Notification to Investigators dated 06-Dec-2022 were based on the new unblinded data analyses to lessen participants' burden by reducing the number of assessments and visits, and therefore risk to the participant, and will be implemented prior to IRB/IEC approval upon receipt by Investigator of the corresponding USM Notifications.

This information was to be shared verbally with ongoing participants with the appropriate note made in the participant's source medical records.

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

This amendment is required for patient safety (i.e., necessary to eliminate immediate hazards to the trial subjects ICH GCP 3.3.8). Therefore, it will be implemented prior to IRB/IEC approval, but will be sent for approval as well.

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

Summary of previous amendments

To date, one global amendment has been released with the respective rationale described below:

Amended Protocol v01 (13-May-2022).

Amendment 01 (13-May-2022)

Amendment rationale

This protocol amendment has been prepared to include:

[redacted]

Changes to the protocol

The changes to the protocol are listed below.

1. Section 2 Objectives and endpoints: [redacted]
2. Section 2 Objectives and endpoints: [redacted]
3. Section 2.1 Primary Estimand: Specifies that the clinical question of interest is the effect of branaplam versus placebo on percent reduction of mHTT protein in cerebrospinal fluid (CSF) from baseline to Week 17 when the assigned treatment had been taken over 16 weeks with only limited interruptions or discontinuation in patients with manifest HD, mHTT protein in CSF above a detectable level, and a UHDRS TFC score of >8.
4. Section 5.2 Exclusion criteria: Exclusion criteria #4 specifies that participants should be on a stable dose and regimen of permitted concomitant medications for at least 6 weeks prior to receiving the first dose of study drug which in the medical judgement of the Investigator is not anticipated to change during the study. Associated updates have been made throughout the protocol for consistency.
5. Section 5.2 Exclusion criteria: Exclusion criteria #11 clarifies that total abstinence is an acceptable form of highly effective contraception when this [total abstinence] is consistent with the preferred and usual lifestyle of the participant.
6. Section 5.2 Exclusion criteria: Exclusion criteria #11 was modified to include “or replaced with a permitted medication”.

7. Section 5.2 Exclusion criteria: For exclusion criteria #13, the following language was removed: “Any elevation above upper limit of normal (ULN) of more than one parameter of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase or serum bilirubin will exclude a participant from participation in the study”. Given the fact that a current exclusion exists for any single parameters in serum of ALT, AST, GGT, and alkaline phosphatase must not exceed 2.0 x ULN.
8. Section 5.2 Exclusion criteria: For exclusion criteria #13, the following language was removed: “any elevation above ULN of creatinine or blood urea nitrogen (BUN) and/or urea values”.
9. Section 5.2 Exclusion criteria: Exclusion criteria #13 language was updated to “Evidence of urinary obstruction potentially leading to an impaired renal function at screening”.
10. Section 5.2 Exclusion criteria: Exclusion criteria #14 language was updated to include: “Diagnosis of chronic thrombocytopenia or a bleeding disorder”.
11. Section 5.2 Exclusion criteria: Exclusion criteria #14 language was updated to “Uncontrolled hypertension (average 3 systolic blood pressure [SBP] readings) at screening >140 mmHg or average diastolic blood pressure [DBP] > 90 mmHg excluding values related to white coat syndrome (anxiety)”.
12. Section 6.2.1.2 New section added: Concomitant SARS-CoV-2 / COVID-19 vaccines.
13. Table 6-2 Prohibited medications: Updates to clarify that initiation of medication(s) with a "Known Risk of Torsade de Pointes (TdP)” or medication(s) with “Potential risk of TdP” only applies after a patient has received study drug if required due to life-threatening conditions or other exceptional circumstances. Updates to include the requirements for ECG monitoring thereafter. In addition, clarifications made to section on medication(s) with a "Conditional Risk of TdP”.
14. Section 6.2.1 Concomitant Therapy: section was updated to include the following language “participants should be on a stable dose and regimen of permitted chronic concomitant medications for at least 6 weeks prior to receiving the first dose of study drug”. Associated updates have been made throughout the protocol for consistency.
15. Table 6-3 Investigator Guidance for Dose interruption/discontinuation, follow-up and re-initiation of study treatment for select Adverse Events: Updates to this table include the addition of amylase and lipase as select adverse events and associated recommendations for study treatment dose interruption/discontinuation.
16. Section 8 Visit Schedule and Assessments: language, such as “missed or rescheduled visits should not lead to automatic discontinuation” was added to this section to comply with language in clinical trial protocol (CTP) v5.0 template. Also added template language “if the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected”.
17. Table 8-1 Allowable Visit Windows: visit window for dose range finding (DRF) period updated to ±1 day.
18. Section 8.3.4 Imaging: language updated to include: “Brain magnetic resonance imaging (MRI) scans will be performed at screening and at each time point without gadolinium

contrast" and "in the event an MRI cannot be performed after randomization, a local computerized tomography (CT) may be collected under exceptional circumstances for safety evaluations only, using the site's local imaging protocol and standard procedures".

19. Table 8-7 Laboratory Assessments: table updated to include the following: "In case of severe amylase/lipase elevations (> 2x ULN), a reflex fractionation amylase test is recommended (local testing acceptable)".
20. Table 8-8 Central ECG collection plan: new formatted table added to improve readability of the protocol required timepoints and fasting status of triplicate ECGs. No new timepoints were added.
21. Section 8.4.2 Cardiac Assessments: updated to include language for the method for calculating for LVEF <50% (biplane Simpson method); and the central reading vendor will only send alert notifications to sites when the LVEF and GLS thresholds defined above are met.
22. Section 8.4.3 Pregnancy and assessments of fertility: language updated to include clarifications for permanent sterilization and post-menopausal status at screening/baseline.
23. Section 8.4.4 Neurological assessments: The language in this section regarding Neurofilament light chain (NfL) has been **deleted** to clarify that NfL concentrations in serum are not considered an established marker of peripheral nerve dysfunction in the study. Safety evaluation of peripheral nerve function will be exam-based and includes neurological examinations and nerve conduction studies. Associated updates have been made throughout the protocol for consistency.
24. Section 9.1.2 Withdrawal of informed consent and exercise of patient's data privacy rights: updates specify WOC definitions.
25. Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse: table **deleted** as it is no longer needed since language was incorporated into section paragraph.
26. Section 10.1 Definition of adverse events and reporting requirements: language included from the new CTP v5.0 template.
27. Section 10.1.3 SAE reporting: updated the language per protocol template v5.0 specifying that every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety immediately, without undue delay, and under no circumstances later than within 24 hours of learning of its occurrence, including follow-up information.
28. Section 10.1.5 Updates to language on reporting of study treatment errors including misuse/abuse.
29. Section 10.2.1 Liver safety monitoring: specifies follow up on potential drug-induced liver injury (DILI) cases.
30. Table 10-1 new table added to include Novartis guidance on specific clinical and diagnostic follow up assessments for potential DILI events.
31. Section 12.1 Data analysis and statistical methods: added new analysis group OLSAF (Open label Safety Analysis Set).

32. Section 12.4.7 Supplementary analysis: following language included: "Supplementary analysis will be specified in the Statistical Analysis Plan (SAP) (including investigating the robustness of the Multiple Comparison Procedures-Modelling (MCP-Mod))".

[redacted]

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 and Health Authority approval according to local regulations 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.

Protocol summary

Protocol number	CLMI070C12203
Full Title	A randomized, double-blind, placebo-controlled dose range finding study with open-label extension to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of Branaplam/LMI070 when administered as weekly oral doses in participants with early manifest Huntington's disease (HD)
Brief title	A dose range finding safety study of Branaplam/LMI070 administered as weekly oral doses in participants with early manifest Huntington's disease
Sponsor and Clinical Phase	Novartis/2b
Investigation type	Drug
Study type	Interventional
Study Indication /Medical Condition:	Huntington's disease
Purpose and rationale	This is the first study of branaplam in adult HD patients. The study aims to explore a range of doses in order to select a safe and tolerable dose that lowers mutant huntingtin protein (mHTT) levels in the cerebrospinal fluid (CSF) to a degree expected to be efficacious over longer periods of time. As a slowing in progression of clinical symptoms or biomarkers of neurodegeneration require large sample size and treatment duration, reduction in the amount of mHTT, in line with branaplam's expected mechanism of action (MoA), is thought to be a relevant biomarker to measure target engagement and demonstrate proof of concept and guide dose selection for later phase confirmatory studies. *S*tudy participants will be randomly assigned to treatment arms in the Core Period, and once all randomized participants have completed the Week 17 visit, an IA will be performed to determine the appropriate dose(s) for the open label extension (OLE). The decision for the OLE dose will be based on mHTT lowering in CSF at the end of the dose-range finding (DRF) period, as well as safety, tolerability and other biomarker data collected throughout the Core Period. All patients will then enter OLE, be assigned to the new dose, and continue to be assessed for safety and efficacy for approximately an additional year. Clinical and biomarker measures of HD will also be evaluated in this study. This includes volumetric magnetic resonance imaging (MRI) of brain, CSF and blood biomarkers, HD rating scales and clinical assessments.
Primary Objective(s)	**As per the Urgent Safety Measure (USM) follow-up notification dated 06-Dec-2022, the original objectives are no longer applicable due to permanent discontinuation of study treatment. All efficacy and safety data collected during the core (double-blinded and unblinded) will be summarized descriptively based on cumulative data.** Pre-USM: • To assess the dose-response relationship of branaplam administered over 16 weeks on mHTT protein change from baseline (BL) in CSF. • To evaluate the safety and tolerability of branaplam when administered for 16 weeks or longer in participants with HD.
Secondary Objectives	**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. All efficacy and safety data collected during the core (double-blinded and unblinded) will be summarized descriptively based on cumulative data.** • Pre-USM:To assess the pharmacodynamics of branaplam in participants with HD on clinical, imaging, and biomarker endpoints relevant to HD. • To assess pharmacokinetics of branaplam and its metabolite UFB112 in plasma and CSF

Study design	**As per the USM follow-up notification dated 06-Dec-2022, the study treatment has been permanently discontinued and only Cohort 1 was enrolled. Participants who received active treatment (branaplam) will remain in the study for follow-up for approximately one year following initial treatment discontinuation. OLE is no longer applicable.**
	Pre-USM:
	This study is a randomized, double-blind, placebo-controlled study with a variable treatment duration (between approximately 17 weeks to approximately 53 weeks) for the core period and a one-year OLE in approximately 75 early-stage manifest HD patients.
	After Screening period and BL assessments, this study will be conducted in two Treatment Periods:
	• The Core Period consists of a 17-week double-blind, placebo-controlled, Dose Range Finding (DRF) portion of the study, followed by a Blinded Extension (BE) of variable duration (up to approximately 53 weeks; duration is dependent on timing of randomization and recruitment rate). The DRF Period will evaluate the safety, tolerability, pharmacokinetic(s) (PK) and pharmacodynamic(s) (PD) of branaplam, as well as determine the optimal dose(s) to explore in further clinical evaluations using all available data collected at the time the last randomized patient in the study completes the Week 17 visit assessments which captures a full 16 weeks of treatment with study drug.
	• The OLE is a one-year open-label extension to assess both long term safety and tolerability, as well as the efficacy of the recommended optimal dose(s) for branaplam. If branaplam development in HD remains ongoing at the end of the OLE, the study will either be (a) amended to extend the OLE beyond a year, or (b) a separate extension study will be initiated to offer continued access to branaplam. Study participants from the OLE may be eligible to roll over into this separate extension study.
	The study design uses a staggered cohort approach, allowing safety and tolerability of lower doses to be assessed before randomizing subjects to higher doses.
	The Core Period consists of 3 treatment arms; each treatment arm will enroll approximately 25 patients, dependent on the total number of cohorts initiated.
	Treatment arms are defined as:
	• Cohort 1: Treatment Arm A: Branaplam 56 mg oral solution or matching placebo (PBO), once weekly
	• Cohort 2: Treatment Arm B: Branaplam 112 mg oral solution or matching PBO, once weekly
	• Cohort 3:
	  • Treatment Arm C: Branaplam 154 mg oral solution or matching PBO, once weekly or
	  • Treatment Arm X: Branaplam 84 mg oral solution or matching PBO, once weekly or
	  • Treatment Arm Y: Branaplam 28 mg oral solution or matching PBO, once weekly
	At the time of the Cohort Gating Assessments (CGAs), all available data will be reviewed from a safety and dose finding perspective by an independent Sponsor team to support the decision to open the next cohort. The independent Data Monitoring Committee (DMC) will review the data separately. The decision to open a new cohort will be made by the Sponsor in consultation with the DMC.
	Cohort 1 includes Treatment Arm A (56 mg or matching placebo). Based on the results from the review of the data during CGA 1, a decision will be made regarding the initiation of Cohort 2 (Treatment Arm B, 112 mg or matching placebo). Based on the results from the review of the data during CGA 2, a decision will be made to select the Treatment Arm in Cohort 3. If Cohort 3 is initiated, and based on the data review during CGA 2, the decision will be made to initiate the next higher dose

	(Treatment Arm C, 154 mg or matching placebo) **or** an intermediary dose (Treatment Arm X, 84 mg or matching placebo) **or** a lower dose (Treatment Arm Y, 28 mg or matching placebo). Participants will be randomized in an equal randomization rate among the open treatment arms, and then in a 4:1 ratio for active vs. placebo within each arm. After a participant completes the DRF period (Week 17) he/she will seamlessly transition to the BE, by continuing on his/her blinded DRF treatment. All patients will remain in the BE until the results of the IA are available and the recommended optimal extension dose(s) is/are selected for OLE. Duration in the BE is therefore variable, longer for those that were randomized earlier in the study. After the last randomized participant in the study completes all the DRF (Week 17) assessments, an un-blinded IA will be conducted. All data available at this time, including, but not limited to safety/tolerability as well as mHTT and total HTT lowering in CSF, plasma [redacted] will be assessed to determine optimal dose(s) for OLE. After the IA and confirmation of selected dose(s), all patients from the blinded Core Period will roll over to OLE; patients will be re-assigned from their blinded Core Period dosing onto the newly selected open label OLE dose(s). OLE is a one-year open label treatment and safety monitoring part of the study.
Population	Approximately 75 male or female patients with confirmed Stage 1 or 2 HD and a UHDRS total functional capacity (TFC) score of >8 will be enrolled in this study to allow for approximately 25 participants per treatment arm. Fewer participants will be enrolled if all treatment arms are not opened. Manifest patients with a TFC >8 are selected because they are late enough in the disease process so that mHTT can be measured in their CSF and clinical symptoms can be readily assessed, and early enough in the disease process so that they can comply with the protocol defined schedule of assessments during Core blinded treatment period (DRF and BE) and be monitored for disease progression and safety throughout the OLE. Eligible patients starting at the age of 25 will be enrolled to avoid the very high CAG repeats associated with early disease onset as these patients could be considered to have a more rapidly progressing phenotype. An age cap of 75 years is employed to avoid age-related comorbidities that typically occur above this age.
Key Inclusion criteria	**As per the USM follow-up notification dated 06-Dec-2022, no further participants will be enrolled in this study**. Participants eligible for inclusion in this study must meet all of the following criteria: 1. Signed informed consent must be obtained prior to participation in the study. 2. Must be capable of providing informed consent (in the opinion of the Investigator). 3. Clinically diagnosed Stage 1 or 2 Huntington's disease with a diagnostic confidence level (DCL) = 4 and a Unified Huntington's Disease Rating Scale (UHDRS) Total Functional Capacity (TFC) >8 at screening. 4. Genetically confirmed Huntington's disease, with presence of ≥40 cytosine-adenine-guanine (CAG) repeats in the huntingtin gene. For participants without prior documentation, a sample must be sent to the central study laboratory and confirmation of the CAG repeat length for these participants must be obtained prior to randomization. For participants with previously existing documentation of their CAG repeat length, it is acceptable to use this prior data to qualify for randomization. These participants must also submit a sample for CAG repeat testing to be conducted by the central study laboratory. 5. Male and female participants between 25 to 75 years of age, inclusive, on the day of Informed Consent signature.
Key Exclusion criteria	**As per the USM follow-up notification 06-Dec-2022, no further participants will be enrolled in this study.** Participants meeting any of the following criteria are not eligible for inclusion in this study:

	1. Use of other investigational drugs within 5 half-lives of the first dose of study drug, or within 30 days, whichever is longer. 2. Prior participation in clinical trial investigating a huntingtin-lowering therapy (unless participant received only placebo). 3. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes. 4a. Participants taking medications prohibited by the protocol. In addition, participants should be on a stable dose and regimen of permitted chronic concomitant medications for at least 6 weeks prior to receiving the first dose of study drug which in the medical judgement of the Investigator is not anticipated to change during the study. If new medications are initiated during Screening, laboratory evaluations must meet eligibility criteria before first dose of study drug. 5. Any medical history, lumbar surgery or condition that would interfere with the ability to complete the protocol specified assessments, (e.g., history of brain or spinal injury that would interfere with the lumbar puncture (LP) or CSF circulation, implanted cerebrospinal shunt, conditions precluding MRI scans, herniated disc, etc.). 6. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, regardless of whether there is evidence of local recurrence or metastases. 7. Participant has other severe, acute or chronic medical conditions including unstable psychiatric conditions, or laboratory abnormalities that in the opinion of the Investigator may increase the risk associated with study participation, or that may interfere with the interpretation of the study results. 8. Score “yes” on item 4 or item 5 of the Suicidal Ideation section of the Columbia Suicide Severity Rating Scale (C-SSRS), if this ideation occurred in the past 6 months from the Screening visit, or “yes” on any item of the Suicidal Behavior section, except for the “Non-Suicidal Self-Injurious Behavior” (item also included in the Suicidal Behavior section), if this behavior occurred in the past 2 years. 9. Pregnant or nursing (lactating) women. Women of child-bearing potential (WOCB) should not become pregnant during the study or 7 months after stopping study medication. 10a.**Sexually active males** unwilling to use a condom during intercourse while taking study treatment and for 120 days (4 months) after the last dose of the study treatment. A condom is required for all sexually active male participants even if they are surgically sterile with a vasectomy to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their female partner. In addition, male participants must not donate sperm for the time period specified above. A condom is required to be used also by vasectomized men as well during intercourse with a male partner of the study participant. The branaplam exposure in body fluids is not known. Since branaplam is genotoxic, sexual partners are advised to avoid direct contact with semen of participants, to prevent exposure to the study drug. 11a. **Women of child-bearing potential**, defined as all heterosexually active women physiologically capable of becoming pregnant, unless they are using one highly effective method of contraception during dosing and for 7 months after stopping the study medication. Highly effective methods of birth control are those methods that have a less than 1% chance of an unwanted pregnancy for 1 year. **In addition to one highly effective method of contraception, a condom is required for all male partners of female participants to prevent fathering a child AND to prevent exposure of study treatment via vaginal fluid to the partner, until at least 7 months following the last dose of study treatment.** WOCB potential must not donate their eggs for 7 months after the last dose of study treatment.

	Oral contraception cannot be considered due to potential decreased efficacy as potential drug-drug interactions (DDI) with branaplam. Highly effective contraception methods include: • Total abstinence (when this is consistent with the preferred and usual lifestyle of the participant). [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are **NOT** acceptable methods of contraception for heterosexually active participants.] • Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy or bilateral tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment. • Male sterilization of partners (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner. • Use of an intrauterine device (IUD) or intrauterine system (IUS) which is MRI compatible. In case local regulations are more stringent than the contraception methods listed above, local regulations apply and will be described in the ICF. Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms). Women are considered not of child-bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks prior to Screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential. The branaplam exposure in body fluids is not known. Since branaplam is genotoxic, sexual partners are advised to avoid direct contact with vaginal fluid of participants, to prevent exposure to the study drug. 12a. History of: • Gene therapy or cell transplantation or any other experimental brain surgery • Hepatitis B or hepatitis C or serologic evidence for active viral hepatitis (HBsAg and HCVab test) • Immunodeficiency diseases, including a positive human immunodeficiency virus (HIV) test result • Current evidence of drug or alcohol abuse in the 12 months prior to screening, as defined by the Diagnostic and Statistical Manual of Mental Disorders Fifth Text revision (DSM-V) criteria for substance abuse. For former abusers, abstinence should be confirmed by laboratory tests (drug testing and/or carbohydrate deficient transferrin (CDT) level in blood). • Use of Tetra-Hydro-Cannabinoid (THC)/ cannabinoid containing substances is allowed as per local regulations and/or local medical practice if in the opinion of the Investigator, use does not represent an exclusionary condition, does not constitute abuse and does not affect cognition, and provided that participants are currently treated with a stable regimen for at least 12 weeks prior to first dose of study drug. Note: If initiated during the study, use must be withheld for 72 hours prior to any cognitive and/or motor assessments. 13a. Any surgical or medical condition which might put the participant at risk in case of participation in the study. The Investigator should make this determination in consideration of the participant's medical history and/or clinical or laboratory evidence of any of the following at the Screening visit: • Unstable chronic gastrointestinal condition such as history of Crohn's disease, Ulcerative colitis, poorly controlled Irritable Bowel Syndrome (IBS) or similar chronic gastrointestinal (GI) conditions • Neurologic or neuromuscular conditions other than HD

	• History of or physical examination consistent with peripheral neuropathy or nerve conduction findings compatible with electrodiagnostic evidence of neuropathy • Participants who have a known diagnosis of diabetes mellitus or who do not have a known diagnosis of diabetes with a glycated hemoglobin (HbA1c) >6.5% • Lipase, total bilirubin or amylase must not exceed the 1.5x ULN • Liver disease or liver injury as indicated by abnormal liver function tests • Any of the following single parameters in serum of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase must not exceed 2.0 x ULN. • History of renal injury / renal disease or presence of severe impaired renal function as indicated by an estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease (MDRD) equation <30 (mL/min/1.73 m²) (allowing for age-related GFR decline in the mild to moderate range) or the presence >3+ proteinuria/ hematuria on a single (one time) repeated urinalysis • Evidence of urinary obstruction potentially leading to an impaired renal function at screening • Diagnosis of testicular atrophy • Diagnosis of primary ovarian failure • Clinically significant retinal abnormalities on ophthalmologic examination by a local Ophthalmologist • Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed at least 3 days prior to first study drug administration (Day 1) • Any objects and/or implants in the body which may be contraindicated for MRI, such as pacemakers and some IUD • Diagnosis of chronic thrombocytopenia or a bleeding disorder 14a. Cardiovascular exclusion criteria: • History or current diagnosis of electrocardiogram (ECG) abnormalities indicating significant risk or safety concern for study participants such as: History of myocardial infarction, angina pectoris, heart failure, or coronary artery bypass graft (CABG). Screening echocardiogram (ECHO) abnormalities per investigator's medical judgement including but not limited to left ventricular ejection fraction (LVEF) <50%. • Screening or baseline not within normal range Troponin or N-terminal (NT)-pro hormone pro B-type natriuretic peptide (NTproBNP) values • History or concomitant clinically significant cardiac arrhythmias (e.g., sustained ventricular tachycardia, atrial fibrillation, etc.), complete left bundle branch block, high-grade atrioventricular (AV) block (e.g., bifascicular block, Mobitz type II and third-degree AV block). • History of familial long QT syndrome or known family history of Torsade de Pointes, risks for Torsades de Pointes (TdP) including uncorrected hypokalemia or hypomagnesemia, history of clinically significant/symptomatic bradycardia and a family history of idiopathic sudden death. • Resting QT interval corrected by Fridericia's formula (QTcF) ≥450 msec (male) or ≥460 msec (female) at pretreatment [screening or baseline] (as mean of triplicate ECGs), or inability to determine the QTcF interval. • Use of agents known to prolong the QT interval or with a known or possible risk of Torsade de Pointes unless it can be permanently discontinued or replaced with a permitted medication for the duration of study. (See Table 6-2) • Uncontrolled hypertension (average 3 systolic blood pressure [SBP] readings) at screening >140 mmHg or average diastolic blood pressure [DBP] > 90 mmHg excluding values related to white coat syndrome (anxiety-related), per Investigator's judgement.

	15a. Any clinically significant hematological abnormality as assessed by the Site Investigator at screening and/or laboratory evidence of any of the following: • International Normalized Ratio (INR), PT, or APTT that are not within normal ranges • Hemoglobin <110 grams per liter (g/L) (females) or <120 g/L (males) • Platelets ≤100 x 10^9/ Liter (L) • Platelet count >500 x 10^9/L • Neutrophil count <1.5 x 10^9/L • Leukocytes <3.0 x 10^9/L
Study treatment	**As per the USM follow-up notification dated 06-Dec-2022, the study treatment has been permanently discontinued; the last dose administered was 08-Aug-22; and no further enrollment is allowed**. The investigational treatment for this study is branaplam and matching placebo. Novartis will supply branaplam and matching placebo in 6 mL vials containing 5 mL of study treatment. The vials will be packed in boxes containing 4 vials each. All eligible participants will be randomized via Interactive Response Technology (IRT) to one of the available treatment arms. At the Week 1 visit, participants will be randomized to one of the following treatment arms in a ratio of 4:1, active vs. PBO: • Treatment Arm A: 56 mg oral solution or matching PBO, weekly • Treatment Arm B: 112 mg oral solution or matching PBO, weekly • Treatment Arm C: 154 mg oral solution or matching PBO, weekly • Treatment Arm X: 84 mg oral solution or matching PBO, weekly • Treatment Arm Y: 28 mg oral solution or matching PBO, weekly Treatment Arm assignment for an individual participant will be determined by which treatment arms are open at the time of the participant screening. For Treatment Arms C, X and Y, only one of the three will be initiated. PBO is embedded within each Treatment Arm.
Efficacy assessments	Efficacy assessments include the following: • Unified Huntington's Disease Rating Scales (UHDRS) components: • Total Functional Capacity (TFC) • Total Motor Scale (TMS) • Independence Scale (IS) [redacted]
Pharmacodynamic assessments	• Volumetric MRI • Mutant Huntingtin Protein (mHTT) and total Huntingtin protein (HTT) in CSF, plasma
Pharmacokinetic assessments	PK samples from plasma and CSF will be obtained from all participants at all dose levels. Branaplam and its metabolite UFB112 will be determined in plasma and CSF by a validated LC-MS/MS method
Key safety assessments	Safety assessments include the following: **Pre-USM:** • Physical Examination • Vital signs • Height and weight • Electrocardiograms (ECGs)

	• Neurological evaluations including neurological Examinations and Nerve conduction study (NCS) • Echocardiograms (ECHO) with Global longitudinal strain (GLS) • Ophthalmological assessments • Laboratory assessments (including cardiac enzymes and Follicle Stimulating Hormone (FSH)) • Pregnancy tests • Columbia Suicide Severity Rating Scale (C-SSRS) [redacted] **Post-USM: refer to Table 8-5 for post-USM safety assessments.**
Other assessments	[redacted]
Data analysis	**Pre- USM follow-up notification dated Dec-06-2022**: There are two primary objectives in this study: 1. To confirm an overall dose-response (DR) relationship and identify optimal dose(s) for open label extension and future studies in HD. 2. To evaluate the safety and tolerability of various doses of branaplam over 16 weeks or longer in patients with HD. The primary data analysis, so called the IA, will be performed at the end of DRF, when all randomized participants have completed their last assessment of this DRF period (Week 17, 16 weeks on treatment). The analysis may include 4 treatment groups (3 active, 1 placebo) depending on the decision(s) of the Cohort Gating Assessment(s). The clinical question of interest is the effect of branaplam versus placebo on percent reduction of mHTT protein in CSF from baseline to Week 17 when the assigned treatment had been taken over 16 weeks with only limited interruptions or discontinuation in patients with manifest HD, mHTT protein in CSF above a detectable level, and a UHDRS TFC score of >8. The primary estimand is described by the following attributes: 1. Population: male or female patients with confirmed Stage 1 or 2 HD (manifest), mHTT protein in CSF above detectable level, and a UHDRS TFC score of >8 in line with protocol defined Inclusion/Exclusion (I/E) criteria. 2. Primary variable: change from BL (%) to Week 17 in mHTT protein in CSF. 3. Treatment of interest: the randomized treatment (allowed medication and prohibited medication) taken for the DRF period (16 weeks of treatment) with a maximum of

	25% missed doses (i.e., 4 doses for weekly dosing during DRF period) AND less than 2 consecutive weeks off treatment prior to the Week 17 visit LP. The summary measure: reduction (%) of mHTT protein in CSF from BL to Week 17 visit for various doses (dose-response relationship). The justification is, that the primary estimand targets the treatment effect of branaplam for those who can tolerate it for 16 weeks (with limited interruption/discontinuation) in order to inform the selection of an optimal dose. The primary estimand will only focus on the efficacy of branaplam on the reduction of mHTT in CSF (one of the primary objectives). The safety perspective will be evaluated in parallel. Dose selection for Open Label Extension and subsequent Phase 3 studies will be based on a combination of efficacy and safety results. However, estimands are not defined for the safety objective, safety analyses will be specified. No inferential and model based statistical analyses are planned for any safety or tolerability endpoints. **Post USM: Refer to** Section 12 **Data Analysis and Statistical Methods**
Data Monitoring/Other Committee	Yes
Key words	Huntington's disease, branaplam, dose range finding, early manifest, LMI070, safety and tolerability

1 Introduction

1.1 Background

Huntington's disease (HD) is a fatal, neurodegenerative disorder for which no disease modifying therapies exist. The disease is characterized by a progressive worsening in motor and cognitive function and psychiatric symptoms (Walker 2007, Ross et al 2014). The current standard of care is limited to therapies for management of symptoms, which have no effect on the course of disease. The medical need for therapies that either slow progression or delay the onset of HD remains unmet (Caron et al 2018).

HD is one of several inherited neurodegenerative diseases caused by trinucleotide repeat expansions in a gene (i.e., a "triplet repeat" disease) (MacDonald et al 1993). Inheritance of HD is autosomal dominant. The causative expansion in the coding region of the huntingtin gene is a series of cytosine-adenine-guanine (CAG) repeats that lead to incorporation of an abnormally long string of glutamine residues in the final protein (mutant huntingtin, (mHTT)), resulting in misfolding and toxic aggregation/accumulation (Shao and Diamond 2007, Ross and Tabrizi 2011). HD occurs when there are at least 40 CAG repeats in the HTT gene, but also occurs with a reduced penetrance in those with 36-39 repeats (McNeil et al 1997).

Adult-onset HD is a slowly progressive neurodegenerative disease. The underlying pathogenic process begins at least 10-15 years before overt motor symptoms appear (Ross et al 2014). Clinical diagnosis is based on unequivocal, extrapyramidal motor symptoms and genetic or family history confirmation (Ross et al 2019). Once symptoms manifest, patients live another 15-20 years. The age of onset of symptoms is inversely proportional to the length of the CAG repeat and is typically between 35 and 50 (Wexler et al 2004). Clinical decline is measured using the Unified Huntington's Disease Rating Scale Total Functional Capacity Scale (UHDRS-TFC). Using this scale, which ranges from 0-13, patients progress from stage 1 (mild) through stage 5 (advanced). Prior to symptom onset, people with HD go through pre-symptomatic and prodromal stages. In the latter, subtle behavioral and cognitive symptoms develop, along with clear signs of brain atrophy (Tabrizi et al 2013). By the time of clinical diagnosis, about half of the striatum in the brain has atrophied, along with significant neurodegeneration in other parts.

It is well established that mutant huntingtin protein (mHTT) is the proximal cause of disease onset and progression (Walker 2007, Ross and Tabrizi 2011). The goal of HTT-lowering therapies is to slow the decline in disease progression by reducing the levels of the toxic protein in the brain (Tabrizi et al 2019a). Complete knockout of HTT is lethal during embryogenesis, but people with only a single copy of the gene develop normally, and animal studies provide evidence that reducing the levels of mutant protein in the brain before or after symptom onset can delay or reduce the phenotypic expression of the disease (Kaemmerer and Grondin 2019). There is abundant pre-clinical evidence to support the idea that lowering HTT transcript and protein should lead to slowing of progression of HD (Kordasiewicz et al 2012, Stanek et al 2013, Southwell et al 2018, Zeitler et al 2019). Further, using multiple modalities (small molecules, ASOs, microRNAs, Zinc Finger Proteins (ZFPs)), it has been demonstrated that lowering the expression of total or mHTT in the brain is associated with a corresponding lowering of protein in the CSF. Lastly, lowering of total HTT following repeated intrathecal (IT) injections of an

ASO has been shown to be safe and tolerable at doses that lower HTT in the CSF by 40-50% (Tabrizi et al 2019b).

Branaplam (LMI070) is a low molecular weight messenger ribonucleic acid (RNA) splicing modifier with clinically demonstrated efficacy in the treatment of infants with Type 1 spinal muscular atrophy (SMA). The efficacy in Type 1 SMA is due to promotion of inclusion of exon 7 during transcription from Survival Motor Neuron 2 (SMN2). This leads to greater production of functional SMN protein from SMN2 and ameliorates the SMN protein deficiency that causes SMA. As of 15-Jan-2021, 38 patients with Type 1 SMA have been treated with weekly doses of branaplam up to 60 mg/m^2 (3.125 mg/kg), several for more than 4 years (age at treatment start: 2-7 months).

The increase in SMN protein is expected to result in improved motor neuron survival with consequent achievement of motor milestones, improved respiratory function and longer survival with less ventilation support and feeding tube dependence in SMA patients.

Branaplam also promotes inclusion of a pseudoexon during transcription from the huntingtin gene (HTT). Because this pseudoexon contains a premature stop codon, this triggers degradation of the HTT messenger RNA (mRNA) before translation, resulting in a decrease in the production of full-length HTT protein. Nonclinical investigations of branaplam in BacHD transgenic mice expressing a neuropathogenic, full-length human mutant Huntingtin (fl-mHTT) gene revealed dose-dependent lowering of mHTT mRNA and mHTT protein concentrations in the brain, liver, and blood. Broad lowering of mHTT throughout the brain and periphery, including the cortex and striatum, suggests that oral dosing of branaplam may be an attractive approach for long-term HTT-lowering in patients with HD, and warrants further investigation of the potential therapeutic utility of branaplam in the treatment of HD**.**

This Phase 2b dose range finding and proof of concept study will be conducted in early stage HD patients. HD is a slowly progressive neurodegenerative disease and generating dose-finding data based on slowing progression of clinical symptoms or biomarkers of neurodegeneration would require large sample sizes and long treatment durations. An alternative strategy utilizes a biomarker approach that is achievable with fewer patients and in a shorter time. Branaplam's expected efficacy is based on its ability to reduce the amount of mHTT protein produced in the brain. Based on animal studies, a reduction of mHTT and normal HTT protein in the brain of 40-50% should be sufficient to slow disease progression without negative consequences from loss of normal HTT protein. The mHTT protein level in the CSF thus represents the best biomarker to measure target engagement, demonstrate proof of concept and select dose regimen(s) for further evaluation Phase 3 trials.

1.2 Purpose

The purposes of this study are two-fold, reflecting the two treatment periods integrated in the study design:

- The Core consists of a 17-week double-blind, placebo-controlled dose range finding (DRF) study followed by a Blinded Extension (BE) of variable duration (up to approximately 12 months (dependent on recruitment rate)) to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of various branaplam doses administered once weekly. The doses will be assessed to support the dose selection for the

OLE and any other future study. The DRF period will be analyzed using all available data collected at the time the last randomized patient in the study completes Week 17 visit assessments which, captures a full 16 weeks of treatment with study drug. Both reduction (%) of mHTT protein (change from Baseline (BL) after16 weeks of treatment) and safety/tolerability will be the primary endpoints.

- The OLE is a one-year extension for participants on the selected dose(s) with the purpose to assess the long-term safety and efficacy of branaplam.

2 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. All efficacy and safety data collected during the core (double-blinded and unblinded) will be summarized descriptively based on cumulative data.

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
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
• 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.
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).
	  • 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

Objective(s)	Endpoint(s)
	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
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
[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]

Objective(s)	Endpoint(s)
[redacted]	[redacted]
[redacted]	[redacted]

2.1 Primary estimands

As per the USM follow-up notification dated 06-Dec-2022, the original estimand definition for dose-response relationship is no longer applicable due to permanent discontinuation of study treatment, and no dose-response modelling will be done. The primary endpoint mHTT in CSF will be summarized descriptively as specified in Section 12.

The clinical question of interest is the effect of branaplam versus placebo on percent reduction of mHTT protein in CSF from baseline to Week 17 when the assigned treatment had been taken over 16 weeks with only limited interruptions or discontinuation (as defined below) in patients with manifest HD, mHTT protein in CSF above a detectable level, and a UHDRS TFC score of >8.

The primary estimand is described by the following attributes:

1. Population: male or female patients with confirmed Stage 1 or 2 HD (manifest), mHTT protein in CSF above detectable level, and a UHDRS TFC score of >8 in line with protocol defined I/E criteria. Further details about the population are provided in Section 5.
2. Primary variable: change from BL (%) to Week 17 in mHTT protein in CSF.
3. Treatment of interest: the randomized treatment (allowed medication and prohibited medication see Section 6) taken for the DRF period (16 weeks of treatment) with a maximum of 25% missed doses (i.e., 4 doses for weekly dosing during DRF period) AND less than 2 consecutive weeks off treatment prior to the Week 17 visit LP.

Handling of remaining intercurrent events:

- Treatment discontinuations or interruptions of dosing beyond acceptable limits for any reason: the treatment effect will be imputed as if the treatment had continued or dosing had not been interrupted (hypothetical strategy). The limit is reached if one or both of the criteria below are met:
  - >25% missed doses (i.e., > 4 doses for weekly dosing during DRF period)
  - 2 or more consecutive weeks off treatment prior to week 17 (LP)
- Intake of prohibited medications without discontinuation of study drug: the treatment effect will be imputed as if the prohibited medications had not been taken (hypothetical strategy)
- Adverse event (AE)/Serious adverse event (SAE)/Death or any other intercurrent events leading to endpoint missing: the treatment effect will be imputed as if the intercurrent event had not occurred and participant behaved like other participants from the same treatment group who did not experience such intercurrent events (hypothetical strategy)

The summary measure: reduction (%) of mHTT protein in CSF from BL to Week 17 visit for various doses (dose-response relationship). The justification is that the primary estimand targets the treatment effect of branaplam for those who can tolerate it for 16 weeks (with limited interruption/discontinuation) in order to inform the selection of an optimal dose. The primary estimand will only focus on the efficacy of branaplam on the reduction of mHTT in CSF (one of the primary objectives). The safety perspective will be evaluated in parallel. Dose selection for Open Label Extension and subsequent Phase 3 studies will be based on a combination of efficacy and safety results. However, estimands are not defined for the safety objective, safety analyses will be specified in Section 12.5.2. No inferential and model based statistical analyses are planned for any safety or tolerability endpoints.

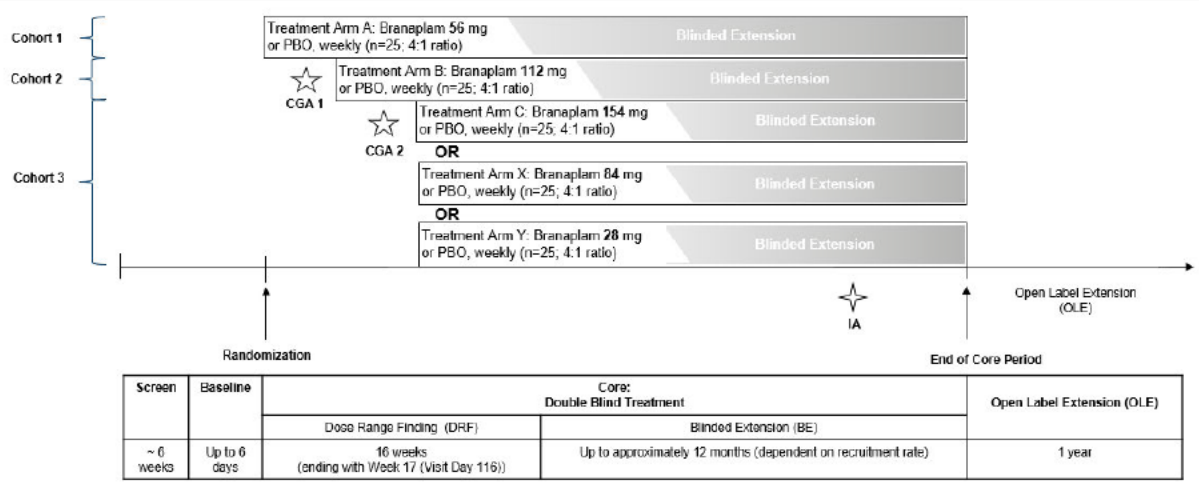
2.2 Secondary estimands

Not applicable.

3 Study design

Pre-USM: This study is a randomized, double-blind, placebo-controlled study with a variable duration (between approximately 17 weeks to approximately 53 weeks) for the core period and a one-year OLE in approximately 75 early-stage manifest HD patients.

Figure 3-1 Study Design Overview



Screen	Baseline	Core: Double Blind Treatment		Open Label Extension (OLE)
		Dose Range Finding (DRF)	Blinded Extension (BE)	
~ 6 weeks	Up to 6 days	16 weeks (ending with Week 17 (Visit Day 116))	Up to approximately 12 months (dependent on recruitment rate)	1 year

= **Cohort Gating Assessment (CGA) 1:** Occurs after the 10th patient from Treatment Arm A in Cohort 1 reaches Week 9 of the DRF; data reviewed to determine the initiation of Treatment Arm B for Cohort 2. During the review period, recruitment continues in Cohort 1.
CGA 2: Occurs after the 10th patient from Treatment Arm B in Cohort 2 reaches Week 9 of the DRF; data reviewed to determine the initiation of Treatment Arm C or X or Y for Cohort 3. During the review period, recruitment continues in Cohort 2.

= **IA:** Interim Analysis: Occurs after the last randomized patient in the study completes the DRF Period (Week 17 visit).

As noted in Figure 3-1, after screening period and BL assessments, this study will be conducted in two Treatment Periods:

- The Core Period consists of a 17-week double-blind, placebo-controlled, Dose Range Finding (DRF) portion of the study, followed by a Blinded Extension (BE) of variable duration (up to approximately 53 weeks; duration is dependent on timing of randomization and recruitment rate). The DRF Period will evaluate the safety, tolerability, PK and PD of branaplam, as well as determine the optimal dose(s) to explore in further clinical evaluations

using all available data collected at the time the last randomized patient in the study completes the Week 17 visit assessments which captures a full 16 weeks of treatment with study drug.

- The OLE is a one-year open-label extension to assess both long term safety and tolerability, as well as the efficacy of the recommended optimal dose(s) for branaplam. If branaplam development in HD remains ongoing at the end of the OLE, the study will either be (a) amended to extend the OLE beyond a year, or (b) a separate extension study will be initiated to offer continued access to branaplam. Study participants from the OLE may be eligible to rollover into this separate extension study.

The study design uses a staggered cohort approach, allowing safety and tolerability of lower doses to be assessed before randomizing subjects to higher doses. The Core Period consists of 3 treatment arms; each treatment arm will enroll approximately 25 patients. Treatment arms are defined as:

- Cohort 1: Treatment Arm A: Branaplam 56 mg oral solution or matching PBO, once weekly
- Cohort 2: Treatment Arm B: Branaplam 112 mg oral solution or matching PBO, once weekly
- Cohort 3:
  - Treatment Arm C: Branaplam 154 mg oral solution or matching PBO, once weekly or
  - Treatment Arm X: Branaplam 84 mg oral solution or matching PBO, once weekly or
  - Treatment Arm Y: Branaplam 28 mg oral solution or matching PBO, once weekly

Randomization into treatment arms will be staggered into 3 Cohorts:

1. Cohort 1 includes Treatment Arm A (56 mg or matching placebo) as noted in Figure 3-1. After the 10th participant in Arm A reaches Week 9 of the DRF Treatment Period, all available data, including relevant post-dose PK time points, will be reviewed from a safety and dose finding perspective by an independent Sponsor team to support the decision to open the next cohort. The independent Data Monitoring Committee (DMC) will review the data separately. The decision to open Cohort 2 at the Cohort Gating Assessment 1 (CGA 1) will be made by the Sponsor in consultation with the DMC. (Also, included in the review will be PK data, [redacted], from a safety and not efficacy perspective, to ensure that HTT lowering is not beyond the anticipated safety threshold.) During this time, recruitment will continue in Cohort 1. Based on the results from the review of the data during CGA 1, a decision will be made regarding the initiation of Cohort 2 (Treatment Arm B, 112 mg or matching placebo). At this time, participants will be eligible to randomize into any open Treatment Arm if it has not yet been completed. Alternatively, if Cohort 1 recruitment is complete prior to the initiation of Cohort 2, participants will then only be eligible for randomization into Cohort 2.
2. Cohort 2: If Cohort 2 is initiated, after approximately the 10th participant in Treatment Arm B has reached Week 9 of the DRF Treatment Period, all available data, including relevant post dose PK time points, will again be reviewed at CGA 2 by the independent Sponsor team and the DMC. Based on the results from the review of the data during CGA 2, a decision will be made to select the Treatment Arm in Cohort 3.

3. Cohort 3: If Cohort 3 is initiated, and based on the data review during CGA 2, the decision will be made to initiate the next higher dose (Treatment Arm C, 154 mg or matching placebo) **or** an intermediary dose (Treatment Arm X, 84 mg or matching placebo) **or** a lower dose (Treatment Arm Y, 28 mg or matching placebo). At this time, participants will be eligible to randomize into any open Treatment Arm if it has not yet been completed. Alternatively, if Cohort 1 and 2 recruitment is complete prior to the initiation of Cohort 3, participants will then only be eligible for randomization into Cohort 3. The interim analysis (IA) will then take place after the last randomized participant completes the DRF period (Week 17 visit).

Participants will be randomized in an equal randomization rate among the open treatment arms, and then in a 4:1 ratio for active vs. placebo within each arm. Refer to Section 4.4.

After a participant completes the DRF period (Week 17) he/she will seamlessly transition to the BE, by continuing on his/her blinded DRF treatment. All patients will remain in the BE until the results of the IA are available and the recommended optimal extension dose(s) is/are selected for OLE. Duration in the BE is therefore variable, longer for those that were randomized earlier in the study.

After the last randomized participant in the study completes all the DRF (Week 17) assessments, an un-blinded IA will be conducted. All data available at this time, including, but not limited to safety/tolerability as well as PK, mHTT and total HTT lowering in CSF, plasma [redacted] will be assessed to determine optimal dose(s) for OLE. After the IA and confirmation of selected dose(s), all patients from the blinded Core Period will roll over to OLE; patients will be re-assigned from their blinded Core Period dosing onto the newly selected open label OLE dose(s).

OLE is a one-year open label treatment and safety monitoring part of the study.

The DMC may recommend to terminate treatment of any dose at any time. All participants will be followed for safety until 30 days after the last dose of study treatment.

Core Period: Dose Range Finding & Blinded Extension.

Following a 6-week Screening period, patients will complete a baseline assessment (can be performed over a 6 day time frame) and a multi-dose, treatment period (with duration varying across patients) at the assigned treatment arm. Safety, tolerability, PD biomarker (fluid and images), PK and clinical endpoints relevant to HD will be collected as outlined in the assessment schedule.

The Screening period may be extended beyond 6 weeks in some cases. See Section 8.1.

After confirming eligibility, participants will be randomized to an open cohort to receive either active or PBO treatment as an oral solution administered once weekly. Although a maximum of 3 treatment arms are planned, timing during the ongoing recruitment will determine which available treatment arms are actively recruiting (refer to Figure 3-1). In addition, not all treatment arms may be initiated, as it is dependent on the available safety profile, PK and mHTT lowering data. Participants will receive at least 16 weeks of treatment and will remain on the initially assigned treatment arm during the Core Period in the BE until IA is completed and optimal dose(s) selected for OLE. After dose selection, which may be more than one selected dose, patients will continue participation in OLE.

Post-USM: As per the USM follow-up notification dated 06-Dec-2022, the study treatment has been permanently discontinued and only Cohort 1 was enrolled. Participants who received active treatment (branaplam) will remain in the study for follow-up for approximately one year following initial treatment discontinuation.

Open-Label Extension (OLE)

OLE is no longer applicable due to permanent discontinuation of study treatment.

Once the optimal dose(s) is/are selected, sites will be notified and active participants will roll over to OLE at a subsequent study visit. The specific timing for each patient will be determined based onsite readiness to conduct the OLE. Prior to commencing dosing in OLE, a series of assessments (re-baselining) may be collected, as outlined in the assessment schedule Table 8-2. If more than one dose is selected for the OLE, then patients will be re-assigned via IRT to one of the selected open label doses.

Study visits will take place every 4 weeks in OLE period (approximately 52 weeks). If branaplam development in HD remains ongoing at the end of the OLE, the study will either be (a) amended to extend the OLE beyond a year, or (b) a separate extension study will be initiated to offer continued access to branaplam.

4 Rationale

4.1 Rationale for study design

This is the first study of branaplam in adult HD patients. The study aims to explore a range of doses in order to select a safe and tolerable dose that lowers mHTT levels in the CSF to a degree expected to be efficacious over longer periods of time. As a slowing in progression of clinical symptoms or biomarkers of neurodegeneration require large sample size and treatment duration, reduction in the amount of mHTT, in line with branaplam's expected mechanism of action (MoA), is thought to be a relevant biomarker to measure target engagement and demonstrate proof of concept and guide dose selection for later phase confirmatory studies.

Study participants will be randomly assigned to treatment arms in the Core Period, and once all randomized participants have completed the Week 17 visit, an IA will be performed to determine the appropriate dose(s) for the OLE. The decision for the OLE dose will be based on mHTT lowering in CSF at the end of the DRF period, as well as safety, tolerability and other biomarker data collected throughout the Core Period. All patients will then enter OLE, be assigned to the new dose, and continue to be assessed for safety and efficacy for approximately an additional year.

Clinical and biomarker measures of HD will also be evaluated in this study. This includes volumetric MRI of brain, CSF and blood biomarkers, HD rating scales and clinical assessments.

Table 4-1 Rationale for Study Design

Study Design Aspect	Rationale
Placebo (PBO) controlled	Use of PBO will help assess if any safety or tolerability findings might be attributed to branaplam and will enable interpretation of any clinical efficacy signal; PBO is justified in this patient population as no approved treatment is available
Randomization	This minimizes bias and helps to decrease the chance of an imbalance in baseline patient characteristics between groups
Staggered cohort	This allows for appropriate review of data at lower dose levels/regimens before proceeding to higher doses.
Duration of study periods	Core: approximately 53 weeks of treatment (minimum of 16 weeks of treatment for dose range finding is considered sufficient to assess preliminary safety, pharmacodynamics (PD) biomarker (mHTT), and PK) Open Label Extension: 1 year duration provides longer term assessment of safety, tolerability and efficacy, to support continued evaluation in larger Phase 3 confirmatory studies. If the interim database lock (iDBL) supports study objectives, the open-label period may extend beyond 12 months until a separate extension study is available.
Blinding	Double blind to mask active or PBO treatment to avoid bias including safety reporting.

4.2 Rationale for dose/regimen and duration of treatment

The dose rationale for the present study is based on (i) safety information from Type 1 Spinal Muscular Atrophy (SMA) patients (CLMI070X2201) and from healthy volunteers (CLMI070A02102), (ii) target engagement information derived from the healthy volunteer study (CLMI070A02102) and (iii) predictions on reduction of mHTT protein in brain using non-clinical investigations in the humanized BacHD mouse model.

To support the dose selection, steady state exposure values of branaplam in plasma were predicted using a preliminary PBPK model. The PBPK model of branaplam was based on the exploratory PK profiles of branaplam in plasma determined after single administration of branaplam (35 mg, 105 mg, 210 mg, and 420 mg) to healthy volunteers (CLMI070A02102) and the derived population-based PK parameters, physicochemical properties of branaplam, and assumptions on elimination pathways (approx. 74% elimination via CYP3A4, 8% of other enzymatic elimination, 9% of renal elimination, and 9% not-defined elimination pathways). Steady state exposure values were predicted for the selected weekly doses using the weekly dosing regimen and the estimated PK parameters.

PK/PD Considerations

Dosing frequency: Branaplam is proposed to be administered with a weekly dosing frequency. This is based on (i) the relatively long apparent terminal elimination T1/2 values of branaplam in plasma observed after single administration in healthy adult volunteers (preliminary T1/2: 120h, 97.9h, 82.2h, and 104h at doses of 35 mg, 105 mg, 210 mg, and 420 mg, respectively, CLMI070A02102) and (ii) the observation, that the target engagement identified by lowering of the HTT mRNA from baseline in blood was maintained across the complete observation period up to 168h at doses of 105 mg, 210 mg, and 420 mg (CLMI070A02102). This maintenance of the target engagement in blood indicated that a weekly dosing frequency is

considered to be sufficient to prolong or to increase the target engagement with a weekly dosing frequency.

Starting dose: The selection of the starting dose in Cohort 1 (56 mg) was based on the considerations to start the study (i) at an exposure range already investigated in Type 1 SMA patients (CLMI070X2201), in which safety and tolerability data have been collected for more than 4 years of treatment, and (ii) showed no safety signals after single dose of branaplam in healthy adult volunteers (CLMI070A02102).

At the highest dose level in Type 1 SMA patients (nominal: 60 mg/m^2 or 3.125 mg/kg, weekly dosing), the mean maximum concentration (Cmax) of branaplam was 96.5 +/- 32.7 ng/mL and the AUC 4280 +/-1030 h*ng/mL. No dose-limiting toxicities were observed and the maximum tolerated dose of branaplam was not determined in a total treatment duration for more than 4 years. After single dose of 35 and 105 mg branaplam in healthy volunteers, no obvious adverse events were identified. The respective preliminary, mean Cmax values were 8.91 ng/mL and 44.5 ng/mL and mean AUCinf values 1370 h*ng/mL and 5720 h*ng/mL. At the proposed lowest weekly dose of 56 mg in the Phase 2b study, the predicted median plasma Cmax at steady state (40.8 ng/mL) and AUCtau at steady state (3098 h*ng/mL) fulfill the considerations to start at an already investigated exposure range.

Target engagement of branaplam (change in HTT mRNA levels from baseline) was investigated in blood following single administration of branaplam to healthy volunteers. Preliminary results showed that HTT mRNA levels were lowered from baseline at all dose levels with a maximum decrease of approximately 20% for the dose range of 35 to 105 mg. Whereas the HTT mRNA levels returned to baseline levels for the 35 mg dose, the lowering of HTT mRNA remained constant over the observation period of 168 h after single dose of 105 mg. Therefore, target engagement is already considered to occur at the starting dose of 56 mg/week with a more pronounced change of HTT mRNA from baseline expected after repeated dosing.

Based on the predictions of the reduction of mHTT protein in brain using non-clinical investigations in the humanized BacHD mouse model, the mHTT protein in the brain was predicted to decrease from baseline at steady state by up to 16% at steady state AUC values of approximately 2500 h*ng/mL. These predictions suggest that already at the starting dose a benefit for HD patients is possible.

Mid dose: At the mid dose of 112 mg, the predicted steady state exposure values (Cmax: 87.5 ng/mL, AUCtau: 7059 h*ng/mL) are either within the already investigated exposure range (Cmax) or higher (AUCtau) compared to the exposure range observed in the Type 1 SMA population (Cmax: 96.5 +/- 32.7 ng/mL, AUC: 4280 +/-1030 h*ng/mL), but is still below the 210 mg dose in the healthy volunteer study (preliminary means, Cmax: 118 ng/mL, AUCinf: 11800 h*ng/mL, CLMI070A02102) where a trend of increase in liver enzymes was noted on Day 8 after branaplam administration.

As discussed above, the target engagement of branaplam (change of HTT mRNA from baseline) and the predicted decrease of mHTT protein in the brain is considered to be more pronounced than at the starting dose.

Highest dose: The weekly dose of 154 mg was selected as the highest dose. The predicted median Cmax and AUCtau values at steady state are 131 ng/mL and 10721 h*ng/mL,

respectively, being in the range of the 210 mg dose in the healthy volunteer study (preliminary means, Cmax: 118 ng/mL, AUCinf: 11800 h*ng/mL, CLMI070A02102) with a trend of liver enzyme increase. However, the liver enzyme levels generally remained within normal range or slightly above that and were considered as not clinically significant.

Preliminary results showed that HTT mRNA in blood were lowered from baseline with a maximum decrease of approximately 40% after a single dose of 210 mg. The lowering of HTT mRNA in blood maintained constant over the observation period of 168 h. Therefore, target engagement at a weekly dose of 154 mg is considered to be more pronounced than in the two lower doses.

In the event that the second cohort gating assessment indicates that doses above 112 mg are not recommended due to safety concerns, including having reached maximal peripheral HTT lowering levels, 84 mg will be selected as option in between the two lowest doses **or** 28 mg will be chosen as an option for a dose lower than the starting dose.

Based on the predictions of the reduction of mHTT protein in brain using non-clinical investigations in the humanized BacHD mouse model, the mHTT protein in the brain was predicted to decrease from baseline at steady state by up to 41% at steady state AUC values of approximately 10600 h*ng/mL. This predicted decrease is considered to be sufficient for clinically meaningful slowing of disease progression without causing safety concerns by removing too much normal HTT protein. (Approximate 35-50% reduction in mHTT protein in the brain is needed (Kaemmerer and Grondin 2019; Caron et al 2018).

Study duration: The 16-week timeframe was selected for the DRF because it allows for sufficient time for changes in mHTT protein to reach near steady-state-levels in CSF (Tabrizi et al 2019a). The additional treatment during the blinded and open-label extension allows for increased exposure to assess the safety and tolerability of repeated dosing of branaplam.

4.3 Rationale for choice of control drugs (comparator/PBO) or combination drugs

Placebo will be used in a double-blind fashion. The use of PBO-control is considered essential to ensure study validity and allow for appropriate assessments of safety, tolerability and efficacy data. No active comparator is used in this study as there is no disease-modifying treatment currently available for early manifest HD patients. Current symptomatic standard of care, except those listed in Prohibited Medications Section 6.2.2, will be used as needed and allowed per protocol.

4.4 Purpose and timing of interim analyses/design adaptations

Staggered Cohort

Staggering the cohorts allows for the time needed to evaluate the safety and tolerability of doses before exploring additional doses arms. The study will be initiated exploring a weekly dose of 56 mg.

A minimum of 8 weeks of exposure is thought to be adequate to assess the initial safety and PK profile of repeated weekly dosing before proceeding to a higher weekly dose (112 mg) at the CGA 1. Similarly, the safety and PK profile of a weekly dose of 112 mg after 8 weeks of exposure will be assessed during CGA 2 before proceeding to a higher weekly dose (154 mg) **or** another intermediary dose (84 mg), **or** lower (28 mg), if warranted.

Given the variable time needed to fully recruit the 10 participants, it is expected that some patients will have longer exposure at the time of the first Cohort Gating Assessment 1 (CGA 1). While the clinical data from the SMA program did not indicate safety risks, the preclinical toxicology data do indicate some potential safety concerns therefore reviewing data for the first 10 patients with a minimum of 8 weeks treatment provides the opportunity to assess these potential risks and to determine initiation of subsequent dosing cohorts. The DMC will be reviewing the data approximately twice a year at a minimum. Since reduction of HTT protein in periphery by more than 80% is undesirable, this staggered approach also allows the decision to not open up the higher dose arms if sufficient HTT lowering is achieved with the lower dose arms.

Interim Analysis

Due to the USM, the timing and purpose of the interim Database Lock (iDBL) has changed. The iDBL will now occur once approximately 70% of the patients in Cohort 1 complete their Week 33 visit. The purpose of this IA is to confirm the CGA review leading to the USM recommendation and to allow earlier communication of interim study results with the broader scientific and HD communities.

Pre-USM: An interim Database Lock (iDBL) was planned after the last randomized patient in the study had completed the Week 17 visit assessments which captures a full 16 weeks of treatment with study drug. Following the iDBL, an IA was planned as a review and evaluation of all available unblinded data (including but not limited to safety, all PK associated with the DRF period, PD, total HTT, mHTT, imaging, clinical and biomarker data) at the time the last randomized patient completes the Week 17 visit assessments, as well as for the overall exposure duration. The purpose of the IA was to identify the optimal dose(s) that would be introduced in the OLE, as well as for any future HD studies with branaplam. Dose selection for the OLE and future clinical development would be determined based on data generated from the 16-weeks DRF treatment period with branaplam.

The dosing for OLE may begin after completion of the safety data review and confirmation of the dose selection.

In addition to the unblinded review for IA, an independent DMC will meet at least twice a year at a minimum and will review safety data. See Section 10.2.4 for more information on the DMC. Guidance on decision rules for the above design adaptations will be outlined in the DMC charter.

4.5 Risks and benefits

The USM Follow up Investigator Notification (06-Dec-2022) was issued by Novartis to inform investigators that Novartis has decided to discontinue development of branaplam as a potential treatment for people with Huntington's disease. The decision followed a review of unblinded data from VIBRANT-HD indicating that the benefit:risk of

branaplam in Huntington's disease is not positive. This decision was endorsed by the independent Data Monitoring Committee (DMC) as well as the VIBRANT-HD Steering Committee (SC). Evaluation of risk for branaplam in patients with HD is based on preclinical data and the current clinical development experience in Type 1 SMA study in young children and healthy adult volunteers.

Table 4-2 summarizes the important potential risks from this experience.

Table 4-2 Summary of important 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 Child Bearing Potential
			Genotoxicity (aneuploidy*)
	Potential	Liver function effects	
	Potential	Cardiovascular effects	
	Potential	Renal toxicity	
	Potential	DDI	
-	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.

Branaplam causes stabilization of tubulin polymerization, resulting in cell cycle arrest within the range of doses that are pharmacologically active. Based on animal studies this cell cycle arrest can potentially present in various organ systems such as gastrointestinal, bone marrow, nervous system, retina, reproductive effects, organs and liver toxicities. The hematologic effects can include various forms of cytopenias such as neutropenia, anemia and thrombocytopenia. Gastrointestinal effects can present as emesis, loose stools, or malabsorption.

Bone Marrow Effects

In the ongoing study in Type 1 SMA patients some events of cytopenias (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 healthy volunteer study in healthy adult participants five subjects in Cohort 4 (420 mg or placebo) showed platelet count increases above the ULN (max increase up to 2x ULN) which were most pronounced in the 3 subjects with liver events and which have not been observed at lower dose levels.

Gastrointestinal effects

In the 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 subjects in this cohort reported diarrhea (5 branaplam and 2 placebo-treated) on Day 1 with a spontaneous recovery by Day 2.

Retinal 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 during the study.

Nerve Fiber Degeneration

As per the USM, the preliminary data from VIBRANT-HD was reviewed as part of the pre-planned CGA and DMC review. Following are some of the key findings:

- **Increased neurofilament light chain (NfL) levels in serum and/or CSF observed in the majority of the participants in active arm.**
- **Changes in the neurological exam on two consecutive visits, predominantly new hypoactive and/or absent deep tendon reflexes (DTRs), observed in more than half of participants in the active arm, and the majority of participants with 12 weeks or more of treatment.**
- **Almost half of the participants in the active arm reported symptoms of peripheral neuropathy, either through the neuropathy questionnaire or as an adverse event report.**
- **Decreased amplitude (50%) in the sural nerve (SNAP) compared to baseline was observed in 7 participants in active arm.**

Following are some of the key findings that may be related to nerve fiber degeneration:

- **Preliminary MRI findings suggestive of an increased volume of the lateral ventricles were seen in majority of patients in active arm**.

Potential risk of neurotoxicity was identified based on a chronic juvenile dog toxicity study with daily dosing of branaplam. Neurotoxicity (axonal degeneration in peripheral nerves and spinal cord) was found in one species (dogs) after 17 weeks of daily administration of branaplam at 1 and 2.5 mg/kg and at 0.25 and 0.75 mg/kg after 52 weeks of daily administration of branaplam. Mechanistic investigations (tubulin polymerization interaction) suggest that neurotoxicity may be a result of the known cell cycle inhibition properties of branaplam. A dose-dependent increase of NfL levels was observed in the CSF of monkeys treated twice weekly with branaplam for a duration of 6 weeks in the absence of histo-morphological findings in the brain, spinal cord, or peripheral nerves. Although an exploratory biomarker, elevations in NfL may be

a consequence of neurotoxicity. The ongoing study in Type 1 SMA has not identified any clear evidence of neurotoxicity in study participants.

NfL levels in serum were monitored at several timepoints in the healthy volunteer 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 potential risk of branaplam-related neurotoxicity will be monitored closely via patient reported symptoms, comprehensive neurological examinations, serum and CSF NfL levels and nerve conduction studies when indicated. Furthermore, weekly dosing is expected to potentially mitigate this risk.

Reproductive Toxicity

Embryofetal toxicity studies have been conducted with branaplam in rats and rabbits. No teratogenic or embryo-toxic potential was observed in the rat. The exposure at the rat NOAEL (2.5 mg/kg/day) are approximately 1.9-fold higher than the predicted AUCweek at the starting dose of 56 mg (3098 h*ng/mL), 4.0-fold higher than predicted AUCweek at the lowest optional dose of 28 mg (1449 h*ng/mL), or 1.8-fold lower than the predicted AUCweek at the highest dose of 154 mg (10721 h*ng/mL). Maternal toxicity and embryo-fetal toxicity were observed in the rabbit pEFD study at high dose levels. The rabbit NOAEL (1.5 mg/kg/day) was associated with maternal exposure approximately 6.5-fold higher than the predicted AUCweek at the optional lowest dose of 28 mg or 1.1-fold lower than the predicted AUCweek of the highest dose of 154 mg. Metabolite UFB112 was not detected in pregnant rats and only to a minor extent in the pregnant rabbits.

Huntingtin (HTT) protein is required for embryogenesis and early development, hence embryo-fetal effects cannot be excluded in humans (Kaemmerer and Grondin 2019). An effect on the HTT transcript and protein is unlikely to occur in rat and rabbits based on mode of action of branaplam (HTT splicing effects and transcript lowering are human specific).

In utero exposure to branaplam is therefore assumed to have serious risks of harm to a fetus including death. Exposure to branaplam in sexual partners of male study participants through contact with seminal fluids is also assumed to carry risks. These risks are mitigated by the contraception eligibility criteria (refer to Section 5.2). Women of child-bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and must agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

Highly effective contraception will be required for all study participants and female partners of male participants as specified in the exclusion criteria. Oral contraception cannot be considered because the potential risk of decrease of efficacy due to DDI has not been investigated yet. Additionally, the cell cycle arrest properties of branaplam may also have an effect on male and female fertility. Study participants need to be counseled for fertility preservation measures.

Gonadal Effects: Testicular/Ovarian

Testicular findings (degenerative changes involving seminiferous tubules of testes and testicular atrophy) were observed in a 52-week (juvenile) dog study with daily administration of branaplam (≥0.25 mg/kg/day) and in a 4-week wild type RasH2 mouse study with daily dosing of branaplam (≥10 mg/kg/day). Testicular findings in the mouse consisted of minimal to severe atrophy/degeneration of testis seminiferous tubules, including germ cells. This potential risk will be monitored by follicle-stimulating hormone (FSH) to identify potential seminiferous tubular injury.

Ovarian findings (decrease of corpora lutea and follicles) were also observed in the wild type RasH2 mouse study with daily dosing of branaplam (≥10 mg/kg/day). No testicular or ovarian findings were observed in a prior 4-week study of branaplam (0, 1, 3, 4, and 10 mg/kg/day) in the same mouse strain or in any other toxicological studies conducted in the rat, dog or monkey. No adverse events relevant to ovarian findings have been reported in the ongoing study in Type 1 SMA patients which enrolled only young children thus ovarian effects may not be evident. In the singe ascending dose (SAD) study in healthy adult volunteers, four post-menopausal female subjects (2 on active and 2 on placebo) were enrolled. No reproductive system-related adverse events were observed in these four subjects.

Genotoxicity (Aneuploidy)

Branaplam has a potential risk of aneugenicity with its potential clinical consequences of tumor formation.

Since the aneugenic effect is considered to be a threshold effect, micronucleus formation was investigated in the healthy volunteer study to further understand the translatability of this risk and inform the balance of potential risks and benefits for the treatment of HD patients. Overall, the MNT results did not indicate a genotoxic potential of branaplam in any of the 4 cohorts. In light of these results, the risk of branaplam-related effects on cell cycle or risk of aneuploidy at the proposed weekly doses in this study are considered to be low.

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 the ongoing study in Type 1 SMA patients there were some reported events of transient increases in aminotransferases. These events resolved without treatment while on study drug. There were no Hy's Law cases. There were no liver related deaths or discontinuations.

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 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 (hADME study). All observed ALT/AST increases in this study recovered spontaneously.

These findings are considered monitorable by safety labs, reversible by drug discontinuation and manageable by clinical care and intrinsic hepatocyte regeneration. Safety monitoring for liver function during ongoing clinical study includes measurement of clinical chemistries.

The effect of branaplam treatment should be promptly reviewed and possibly discontinued if there should be a safety concern regarding liver function.

Cardiovascular System

Branaplam showed a concentration-related inhibition of hERG channel currents, with an IC50 of 2.4 µM in a GLP-compliant assay and 15.7 µM in a non-GLP study. The 2.4 µM IC50 is 27.9-fold higher than the predicted, free Cmax (33.9 ng/mL) at the highest dose of this study (154 mg). The specific risk from hERG inhibition in the Type 1 SMA and HD populations is unknown and considered low with a positive benefit-risk for both indications.

No heart functional changes were observed in the dog safety pharmacology study or in the 6 weeks monkey study with twice-weekly dosing. The Cmax at the highest dose in the monkey (436 ng/mL) were 4.5-fold higher compared to Cmax observed in Type 1 SMA patients and 3.3-fold higher compared to predicted Cmax at the highest dose of this study.

Microscopic findings (cardiomyocyte vacuolation) were observed only in one mouse study. The species specificity and mechanism underlying this finding will be further explored.

In the 4 week wild type RasH2 mouse dose-range finding study with daily administration of 10, 30, and 60 mg/kg/day of branaplam, histological findings of vacuolation of cardiomyocytes were noted. The estimated AUCweek at the highest dose in male and female mice without heart findings (4 mg/kg/day) was about 9345 h*ng/mL being approximately 3-fold and 0.86-fold higher than the predicted AUCweek at the starting and highest dose of this study, respectively. The heart was not identified as a target organ in previous animal safety studies in rat and dog with daily administration of branaplam up to 2.5 and 2 mg/kg/day in rat and dog, respectively. No heart findings were observed in a 6-week monkey study with twice weekly branaplam dosing up to 6 mg/kg/dose.

In the ongoing study CLMI070X2201 in Type 1 SMA patients there have been 3 cardiovascular Suspected Unexpected Serious Adverse Reactions (SUSARs) reported in 3 patients, PTs were left ventricular hypertrophy and hypertension in one patient and PTs sinus tachycardia and left ventricular dysfunction in one patient and pericardial effusion in one patient. Overall, the majority of TEAEs in the cardiac and vascular disorders were Grade 1 and 2 and resolved on treatment. There were no clinically meaningful changes in any of the ECG parameters (PR, RR, QRS, QT, QTcB, and QTcF).

In the SAD study in healthy subjects no abnormalities of clinical relevance and no trends were observed in standard safety electrocardiograms and no relevant arrhythmia events were detected in the 25-hour Holter ECG-based arrhythmia analysis in any of the subjects. Vital signs assessments did not show any abnormalities or trends of clinical relevance. Orthostatic vital signs assessment (supine and standing SBP, DBP and pulse rate) did not reveal any signs of orthostatic dysregulation/postural hypotension, except for 1 subject in the 420-mg group.

Concentration-response analyses revealed a positive correlation between the branaplam plasma concentration and the placebo-adjusted mean change from baseline in QTcF (ΔΔQTcF),

characterized by the equation: ΔΔQTcF (ms) = 0.04912 x LMI070 plasma concentration (ng/mL). The estimated mean ΔΔQTcF exceeded 10 ms in the investigated exposure range while it appeared to be less than 5 ms at the Cmax of the 210 mg dose. In addition, a trend of mean ΔΔHR increase of approximately 2 bpm was observed in the investigated exposure range, which was not considered to be of clinical relevance.

There was no apparent trend of clinical relevance in the concentration-response analyses of other ECG variables. Categorical outlier analyses revealed a single treatment-emergent new QTcF > 450 ms and an increase of QTcF from baseline > 30 ms at the 420-mg dose. There were no treatment-emergent QTcF values > 480 ms, no increase in QTcF or QT from baseline > 60 ms and no ECG events or imbalance of clinical relevance for other ECG variables.

Concentration-response analyses of branaplam plasma concentration and the placebo-adjusted mean change from baseline in systolic and diastolic blood pressure showed no clear correlation (slopes of prediction lines for the mean effect were 0.00404 and – 0.00714, respectively).

The potential cardiovascular risks will be mitigated and monitored by following the appropriate exclusion criteria, adherence to protocol specified prohibited medications (Section 6.2.2), history and physicals including vital signs (HR, RR, BP), ECG, ECHO, and cardiac enzymes (Troponin and NT ProBNP) at protocol defined time points. Investigators should follow the guidelines in the protocol for detection and management of potential cardiac findings.

Renal Toxicity

Kidney findings were observed after chronic daily dosing only in the dog. In the current ongoing CLMI070X2201 study in Type 1 SMA no relevant renal adverse events have been identified. In the SAD and hADME studies in healthy subjects there have been no relevant abnormalities or changes in blood pressure, serum electrolyte levels or renal function variables or in the urinalysis assessments.

Other potential risks

Other potential risks of participation in this study include those related to procedures (e.g., venipuncture, LP) as well as those associated with study drug administration. The oral solution formulation contains a cyclodextrin (specifically hydroxyproply beta (HP-β)-cyclodextrin) to improve the aqueous solubility of branaplam. The matching placebo solution for this study will contain the same amount of cyclodextrin. Therefore, the potential risks of study drug administration include those associated with branaplam and cyclodextrin.

High daily oral doses of HP-β-cyclodextrin (>16 g/day (270 mg/kg for 60 kg body weight)) may potentially cause digestive problems such as diarrhea and should be justified based on branaplam benefit-risk considerations (Stella and He 2008).

The overall risk to HD patients in this study is expected to be low and manageable due to considerable risk mitigation strategies and planned safety monitoring. The risks are further minimized by the design of the study, including limiting accumulation of branaplam via weekly dosing, adherence to the inclusion/exclusion criteria, avoidance of prohibited concomitant medications, close clinical monitoring, a staggered dose escalation design requiring safety-

driven cohort gating assessments and endorsement from an independent DMC before each dose escalation.

See Section 10.2.4 for more information on the DMC.

In addition, all available unblinded safety data will be regularly reviewed by an independent DMC for the duration of the trial.

Given the safety profile of branaplam to date and positive data on HTT target engagement, an investigation of slowing the progression of symptoms and neurodegeneration in HD patients offers important benefits.

The available safety information, combined with both the potential of branaplam to lower mHTT levels in patients with HD and the lack of therapies for these patients, suggests a favorable risk-benefit ratio to evaluate branaplam in this population in a dose-finding study. Branaplam exposure beyond the initial DRF will continually be evaluated, individually and globally, and will inform the dose selection for Part 2 and future studies, and help establish the benefit/risk for branaplam in this population.

4.6 Rationale for Public health Emergency mitigation procedures

In the event of a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures may be required to ensure participant safety and trial integrity and are listed in relevant sections of the study protocol. Notification of the Public Health emergency should be discussed with Novartis prior to implementation of mitigation procedures and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

Potential risk associated with the COVID-19 Pandemic

Novartis is committed to supporting the safety and wellbeing of our study participants, investigators and site staff. All local regulations and site requirements will be applied in the countries that are affected by the COVID-19 pandemic.

The Novartis clinical trial team will review the situation in each participating country and work with investigators to continue to ensure the safety of participants during the conduct of the trial. As the COVID-19 situation evolves, investigators must use their best judgement to minimize risk to participate during the conduct of the study. Lastly, the COVID mRNA vaccines consist of processed, mature mRNA, which are not expected to be a substrate for branaplam.

5 Study Population

As per the USM follow-up notification dated 06-Dec-2022, no further participants will be enrolled in this study. The inclusion and exclusion criteria in Section 5.1 and Section 5.2 below, were applicable to those participants enrolled to Cohort 1.

Approximately 75 male or female patients with confirmed Stage 1 or 2 HD and a UHDRS TFC score of >8 will be enrolled in this study to allow for of approximately 25 participants per treatment arm. Fewer participants will be enrolled if all treatment arms are not opened. Manifest patients with a TFC >8 are selected because they are late enough in the disease process so that

mHTT can be measured in their CSF and clinical symptoms can be readily assessed, and early enough in the disease process so that they can comply with the protocol defined schedule of assessments during Core blinded treatment period (DRF and BE) and be monitored for disease progression and safety throughout the OLE. Eligible patients starting at the age of 25 will be enrolled to avoid the very high CAG repeats associated with early disease onset as these patients could be considered to have a more rapidly progressing phenotype. An age cap of 75 years is employed to avoid age-related comorbidities that typically occur above this age.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. Must be capable of providing informed consent (in the opinion of the Investigator)
3. Clinically diagnosed Stage 1 or 2 Huntington's disease with a diagnostic confidence level (DCL) = 4 and a UHDRS Total Functional Capacity (TFC) >8 at screening
4. Genetically confirmed Huntington's disease, with presence of ≥40 CAG repeats in the huntingtin gene.
   - For participants without prior documentation, a sample must be sent to the central study laboratory and confirmation of the CAG repeat length for these participants must be obtained prior to randomization
   - For participants with previously existing documentation of their CAG repeat length, it is acceptable to use this prior data to qualify for randomization. These participants must also submit a sample for CAG repeat testing to be conducted by the central study laboratory.
5. Male and female participants between 25 to 75 years of age, inclusive, on the day of Informed Consent signature

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study:

1. Use of other investigational drugs within 5 half-lives of the first dose of study drug, or within 30 days, whichever is longer.
2. Prior participation in clinical trial investigating a huntingtin-lowering therapy (unless participant received only placebo)
3. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes.

4a. Participants taking medications prohibited by the protocol (Table 6-2 Prohibited Medications). In addition, participants should be on a stable dose and regimen of permitted chronic concomitant medications for at least 6 weeks prior to receiving the first dose of study drug which in the medical judgement of the Investigator is not anticipated to change during the study. If new medications are initiated during Screening, laboratory evaluations must meet eligibility criteria before first dose of study drug.

5. Any medical history, lumbar surgery or condition that would interfere with the ability to complete the protocol specified assessments, (e.g., history of brain or spinal injury that

would interfere with the LP or CSF circulation, implanted cerebrospinal shunt, conditions precluding MRI scans, herniated disc, etc.).

6. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in situ* cervical cancer), treated or untreated, regardless of whether there is evidence of local recurrence or metastases.
7. Participant has other severe, acute or chronic medical conditions including unstable psychiatric conditions, or laboratory abnormalities that in the opinion of the Investigator may increase the risk associated with study participation, or that may interfere with the interpretation of the study results.
8. Score "yes" on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS, if this ideation occurred in the past 6 months from the Screening visit, or "yes" on any item of the Suicidal Behavior section, except for the "Non-Suicidal Self-Injurious Behavior" (item also included in the Suicidal Behavior section), if this behavior occurred in the past 2 years.
9. Pregnant or nursing (lactating) women. WOCB potential should not become pregnant during the study or within 7 months from stopping study medication.

10a. Sexually active males unwilling to use a condom during intercourse while taking study treatment and for 120 days (4 months) after the last dose of the study treatment. A condom is required for all sexually active male participants even if they are surgically sterile with a vasectomy to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their female partner. In addition, male participants must not donate sperm for the time period specified above.

A condom is required to be used also by vasectomized men as well during intercourse with a male partner of the study participant.

The branaplam exposure in body fluids is not known. Since branaplam is genotoxic, sexual partners are advised to avoid direct contact with semen of participants, to prevent exposure to the study drug.

11a. **Women of child-bearing potential**, defined as all heterosexually active women physiologically capable of becoming pregnant, unless they are using one highly effective methods of contraception during dosing and for 7 months after stopping the study medication. Highly effective methods of birth control are those methods that have a less than 1% chance of an unwanted pregnancy for 1 year.

In addition to one highly effective method of contraception, a condom is required for all male partners of female participants to prevent fathering a child AND to prevent exposure of study treatment via vaginal fluid to your partner, until at least 7 months following the last dose of study treatment.

WOCB potential must not donate their eggs for 7 months after the last dose of study treatment.

Oral contraception cannot be considered due to potential decreased efficacy as potential DDI with branaplam.

Highly effective contraception methods include:

- Total abstinence (when this is consistent with the preferred and usual lifestyle of the participant). [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation

methods) and withdrawal are **NOT** acceptable methods of contraception for heterosexually active participants.]

- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy or bilateral tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization of partners (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner.
- Use of an intrauterine device (IUD) or intrauterine system (IUS) which is MRI compatible.

In case local regulations are more stringent than the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms). Women are considered not of childbearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks prior to Screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential.

The branaplam exposure body fluids is not known. Since branaplam is genotoxic, sexual partners are advised to avoid direct contact with vaginal fluid of participants, to prevent exposure to the study drug.

12a. History of:

- Gene therapy or cell transplantation or any other experimental brain surgery
- Hepatitis B or hepatitis C or serologic evidence for active viral hepatitis (HBsAg and HCVab test)
- Immunodeficiency diseases, including a positive human immunodeficiency virus (HIV) test result
- Current evidence of drug or alcohol abuse in the 12 months prior to screening, as defined by the DSM-V criteria for substance abuse. For former abusers, abstinence should be confirmed by laboratory tests (drug testing and/or CDT level in blood).
- Use of Tetra-Hydro-Cannabinoid (THC)/ cannabinoid containing substances is allowed as per local regulations and/or local medical practice if in the opinion of the Investigator, use does not represent an exclusionary condition, does not constitute abuse and does not affect cognition, and provided that participants are currently treated with a stable regimen for at least 12 weeks prior to first dose of study drug. Note: If initiated during the study, use must be withheld for 72 hours prior to any cognitive and/or motor assessments.

13a. Any surgical or medical condition which might put the participant at risk in case of participation in the study. The Investigator should make this determination in consideration of the participant's medical history and/or clinical or laboratory evidence of any of the following at the Screening visit:

- Unstable chronic gastrointestinal (GI) condition such as history of Crohn's disease, Ulcerative colitis, poorly controlled irritable bowel syndrome (IBS) or similar chronic GI conditions
- Neurologic or neuromuscular conditions other than HD
- History of or physical examination consistent with peripheral neuropathy or nerve conduction findings compatible with electrodiagnostic evidence of neuropathy
- Participants who have a known diagnosis of diabetes mellitus or who do not have a known diagnosis of diabetes with a glycated hemoglobin (HbA1c) > 6.5%
- Lipase, total bilirubin or amylase must not exceed the 1.5x ULN
- Liver disease or liver injury as indicated by abnormal liver function tests
  - Any of the following single parameters in serum of ALT, AST, GGT, and alkaline phosphatase must not exceed 2.0 x upper limit of normal (ULN).
- History of renal injury / renal disease or presence of severe impaired renal function as indicated by an estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease (MDRD) equation < 30 (mL/min/1.73 m^2) (allowing for age-related GFR decline in the mild to moderate range) or the presence >3+ proteinuria/ hematuria on a single (one time) repeated urinalysis.
- Evidence of urinary obstruction potentially leading to an impaired renal function at screening
- Diagnosis of testicular atrophy
- Diagnosis of primary ovarian failure
- Clinically significant retinal abnormalities on ophthalmologic examination by a local Ophthalmologist
- Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed at least 3 days prior to first study drug administration (Day 1)
- Any objects and/or implants in the body which may be contraindicated for MRI, such as pacemakers and some IUD
- Diagnosis of chronic thrombocytopenia or a bleeding disorder

14a. Cardiovascular exclusion criteria:

- History or current diagnosis of ECG abnormalities indicating significant risk or safety concern for study participants such as: History of myocardial infarction, angina pectoris, heart failure, or coronary artery bypass graft (CABG).
- Screening ECHO abnormalities per investigator's medical judgement including but not limited to left ventricular ejection fraction (LVEF) <50%.
- Screening or baseline not within normal range Troponin or NTproBNP values.
- History or concomitant clinically significant cardiac arrhythmias (e.g., sustained ventricular tachycardia, atrial fibrillation, etc.), complete left bundle branch block, high-grade atrioventricular (AV) block (e.g., bifascicular block, Mobitz type II and third-degree AV block).
- History of familial long QT syndrome or known family history of Torsade de Pointes risks for TdP including uncorrected hypokalemia or hypomagnesemia, history of

clinically significant/symptomatic bradycardia and a family history of idiopathic sudden death.

- Resting QTcF ≥450 msec (male) or ≥460 msec (female) at pretreatment [screening or baseline] (as mean of triplicate ECGs), or inability to determine the QTcF interval.
- Use of agents known to prolong the QT interval or with a known or possible risk of Torsade de Pointes unless it can be permanently discontinued or replaced with a permitted medication (refer to Table 6-2).

15a. Uncontrolled hypertension (average 3 systolic blood pressure [SBP]readings) at screening >140 mmHg or average diastolic blood pressure [DBP] > 90 mmHg excluding values related to white coat syndrome (anxiety-related), per Investigator's judgement. Any clinically significant hematological abnormality as assessed by the Site Investigator at screening and/or laboratory evidence of any of the following:

- INR, PT, or activated partial thromboplastin time (APTT) that are not within normal ranges
- Hemoglobin <110 g/L (females) or <120 g/L (males)
- Platelets ≤100 x 10^9/L
- Platelets count >500 x 10^9/L
- Neutrophil count <1.5 x 10^9/L
- Leukocytes <3.0 x 10^9/L

6 Treatment

6.1 Study treatment

As per the USM follow-up notification dated 06-Dec-2022, the study treatment has been permanently discontinued; the last dose administered was 08-Aug-2022.

The investigational treatment for this study is branaplam and matching placebo. Novartis will supply branaplam and matching placebo in 6 mL vials containing 5 mL of study treatment. The vials will be packed in boxes containing 4 vials each. All eligible participants will be randomized via Interactive Response Technology (IRT) to one of the available treatment arms.

Details on the requirements for storage and management of study treatment, and instructions to be followed for preparation /dispensing, and administration of study treatment are outlined in the Instructions for Use.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
LMI070 (branaplam) 17.5 mg/5 mL	Oral solution	Oral use	Double blind; vials	Sponsor (global)

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
matching placebo 5 mL	Oral solution	Oral use	Double blind; vials	Sponsor (global)

6.1.2 Treatment arms/group

At the Week 1 visit, participants will be randomized to one of the following treatment arms in a ratio of 4:1, active vs. PBO

- Cohort 1: Treatment Arm A: Branaplam 56 mg oral solution or matching PBO, once weekly
- Cohort 2: Treatment Arm B: Branaplam 112 mg oral solution or matching PBO, once weekly
- Cohort 3:
  - Treatment Arm C: Branaplam 154 mg oral solution or matching PBO, once weekly or
  - Treatment Arm X: Branaplam 84 mg oral solution or matching PBO, once weekly or
  - Treatment Arm Y: Branaplam 28 mg oral solution or matching PBO, once weekly

Treatment Arm assignment for an individual participant will be determined by which treatment arms are open at the time of the participant screening.

For Treatment Arms C, X and Y, only one of the three will be initiated in Cohort 3. PBO is embedded within each Treatment Arm.

6.1.3 Treatment duration

All participants who are randomized will enter the Core Treatment Period, receiving the investigational treatment or PBO for at least 16-weeks in the DRF portion. After the DRF period, all participants will continue on their assigned study treatment in the BE for up to approximately 53 weeks in total. The participants who are randomized earlier will have longer treatment durations. This will be impacted by the recruitment rate as well as the time necessary to complete the IA to confirm the OLE dose(s) account for the estimated variable time range for the BE. The Core Period duration (Dose Range Finding + Blinded Extension) may be extended beyond the estimated 53 weeks if recruitment is slower than planned.

Once the last randomized participant within all open Cohorts completes the DRF period, the data for the IA will be compiled while this last randomized participant continues to the BE. This timing will be closely monitored to assess the appropriate timing of the End of the Blinded Extension, and all sites will be notified in the preceding months so they can plan accordingly. All assessments for the End of Core visit will be completed as specified in Table 8-2,Table 8-3 and Table 8-4.

Treatment duration for OLE is for approximately 52 weeks, after which a subsequent extension study will be available for participants to roll into if this protocol was not previously amended to extend the OLE.

Participants may be discontinued from treatment with the study drug at any time due to unacceptable toxicity, disease progression and/or at the discretion of the investigator or the participant.

6.2 Other treatment(s)

No additional treatment beyond investigational drug is provided in this trial. An overview of the prohibited medication is given in Table 6-2.

6.2.1 Concomitant therapy

As per the USM, study treatment has been permanently discontinued after approximately 4 months of temporary suspension; thus, there are no longer restrictions for concomitant drugs. Investigators should follow medical judgment and standard of care when prescribing new medications.

All medications administered must be recorded on the Prior and Concomitant Medications electronic case report form (eCRF). All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered within 6 months prior to the Screening visit, and after the participant was enrolled into the study, must be recorded on the Prior and Concomitant Medications eCRF. Any medications, procedures, and significant non-drug therapies taken by the participant within the timeframe defined in the entry criteria prior to the start of the study should also be recorded.

Each concomitant drug must be individually assessed against all exclusion criteria and prohibited medication. If in doubt, the Investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already randomized and/or has received treatment with study drug, contact Novartis to determine if the participant should continue participation in the study.

Pre-USM : In addition, participants should be on a stable dose and regimen of permitted chronic concomitant medications for at least 6 weeks prior to receiving the first dose of study drug which in the medical judgement of the Investigator is not anticipated to change during the study. If new medications are initiated during Screening, laboratory evaluations must meet eligibility criteria before first dose of study drug.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

THC /Cannabinoid containing substances are neither categorized as CYP3A4/5 substrates with narrow therapeutic index or as a sensitive CYP3A4/5 substrate nor as strong or moderate CYP3A4 inhibitors by e.g. FDA (see Table 6-2). However, interaction as substrate and/or inhibitor of CYP3A4 cannot completely be excluded. Therefore, the use of THC /Cannabinoid containing substances is allowed as per local regulations and/or local medical practice with caution if in the opinion of the Investigator, use does not represent an exclusionary condition, does not constitute abuse and does not affect cognition, and provided that participants are currently treated with a stable regimen for at least 12 weeks prior to first dose of study drug. If initiated during the study, use must be withheld for 72 hours prior to any cognitive and/or motor assessments.

6.2.1.2 Concomitant SARS-CoV-2 / COVID-19 vaccines

SARS-CoV-2 / COVID-19 vaccines are not prohibited and there is no requirement for specific timing of receiving a vaccine prior to or after branaplam. Any instructions provided in the package inserts for each vaccine should be followed.

- Mechanistic studies have shown that branaplam acts as a glue between specific, un-spliced pre-mRNA sequences and the spliceosome Currently available COVID mRNA vaccines consist of processed, mature mRNA which are not expected to be a substrate for branaplam
- Currently available non-replicating viral vector SARS-CoV-2 vaccines require further cellular processing of resulting mRNA to produce the Spike protein. The distinct sequence of the Spike mRNA and the known MoA of branaplam make it unlikely that branaplam would interfere with processing of Spike mRNA.
- Based on the MoA of SARS-CoV-2 DNA based / Naked plasmid DNA and Inactivated SARS-CoV-2, vaccines are not expected to interact with branaplam.

Live attenuated SARS-COV-2 vaccines are not contraindicated unless patient is immunocompromised.

6.2.2 Prohibited medication

As per the USM follow-up notification dated 06-Dec-2022, the study treatment has been permanently discontinued, therefore the prohibited medications referenced below in Table 6-2 are no longer applicable.

In vitro experiments showed that branaplam can be metabolized via Human Cytochrome P450 3A4 (CYP3A4) and direct 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 or with strong systemic inducers such as examples provided in the table below. Use of weak to moderate inhibitors of CYP3A4 should be avoided unless absolutely necessary.

Considering the direct glucuronidation pathway, there is a potential for inhibitors or inducers of UGT1A4, UGT1A7, and UGT1A9 to alter the clearance of branaplam *in vivo* if direct glucuronidation is the major clearance pathway of branaplam. However, no clinical relevant pan-UGT inhibitor is described in the literature and clinical relevant inhibition of all three identified UGTs is considered to be unlikely. Similar is true for the induction of UGTs. Therefore, potential UGT inhibitors/inducers are not prohibited and can be used with caution.

In vitro, results indicated that branaplam has a potential perpetrator risk on MATE2-K and OCT1 transporters, which might alter the disposition of MATE2-K and OCT1 substrates. Therefore, co-administration should be considered with caution and be avoided if possible as described in Table 6-2.

Branaplam is considered to have a minor-to-moderate potential to inhibit CYP3A4/5 in a time-dependent manner impacting co-medications metabolized via CYP3A4/5 with a narrow therapeutic index. Due to the time-dependent inhibition, the decrease in enzyme activity may be amplified by administration of multiple doses. Therefore, use of known sensitive CYP3A4/5 substrates should be considered with caution and be avoided if possible (Table 6-2).

Use of the treatments displayed in the Table 6-2 are not allowed after screening and at the time points specified.

Table 6-2 Prohibited Medications

Medications	Prohibition period	Action taken
Strong systemic inhibitors of CYP3A4 examples include, but are not limited to boceprevir, clarithromycin, cobicistat, conivaptan, grapefruit juice, idelalisib, indinavir, itraconazole, ketoconazole, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, telaprevir, telithromycin, troleandomycin, voriconazole. As strong systemic inhibitors of CYP3A4 are also combination of ritonavir-boosted regimens considered: ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak), indinavir/ritonavir, tipranavir/ritonavir, danoprevir/ritonavir, elvitegravir/ritonavir, saquinavir/ritonavir, lopinavir/ritonavir, atazanavir/ritonavir, darunavir/ritonavir For a complete list and additional information, please visit the following FDA website on the respective table and discuss with Sponsor (Table 3-2) fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm	Within 14 days prior to first study dose administration or during the study	If available, substitute with an alternative medication without CYP3A4 inhibition. If no alternative is available then it should be taken with caution based on the Investigator's medical judgment
Strong systemic inducers of CYP3A4 examples include, but are not limited to apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort For a complete list and additional information, please visit the FDA website noted above, on the respective table and discuss with Sponsor (Table 3-3)	Within 14 days prior to first study dose administration or during the study	Prohibited. Alternative medication without CYP3A4 induction can be used, otherwise discontinue patient from study
Co-medications metabolized via CYP3A4/5 with narrow therapeutic index examples include but are not limited to	Within 14 days prior to first study dose administration or during the study	If available, substitute with an alternative medication without CYP3A4 interaction, If no alternative is available then it

Medications	Prohibition period	Action taken
alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus For a complete list of CYP3A4/5 substrates and additional information, please visit the FDA website noted above, on the respective table and discuss with Sponsor (Table 3-1)		should be taken with caution based on the Investigator's medical judgment
Co-medications eliminated via renal MATE2K transporter of clinical-relevant examples include, but are not limited to fexofenadine, glycopyrronium, metformin **Co-medications substrate of OCT1 transporter** of clinical-relevant examples include, but not limited to cephalexin, dofetilde, pilsicainide, pindolol, procainamide, ranitidine, varenicline, umeclidinium, zidovudine. For a complete list and additional information, please visit the FDA website noted above, on the respective tables and discuss with Sponsor (*in vitro*: Table 4-1, clinics: Table 5-1).	Within 14 days prior to first study dose administration or during the study	If available, substitute with an alternative medication without MATE2K or OCT 1 transporter interaction, If no alternative is available then it should be taken with caution based on the Investigator's medical judgment
Medication(s) with a "Known Risk of Torsade de Pointes" per qtdrugs list (Woosley RL)These drugs include but are not limited to the following: escitalopram, citalopram, haloperidol, sulpiride, chlorpromazine, ondansetron, hydroxychloroquine ciprofloxacin, clarithromycin For a complete list and additional information, please visit www.CredibleMeds.org (website) and discuss with Sponsor	Within 14 days prior to first study dose administration or during the study	Discontinue the prohibited medication and substitute with an alternative medication without known or potential risk. See below for use of drugs with conditional risk of TdP After a patient has received study drug and if required due to life-threatening conditions or other exceptional circumstances indicating a high medical need for the use of these drugs the Investigator should use medical judgment carefully assessing benefit risk for an individual patient under consideration. However, ECG monitoring will be required before starting these drugs and repeated once again when steady state (5 half-lives) of this drug is achieved. In case of any abnormality on a single ECG (>480 QTc) triplicate ECGs should be performed and mean values should be used for confirmation (mean QTc > 480 ms).

Medications	Prohibition period	Action taken
Medication(s) with "Potential risk of TdP" per qtdrugs list (Woosley RL) These drugs include but are not limited to the following: aripiprazole, clozapine, deutetrabenazine, tetrabenazine, tiapride, levetiracetam, venlafaxine For a complete list and additional information, please visit CredibleMeds.org (website) and discuss with Sponsor	Within 14 days prior to first study dose administration or during the study	Discontinue the prohibited medication and substitute with an alternative medication without or with conditional risk of TdP (see recommendation for conditional TdP drugs below). After a patient has received study drug and if required due to life-threatening conditions or other exceptional circumstances indicating a high medical need for the use of these drugs the Investigator should use medical judgment carefully assessing the benefit risk for an individual patient under consideration. However, ECG monitoring will be required before starting these drugs and repeated once again when steady state (5 half-lives) of this drug is achieved. In case of any abnormality on a single ECG (>480 QTc) triplicate ECGs should be performed and mean values should be used for confirmation (mean QTc > 480 ms).
Medication(s) with a "Conditional Risk of TdP" per qtdrugs list (Woosley RL) These drugs include but are not limited to the following: diphenhydramine, doxepin , fluoxetine, hydrochlorothiazide, furosemide, lansoprazole, metoclopramide, olanzapine, omeprazole, paroxetine, quetiapine,risperidone, sertraline, trazodone,ziprasidone For a complete list and additional information, please visit www.CredibleMeds.org website and discuss with Sponsor	May participate in the study and continue medication if they have been on a stable dose (at least 6 weeks, based on the medical judgement of the Investigator) of these drugs prior to the initiation of study drug. Furthermore, based on the opinion of the Investigator, the participant is anticipated to remain on the same dose/regimen throughout the duration of the study.	If no alternative is available and medications in this category are felt to be necessary based on the medical judgment of the Investigator then they may be continued with caution. However, if initiated after the administration of study drug, ECG monitoring will be required before starting these drugs and repeated once again when steady state (5 half-lives) of this drug is achieved. In case of any abnormality on a single ECG (>480 QTc) triplicate ECGs should be performed and mean values should be used for confirmation (mean QTc > 480 ms).
Antiplatelet or anticoagulant therapy including but not limited to aspirin (unless ≤ 81 mg/day), clopidogrel, dipyridamole, warfarin, heparinoids and direct coagulation factor inhibitors e.g. apixaban, dabigatran, rivaroxaban	Within 14 days prior to screening and during study	Discontinue the prohibited medication

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a unique Participant Number (Participant No.), that is assigned when the participant is first enrolled for screening and is retained as the primary identifier for the participant throughout his/her entire participation in the trial. The Participant No. consists of the Site Number (Site No.) (assigned by Novartis to the investigative site) with a sequential Participant Number suffixed to it, so that each participant is numbered uniquely across the entire database. The sequential numbers are assigned by the RAVE electronic data capture (EDC) system and are dependent upon when the site enters data into RAVE EDC. For example, Participant A signs the consent on 10-Jan-2021 and Participant B signs on 11-Jan-2021; however if the site enters the data for Participant B first in RAVE, Participant B will be assigned the first sequential number #001 and Participant A will be assigned the next sequential number which is #002.

6.3.2 Treatment assignment, randomization

At the randomization visit, all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The Investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify unique medication numbers for the packages of investigational treatment to be dispensed to the participant. The randomization number will not be communicated to the Investigator staff.

Patients should not be randomized in IRT nor receive study drug treatment until the baseline MRI scan has passed quality control (QC) at central vendor (expected turnaround time is approximately 3 days).

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and Investigator staff. A participant randomization list will be produced by the IRT supplier using a validated system that automates the random assignment of Participant Numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s). Randomization will not be stratified in the study. The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

Randomization will begin first in Treatment Arm A. Within each Treatment Arm, a randomization ratio of 4:1 will be implemented, active vs. PBO. Since the study has a staggered design and new Treatment Arms are open only after decisions are made at the time of CGAs, it is possible that one or more Treatment Arms are open at the same time in case the sample size of 25 on a previously open arm has not been met (See Section 3). Therefore, eligible participants will be randomized via IRT with an equal randomization rate across arms in case more than one Treatment Arm is open at the same time. Again, the same randomization ratio of 4:1 (within each treatment arm) will be used, active vs. PBO.

6.4 Treatment blinding

Per the USM, the sites, Investigators and participants were unblinded on 07-Dec-2022. The Sponsor study team was unblinded on 02-Nov-2022.

Pre-USM: For the Core Period, participants, Investigator staff, persons performing the assessments, and Sponsor study team will remain blind to the identity of the treatment within each cohort from the time of randomization until interim analysis for the Core Period using the following methods: Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the following exceptions: independent PK analyst, independent statistician and independent programmer supporting the Cohort Gating Decision Board and the DMC members.

- The identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor.
- The randomization codes associated with participants from whom PK samples are taken will be disclosed to PK analysts who will keep PK results confidential until data base lock.
- The data with a potential to unblind recipients (typically markers of the treatment effect) will be stored in a restricted area of the database until database lock. Although the randomization list and/or treatment allocation information will NOT be communicated to them, the following personnel will be considered as unblinded due to the results post-baseline:
  - HD biomarker analysts (data including but not limited to HTT/mHTT in plasma (protein [redacted]), [redacted] and CSF (protein)
- All other data with potential for unblinding i.e., tolerability data) will be treated similarly as randomization data with regards to blinding: the data will be loaded into a restricted area. Access will only be granted to members of the authorized independent unblinded team.

Unblinding during the Core period will occur in the case of participant emergencies.

In the open-label extension (OLE), treatment will be open to participants, Investigator staff, persons performing the assessments, and the Clinical Trial Team (CTT).

6.5 Dose escalation and dose modification

As per the USM follow-up notification dated 06-Dec-2022, the study treatment has been permanently discontinued, therefore this section is no longer applicable.

Investigational or other study treatment dose adjustments are not permitted.

6.5.1 Definitions of dose limiting toxicities (DLTs)

Not applicable.

6.5.2 Dose modifications

For participants who do not tolerate the protocol-specified dosing schedule, dose interruptions are permissible, in order to allow participants to continue the study treatment.

Any changes in study treatment administration must be recorded on the Drug Administration Record eCRF.

If the administration of study treatment is temporarily interrupted for reasons other than toxicity, then treatment may be resumed at the same dose level and same dosing frequency.

If the study treatment is withheld due to toxicity, refer to Safety Monitoring Section 10; scheduled visits and all assessments should continue to be performed (with the exception of the dosing of the withheld study drug), as described in the visit assessment schedule (Table 8-2, Table 8-3 and Table 8-4).

Beyond the DRF period and upon consultation with the Sponsor, the Investigator may consider to permanently discontinue a participant from the study in cases of extended interruptions and/or suspected non-compliance with study treatment (e.g. extended interruptions of study treatment not described in Table 6-3 and in Safety Monitoring and Reporting Section 10).

All participants will be followed for safety until 30 days after the last dose of study treatment.

Deviations from mandatory dose interruptions are not allowed. Permanent study drug discontinuation is mandatory for specific events indicated in the Table 6-3.

Table 6-3 Investigator Guidance for Dose interruption/discontinuation, follow-up and re-initiation of study treatment for select Adverse Events

Investigations (Hematologic)	
Neutropenia (absolute neutrophil count (ANC))	
Mild (ANC < lower limit of normal (LLN) - 1500/mm^3)	**Recommendation**: May maintain dose
Moderate (ANC < 1500 - 1000/mm^3)	**Recommendation**: May maintain dose
Severe (ANC < 1000 - 500/mm^3)	**Recommendation**: Hold the study drug until resolved to mild or moderate, then maintain dose or consider every other week dosing after discussing with Sponsor **Mandatory**: If ANC < 500 mm^3, hold the study drug until resolved to mild or moderate; if resuming dose use clinical judgement.
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	**Recommendation**: Hold the study drug and consider permanent discontinuation
Thrombocytopenia	
Mild (platelets (PLT) < LLN - 75,000/mm^3)	**Recommendation**: May maintain dose
Moderate (PLT < 75,000 - 50,000/mm^3)	**Recommendation**: May maintain dose
Severe (PLT < 50,000 - 25,000/mm^3)	**Recommendation**: Hold the study drug until resolved to mild; • If resolved in ≤ 7 days, then maintain dose • If not resolved in ≤ 7 days, then may consider permanent discontinuation at • Investigator's discretion or if resolved > 7 days to mild consider every other week dosing after discussing with Novartis **Mandatory**: If platelets <25,000/mm^3, Hold the study drug and permanently discontinue or if resolved > 7 days to mild consider every other week dosing after discussing with Novartis
Thrombocytosis	
Mild (PLT > 500,000-700,000/mm^3)	**Recommendation**: May maintain dose (monitor prior to next dose)
Moderate (PLT >700,000 – 900,000/mm^3)	**Recommendation**: May hold dose until resolved to mild (monitor prior to next dose)

	• If resolved in ≤7 days, then maintain dose • If not resolved in ≤7 days, hold dose until resolved to mild, may consider permanent discontinuation at Investigator's discretion or if resolved > 7 days to mild consider every other week dosing after discussion with Novartis
Severe (PLT > 900,000/mm^3)	**Recommendation**: Hold the study drug until resolved to mild (monitor prior to next dose) • If resolved in ≤7 days, then maintain dose • If not resolved in ≤7 days, then may consider permanent discontinuation at Investigator's discretion or if resolved > 7 days to mild consider every other week dosing after discussion with Novartis **Mandatory**: If platelets >1,000,000/mm, permanently discontinue study drug. Manage per standard of care.
Cardiovascular disorders	
Hypertension	
(Systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg)	**Recommendation**: Hold the study drug, treat per standard of care until resolved **Mandatory**: In case of life threatening consequences of hypertension e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis, permanently discontinue study drug immediately. Manage per standard of care
Cardiac Echocardiogram Left Ventricular Ejection Fraction (LVEF) <50% and/or Reductions in LVEF ≥10 % units and/or GLS ≥15 % units change from baseline	**Recommendation**: Hold the study drug and continuing study treatment should be done in consultation with a cardiologist. Manage per standard of care.
Clinically significant increase in cardiac enzymes (Troponin and NTproBNP)	**Recommendation**: Hold the study drug, perform echocardiogram and ECG if not already done. Continuing study treatment should be done in consultation with a cardiologist. Manage per standard of care.
Other cardiovascular events	-
Mild	**Recommendation:** Maintain Dose
Moderate	**Recommendation:** Hold dose until resolved to mild
Severe	**Recommendation:** Hold the study drug and continuation of study treatment should be done in consultation with a cardiologist. Manage per standard of care
Gastro intestinal	
Diarrhea	
Mild (Increase of <4 stools per day over baseline)	**Recommendation**: May maintain dose
Moderate (Increase of 4 - 6 stools per day over baseline)	**Recommendation**: Hold the study drug until resolved to mild, then maintain dose If diarrhea returns as moderate to severe, then hold the study drug until resolved to mild. Manage per standard of care. Use clinical judgement before resuming study drug.

Severe (Increase of ≥7 stools per day over baseline)	**Recommendation**: Hold the study drug until resolved to mild **Mandatory**: In case of life-threatening consequences; urgent intervention indicated. Permanently discontinue study drug immediately. Manage per standard of care.
Investigation (metabolic)	
Amylase and/or lipase elevation	
Mild (> ULN - 1.5 x ULN)	**Recommendation**: May maintain dose and monitor prior to next dose
Moderate (> 1.5 - 2.0 x ULN)	**Recommendation:** May maintain dose and monitor prior to next dose
Severe (> 2.0 x ULN) A reflex amylase fractionation test is recommended. An exception to the recommendation on study drug will be made for cases of isolated amylase elevations in which amylase fractionation demonstrates that pancreatic amylase (isoenzymes) elevations are mild or normal	**Recommendation:** Hold the study drug until resolved to mild or baseline (monitor prior to next dose), test weekly until resolution to mild/baseline. • If resolved in ≤7 days, then maintain dose • If not resolved in >7 days, then may consider permanent discontinuation at Investigator's discretion or if resolved > 7 days to mild/baseline consider every other week dosing after discussion with Novartis **Mandatory:** If >5.0x ULN and symptomatic hold the study drug and permanently discontinue. Manage per standard of care.
Testicular	-
Testicular atrophy	**Recommendation**: If FSH level doubles from baseline and absolute value is above 5 IU/L then consult endocrinologist. Use clinical judgment for continuation of study drug; discuss with participant.
Neurologic Findings	
Neurologic Findings suggestive of peripheral neuropathy	**Recommendation**: Consider withholding study drug under the following conditions: • Any clinically significant neurologic finding on the comprehensive neurologic exam with or without a positive response on neurology questionnaire. The following should be actioned: • Perform Compound Motor Action Potential (CMAP)/ Sensory Nerve Action Potential (SNAP) Follow-up as per Investigators judgement • In case of inconclusive CMAP or SNAP results, Investigator may use clinical judgement regarding discontinuation or withholding study drug **Mandatory**: Discontinue study drug immediately and permanently under the following conditions: • Any clinically significant abnormality in the comprehensive neurology exam **and** CMAP or SNAP. Continue to follow patient (to resolution). Refer to Section 8.4.4
Ophthalmological Findings	-
Retinal Atrophy	**Recommendation**: Any new retinal findings from baseline which in the opinion of the Investigator is related to the study drug, discontinue the study drug permanently. Manage as per standard of care.

Refer to Appendix 1 (Table 16-1 and Table 16-2) for guidance on hepatic events and Appendix 2 (Table 16-3 and Table 16-4) for guidance on renal events.

This guidance does not provide an exhaustive list of AEs and Investigators should use their clinical judgement when assessing dose interruption for those AEs not mentioned in the table.

Participants whose study treatment is temporarily interrupted or permanently discontinued due to an AE or abnormal laboratory value must be followed until resolution or stabilization of the event, whichever comes first, including all study assessments appropriate to monitor the event as described in this section. In the event study treatment has been temporarily interrupted (> 7 days) due to an AE or laboratory abnormality not listed in Table 6-3, study treatment may be re-challenged to an every other week dosing after discussing with the Novartis.

6.5.2.1 Dose adjustments for QTcF prolongation

As dose adjustments are not allowed, this section describes criteria for participant treatment interruption and permanent treatment discontinuation in case of QTcF prolongation. The Investigator should discontinue study treatment for a given participant if, on balance, he/she is of the opinion that continuation is not in the best interest of the participant or would be detrimental to the participant's well-being.

Clinically significant results or safety assessments that might put the participant at risk, including, but not limited to:

- Absolute QTcF >500 msec, confirmed by repeat ECG measurements
- Resting heart rate <30 or >120 bpm
- QRS >120 msec and increase >25% from Baseline
- Sustained ventricular tachycardia lasting 30 sec or more, ventricular fibrillation, or any hemodynamically compromising cardiac arrhythmia
- New complete heart block (Grade III AV block) or second-degree AV block Mobitz type II

In case of QTcF >500 msec (or QTcF prolongation >60 msec from baseline)

- Assess the quality of the ECG recording and the QT value and repeat if needed
- Interrupt study treatment
- Determine the serum electrolyte levels (in particular hypokalemia and hypomagnesemia). If abnormal, correct abnormalities before resuming study treatment.
- Review concomitant medication use for other causes for QT prolongation and for drugs with the potential to increase the risk of drug exposure related QT prolongation
- Check the dosing schedule and treatment compliance
- Consider collecting a time-matched PK sample and record time and date of last study treatment intake.

After confirming ECG reading at site, if QTcF >500 msec

- Interrupt study treatment
- Repeat ECG and confirm ECG diagnosis by a cardiologist or central ECG lab
- If QTcF confirmed >500 msec:

- Correct electrolytes, eliminate culprit concomitant treatments, and identify clinical conditions that could potentially prolong the QT as per the ECG and QTc Clinical Safety Standards Guidelines
- Consult with a cardiologist (or qualified specialist)
- Increase cardiac monitoring twice weekly until normalization or stabilization of the ECG findings, until the QTcF returns to ≤480 msec

- After resolution to ≤480 msec, consider permanent discontinuation of study drug treatment

6.6 Additional treatment guidance

As per the USM follow-up notification dated 06-Dec-2022, the study treatment has been permanently discontinued, therefore this section is no longer applicable.

6.6.1 Treatment compliance

All doses of study treatment administration, including the weekly dosing not reflected on the visit assessment schedule (Table 8-2, Table 8-3 and Table 8-4), will be recorded on the appropriate Dosage Administration Record eCRF page. Compliance will be assessed by the Investigator and/or study personnel at each visit using empty medication packaging, and any other information provided by the participant. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log. Compliance will also be assessed and confirmed by a field monitor by drug accountability logs, by documentation and information provided by IRT and by the qualified site personnel that is responsible for treatment dispensation, administration and accountability. Cross-checks should be performed for home administrations and empty medication outer packing should be collected for compliance checks by field monitors. Site staff will review compliance with the participant at each visit including, if applicable, compliance with home administration of study treatment through weekly telephone contacts.

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all participants treated with branaplam, as detailed in the PK section (Section 8.5.2).

6.6.2 Recommended treatment of adverse events

At present there is insufficient information to provide specific recommendations regarding treatment of adverse events (AEs). Treatment of AEs should be according to the judgement of the Investigator and in accordance to local guidance.

Medication used to treat AEs must be recorded on the appropriate eCRF.

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks by site during the Core Period must only be undertaken when it is required in order to treat the participant safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the Investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The Investigator will then receive details of the

investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the Investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The Investigator will provide:

- protocol number
- participant number

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

Participants requiring an emergency code break during the Core period should be discontinued from further study participation.

6.7 Preparation and dispensation

As per the USM follow-up notification dated 06-Dec-2022, the study treatment has been permanently discontinued, therefore this section is no longer applicable.

The investigational drug, branaplam, and its matching placebo, identical in appearance, will be supplied to the site by Novartis. A unique medication number is printed on the study medication label. Each study site will be supplied with study drug in packaging as described under investigational and control drugs in Section 6.1.1.

Investigator and/or designated site personnel will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s).

The study medication can be administered to the participant on site, or can be taken home for self-administration or administration with support from a home nurse or companion/care giver if needed (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate). If the study medication is taken home, the site will make necessary arrangements to supply the medication to the participant.

Further details on the storage and management of study medication, instructions for dispensing and administering, and the return of study treatment to the site are outlined in the Instructions For Use.

As per Section 4.6, 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. Delivery of Investigational Medicinal Product (IMP) directly to the participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate). The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator, and is described in the Instructions For Use.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the Investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The Investigator or designated site staff must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

Participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the Investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the Investigator folder at each site.

6.7.1.2 Handling of additional treatment

No additional treatment beyond investigational drug and PBO control are included in this trial.

6.7.2 Instruction for prescribing and taking study treatment

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

Each study site will be supplied with study drug and matching placebo as described under the Section 6.1.1 (Investigational and control drugs).

Participants should take the study treatment as instructed by the study staff. Study treatment may be administered to participants during site visits or on an outpatient basis (at the participant's home) with support from a home nurse or companion/care giver if needed. Detailed instructions on drug preparation are included in the separate Instructions For Use.

- Day 1 is defined as the first day where study treatment is administered to the participant
- All participants should take study treatment once a week at the same day of the week and approximately the same time each day in the morning.
- The window for study drug administration is ±1 days from the scheduled weekly dosing (with the exception of Day 1)
- On days that PK samples are obtained, the participant will take study treatment during the site visit after the pre-dose PK samples and prior to post-dose PK samples, when instructed by the study staff.

- Participants should take study treatment on an empty stomach (i.e. fast from food and drink, except water) at least 1 hour before and 2 hours after taking the study treatment. Study medication can be taken with a glass of water. Entire dose should be taken within 5 minutes.
- Participants should be instructed to drink the whole volume (in mL) of study drug according to the following table.

Table 6-4 Treatment Dose and Regimen Schedule

Treatment Arm	Investigational / Control Drug (Name and Strength)	Dose and Regimen	Volume
A	branaplam 17.5 mg/5 mL or matching placebo	56 mg weekly	16 mL weekly
B	branaplam 17.5 mg/5 mL or matching placebo	112 mg weekly	32 mL weekly
C	branaplam 17.5 mg/5 mL or matching placebo	154 mg weekly	44 mL weekly
X	branaplam 17.5 mg/5mL or matching placebo	84 mg weekly	24 mL weekly
Y	branaplam 17.5 mg/5mL or matching placebo	28 mg weekly	8 mL weekly

- If vomiting occurs during the administration, or shortly thereafter, no re-dosing of the participant is allowed before the next scheduled dose.
- Participants should be instructed not to make up missed doses (i.e. when the entire dose is not taken as instructed). A missed dose will be defined as a case when the full dose is not taken within 24 hours after the approximate time of the usually weekly dosing. That week's dose should be omitted and the participant should continue treatment with the next scheduled dose on the following week.

6.7.2.1 Additional considerations for PK sampling

- On days on which PK samples are obtained (refer to Section 16.3, PK Sample Log), the participant should wait until after the pre-dose PK sample is collected to take the assigned study medication. (The pre-dose PK sample represents the Ctrough concentration and, therefore, the last dose of branaplam should be 168 h (weekly dose regimen) before the pre-dose PK sample.)
- For the PK samples that are to be collected post dose, (refer to Section 16.3, PK Sample Log), the time of administration is defined as time 0 h; any post dose samples are to be taken as noted as per the visit assessment schedule (Table 8-2, Table 8-3 and Table 8-4) and Section 16.3. Actual time of samples must be recorded in the eCRF.
- Day 1 - Study participants should avoid any food intake within at least 4 h prior to pre-dose triplicate BP, pulse and ECG assessments/PK sampling on the day of first study drug administration. Breakfast/snack can be served after dose administration. Food intake should further be avoided within at least 4 h prior to the triplicate ECG assessments/PK sampling at 12 hours post dose.
- Week 9 (+/- 1 week) - Food intake should be avoided within at least 4 h prior to the pre-dose triplicate BP, pulse and ECG assessments/PK sampling on week 9 (+/- 1 week)

(breakfast/snack should be served after dose administration). Food intake should further be avoided within at least 4 h prior to the triplicate ECG assessments/PK sampling at 12 hours post dose.

- If the participant has skipped the dose the week prior to the scheduled lumbar puncture, guidance will be provided to the Investigator to clarify which biomarker/pk samples may be deferred to ensure alignment with the planned lumbar puncture. See also Section 8.5.4.1.

7 Informed consent procedures

Per the USM follow-up notification dated 06-Dec-2022, sites are required to update and submit for approval an addendum to the Informed Consent that takes into account the changes described in this protocol amendment.

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of FDA 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

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

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 90 days from the previous ICF signature date unless otherwise indicated per local regulations.

The ICF will contain a separate section that addresses the use of remaining mandatory samples (e.g. collected as per protocol as described in the visit evaluation schedule) for optional additional research (e.g. research beyond what is described in the study protocol). The Investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for additional research. Participants who decline to participate in this optional additional research will document this.

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation) Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be fully informed about the study to the extent possible given his/her level of understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Information about common side effects already known about the investigational treatment can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant upon obtaining consent and also during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also includes:
- A subsection that requires a separate signature for the 'Optional Consent additional research using your Coded Data' to allow future research on data and samples collected during this study
- As applicable, Pregnancy Outcomes Reporting Consent and Information Sheet for Female Participants
- Patient information sheet for female partners of any male participants who took study treatment

[redacted]

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

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

As per the USM, participants were to continue with their original VES up to and including Week 29. A new VES was created for Weeks 33, 53 and 69 (see Table 8-5).

The assessment schedule (Table 8-2, Table 8-3 and Table 8-4) lists all of the assessments and when they are performed. All data obtained from these assessments must be supported in the participant's source documentation, as appropriate.

Participants should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Refer to Table 8-1 for allowable visit windows. Missed or rescheduled visits should not lead to automatic discontinuation.

If the end of the Blinded Extension has not been triggered by the time participants reach week 53 (i.e., because the results of the DRF are not available), the BE will continue beyond week 53. Participants beyond Week 53 will remain on the assigned dose until the End of Blinded Extension is triggered. Refer to Table 8-3.

The Baseline visit in the OLE is equivalent to the End of Treatment (EOT)-Blinded Extension visit for participants who are still ongoing at the time the End of the BE is declared. Investigators will be notified ahead of time in preparation for transition to OLE. Since the duration of the BE may be different for individual participants, and in order to minimize participant burden, guidance will be provided to Investigators to clarify what BE assessments may be deferred at the final regular BE visit to ensure that they are performed only once as part of the OLE baseline visit, such as LP and MRI.

If the COVID-19 or similar pandemic limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls, virtual contacts (e.g. teleconsult) or visits by site staff/home nursing service to the participant´s home depending on local regulations and capabilities, may replace on-site study visits, for the duration of the pandemic until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

If such situation emerges, the Investigator should consult the Novartis to evaluate the suitability of remote options and the potential impact on study outcomes.

All visits are to be scheduled according to the appropriate number of calendar days from Day 1 of study drug administration, and not from the previous visit date.

Table 8-1 Allowable Visit Windows

Post-USM visits are +/- 2 weeks. The below visit windows are no longer applicable.

Visit Name	Window
DRF visits	± 1 day
Blinded Extension visits	± 1week
Open Label Extension visits	± 1 week
Imaging (MRI) for all visits excluding Baseline*	± 7 days

Visit Name	Window
Study drug administration for all weekly dosing (excluding Day 1)**	± 1 day
*allowable visit window for Baseline visit is Day -14 to -3 ** If study drug administration is adjusted to ± 1 day for any given Scheduled visit, all associated PK and biomarker samples for that visit should be adjusted accordingly using the same window.	

Table 8-2 Assessment Schedule, Part 1 - Core (DRF and BE)

Period	**Screening**	**Baseline**	**Dose Range Finding**																	
Visit Name	**Screening**	**Baseline**	**Wk 1**						**Wk 2**	**Wk 3**	**Wk 5**	**Wk 9**				**Wk 13**	**Wk 17[1]**			
Days	**-42 to -7**	**-6 to -1**	**1 to 7**						**8**	**15**	**29**	**57**				**85**	**113 to 116**			
Weeks	**-6 to -1**	**-1**	**1**						**2**	**3**	**5**	**9**				**13**	**17**			
Time (post-dose)	**-**	**-**	**0h**	**4h**	**7h**	**12h[2]**	**22h**	**72h**	**-**	**-**	**-**	**0h**	**4h**	**12h[2]**	**22h**	**-**	**0h**	**4h**	**7h**	**12h[2]**
Informed consent	X																			
Pharmacogenetic Informed Consent	X																			
Demography	X																			
Inclusion / Exclusion criteria	X	X																		
Medical history/current medical conditions	X																			
History of Huntington's Disease	X																			
Smoking and Alcohol history	X																			
CAG repeat length	X																			
HIV and Hepatitis screen	X[3]																			
Physical Examination[4,5]	S[3]	S	S						S	S	S	S				S	S			
Neurological Examination	X[3]	X	X						X	X	X	X				X	X			
Body Height[6]	X																			
Body Weight[7]	X	X	X						X	X	X	X				X	X			
Vital Signs	X	X	X[8]	X[8]					X	X	X	X[8]	X[8]			X	X			
Electrocardiogram (ECG)	X	X	X[9]	X		X[9]			X	X	X	X[9]	X	X[9]		X	X			
Hematology	X[3]	X						X	X	X	X	X				X	X			
Clinical Chemistry	X[3]	X						X	X	X	X	X				X	X			
Thyroid Function	X	X										X					X			

Period	**Screening**	**Baseline**	**Dose Range Finding**																	
Visit Name	**Screening**	**Baseline**	**Wk 1**						**Wk 2**	**Wk 3**	**Wk 5**	**Wk 9**				**Wk 13**	**Wk 17[1]**			
Days	**-42 to -7**	**-6 to -1**	**1 to 7**						**8**	**15**	**29**	**57**				**85**	**113 to 116**			
Weeks	**-6 to -1**	**-1**	**1**						**2**	**3**	**5**	**9**				**13**	**17**			
Time (post-dose)	**-**	**-**	**0h**	**4h**	**7h**	**12h[2]**	**22h**	**72h**	**-**	**-**	**-**	**0h**	**4h**	**12h[2]**	**22h**	**-**	**0h**	**4h**	**7h**	**12h[2]**
HbA1c	X																			
NTproBNP, Troponin	X	X						X	X		X	X				X	X			
Coagulation Panel	X[3]	X						X	X	X	X	X				X	X			
Follicle stimulating hormone - FSH[10]		X														X				
Serum Bile Acid[11]		X										X								
Pregnancy Test - Serum	X	X									X	X				X	X			
Pregnancy Test (urine)[12]			X						X	X										
Urinalysis[13]	X[3]	X						X	X	X	X	X				X	X			
Fasting glucose	X															X				
Columbia-Suicide Severity Rating Scale (C-SSRS)	X[3]	X							X	X	X	X				X	X			
Serum Biomarkers (NfL and others)[14,21]	X	X							X	X	X	X				X	X			
Echocardiogram[15]	X										X					X				
Nerve Conduction Studies (tibial nerve CMAP/sural nerve SNAP)	X		Only performed if positive findings on neurologic exam or per Investigator judgement																	
Ophthalmologic examination[16]	X															X				
[redacted]																				
Brain MRI[17,18]		X															X			

Period	**Screening**	**Baseline**	**Dose Range Finding**																
Visit Name	**Screening**	**Baseline**	**Wk 1**						**Wk 2**	**Wk 3**	**Wk 5**	**Wk 9**				**Wk 13**	**Wk 17[1]**		
Days	**-42 to -7**	**-6 to -1**	**1 to 7**						**8**	**15**	**29**	**57**				**85**	**113 to 116**		
Weeks	**-6 to -1**	**-1**	**1**						**2**	**3**	**5**	**9**				**13**	**17**		
Time (post-dose)	**-**	**-**	**0h**	**4h**	**7h**	**12h[2]**	**22h**	**72h**	**-**	**-**	**-**	**0h**	**4h**	**12h[2]**	**22h**	**-**	**0h**	**4h**	**7h**	**12h[2]**
UHDRS - TFC, TMS, IS, [redacted][17]	X	X															X			
[redacted]																				
Plasma (mHTT/total HTT)[20]		X[22]	X[21]				X	X	X[21]	X[21]	X[21]	X[21]			X	X[21]	X[21]			
PK blood collection			X[21,9]	X	X	X[9]	X	X	X[21]	X[21]	X[21]	X[21,9]	X	X[9]	X	X[21]	X[21]	X	X	X
[redacted]																				
mRNA[20]		X[22]	X[21]	X	X		X	X	X[21]	X[21]	X[21]	X[21]			X	X[21]	X[21]	X	X	
Lumbar puncture ([redacted] NfL, [redacted])[21]			X									X					X			
Lumbar puncture - PK[21]			X									X					X			
Randomization			X																	

Period	**Screening**	**Baseline**	**Dose Range Finding**																	
Visit Name	**Screening**	**Baseline**	**Wk 1**						**Wk 2**	**Wk 3**	**Wk 5**	**Wk 9**				**Wk 13**	**Wk 17[1]**			
Days	**-42 to -7**	**-6 to -1**	**1 to 7**						**8**	**15**	**29**	**57**				**85**	**113 to 116**			
Weeks	**-6 to -1**	**-1**	**1**						**2**	**3**	**5**	**9**				**13**	**17**			
Time (post-dose)	**-**	**-**	**0h**	**4h**	**7h**	**12h[2]**	**22h**	**72h**	**-**	**-**	**-**	**0h**	**4h**	**12h[2]**	**22h**	**-**	**0h**	**4h**	**7h**	**12h[2]**
Period completion/disposition																				
[redacted]																				
Drug dispensation[23]			X						X	X	X	X				X	X			
Drug administration record[24]			X						X	X	X	X				X	X			
Prior and concomitant medications	X	X							Update as necessary											
Serious Adverse Events[25]	X	X	X						Update as necessary											
Adverse Events[25]	X	X	X						Update as necessary											

Period	**Dose Range Finding**		**Blinded Extension**								
Visit Name	**Wk 17[1]**		**Wk 21**	**Wk 25**	**Wk 29**	**Wk 33**	**Wk 37**	**Wk 41**	**Wk 45**	**Wk 49**	**Wk 53 - EOT Blinded[26],[27, 28]**
Days	**113 to 116**		**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**
Weeks	**17**		**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**	**53**
Time (post-dose)	**22h**	**72h**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Informed consent											
Pharmacogenetic Informed Consent											
Demography											
Inclusion / Exclusion criteria											

Period	**Dose Range Finding**		**Blinded Extension**								
Visit Name	**Wk 17[1]**		**Wk 21**	**Wk 25**	**Wk 29**	**Wk 33**	**Wk 37**	**Wk 41**	**Wk 45**	**Wk 49**	**Wk 53 - EOT Blinded[26],[27, 28]**
Days	**113 to 116**		**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**
Weeks	**17**		**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**	**53**
Time (post-dose)	**22h**	**72h**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Medical history/current medical conditions											
History of Huntington's Disease											
Smoking and Alcohol history											
CAG repeat length											
HIV and Hepatitis screen											
Physical Examination[4,5]			S	S	S	S	S	S	S	S	S
Neurological Examination			X	X	X	X	X	X	X	X	X
Body Height[6]											
Body Weight[7]			X	X	X	X	X	X	X	X	X
Vital Signs			X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)			X	X	X	X	X	X	X	X[26]	X
Hematology			X	X	X	X	X	X	X	X	X
Clinical Chemistry			X	X	X	X	X	X	X	X	X
Thyroid Function				X		X		X		X	X
HbA1c											
NTproBNP, Troponin			X	X	X	X	X	X	X	X	X
Coagulation Panel			X	X	X	X	X	X	X	X	X
Follicle stimulating hormone - FSH[10]				X			X				X
Serum Bile Acid[11]											
Pregnancy Test - Serum			X	X	X	X	X	X	X	X	X
Pregnancy Test (urine)[12]											
Urinalysis[13]		X	X	X	X	X	X	X	X	X	X
Fasting glucose											

Period	**Dose Range Finding**		**Blinded Extension**								
Visit Name	**Wk 17[1]**		**Wk 21**	**Wk 25**	**Wk 29**	**Wk 33**	**Wk 37**	**Wk 41**	**Wk 45**	**Wk 49**	**Wk 53 - EOT Blinded[26],[27, 28]**
Days	**113 to 116**		**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**
Weeks	**17**		**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**	**53**
Time (post-dose)	**22h**	**72h**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Columbia-Suicide Severity Rating Scale (C-SSRS)			X	X	X	X	X	X	X	X	X
Serum Biomarkers (NfL and others)[14, 21]			X	X	X	X	X	X	X	X	X
Echocardiogram[15]			X		X		X		X		X
Nerve Conduction Studies (tibial nerve CMAP/sural nerve SNAP)	Only performed if positive findings on neurologic exam or per Investigator judgement										
Ophthalmologic examination[16]							X				X
[redacted]											
Brain MRI[17,18]						X					X
UHDRS - TFC, TMS, IS, [redacted][17]						X					X
[redacted]											
Plasma (mHTT/total HTT)[20]	X	X		X[21]		X[21]		X[21]			X[21]
PK blood collection	X	X		X[21]		X[21]		X[21]			X[21]
[redacted]											

Period	**Dose Range Finding**		**Blinded Extension**								
Visit Name	**Wk 17[1]**		**Wk 21**	**Wk 25**	**Wk 29**	**Wk 33**	**Wk 37**	**Wk 41**	**Wk 45**	**Wk 49**	**Wk 53 - EOT Blinded[26,27,28]**
Days	**113 to 116**		**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**
Weeks	**17**		**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**	**53**
Time (post-dose)	**22h**	**72h**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
mRNA[20]	X	X		X[21]		X[21]		X[21]			X[21]
Lumbar puncture ([redacted] NfL[redacted])[21]						X					X
Lumbar puncture - PK[21]						X					X
Randomization											
Period completion/disposition											
[redacted]											
Drug dispensation[23]			X	X	X	X	X	X	X	X	X
Drug administration record[24]			X	X	X	X	X	X	X	X	X
Prior and concomitant medications	Update as necessary										
Serious Adverse Events[25]	Update as necessary										
Adverse Events[25]	Update as necessary										

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
1 Week 17 is the last visit within the dose range finding part of the study. Therefore, a full 16 weeks of treatment data are captured.
2 For patients staying overnight at site/hospital
3 If required, assessment may be repeated during the initial screening phase
4 Findings must be recorded on the appropriate Medical History or Adverse Events eCRF
5 A complete physical exam is done at screening and baseline
6 Only at Screening
7 In indoor clothing, but without shoes
8 Triplicate blood pressures - 1) pre-dose after 10 minutes supine rest and 2) repeated in the same manner after 4 hours post dose
9 After 4 hours of fasting and 10 minutes supine rest 10 Male patients only
11 Participants must be fasting
12 Urine dipstick for pregnancy performed at site. Positive urine dipstick result must be confirmed with a central laboratory serum pregnancy test. Refer to Section 8.4.3

Period	Dose Range Finding		Blinded Extension								
Visit Name	Wk 17[1]		Wk 21	Wk 25	Wk 29	Wk 33	Wk 37	Wk 41	Wk 45	Wk 49	Wk 53 - EOT Blinded[26,27,28]
Days	113 to 116		141	169	197	225	253	281	309	337	365
Weeks	17		21	25	29	33	37	41	45	49	53
Time (post-dose)	22h	72h	-	-	-	-	-	-	-	-	-

13 Urine dipstick done at site; if findings then send urine to central lab for microanalysis
14 Serum Biomarkers, including NFL. See Biomarkers Assessments in Blood and CSF, Section 8.5.3
15 Echocardiogram with GLS
16 Indirect with scleral indentation (if necessary) and Direct ophthalmoscopy
17 To minimize burden to patients, it is recommended that Post-baseline MRI and UHDRS assessments are done up to 1 day prior to the planned study drug dosing date at any given visit. If done same day as Lumbar Puncture, MRI and UHDRS should be done first.
18 Patients should not be randomized and receive study drug treatment until the baseline MRI scan has passed QC at central vendor
[redacted]
20 For visits where samples are collected only once a day, they must always be collected at approximately the same time of the day
21 Pre-dose
22 The baseline sample may be collected at any time during Day -6 to -1. This sample is different from the 0 hr pre-dose sample to be collected before the first dose of study drug on Day 1
23 IRT call and drug preparation by site personnel
24 Weekly dosing, not reflected on the VES, should be confirmed with weekly telephone calls to the participant and will be collected on the eCRF.
25 Adverse Events and Serious Adverse Events are collected after the Informed Consent Form is signed by the participant
26 Participants beyond Week 53 in the Blinded Extension will follow visit structure as per Table 8-3 remain on the assigned dose until End of Blinded Extension is triggered.
27 If a participant prematurely discontinues study treatment before or at Week 17 visit during the DRF period (for reasons other than withdrawal of consent), all assessments corresponding to all visits during the DRF period should still be completed up to and including Week 17 as described in the VES. If a participant prematurely discontinues study treatment during the blinded extension after the Week 17 visit during the Core period (for reasons other than withdrawal of consent) and therefore does not continue in the OLE, all assessments as described under the EOT/Week53 visit in the VES should be completed during the last visit. Participants that prematurely discontinue blinded study treatment during the Core period and do not continue in the OLE study period must be followed up for safety for 30 days after the last dose of blinded study drug is administered.
28 Participants who discontinue study treatment should be scheduled for an EOT Blinded visit at which time all of the assessments listed for the EOT Blinded visit will be performed.

Table 8-3 Assessment Schedule, Part 2 - BE beyond 53 weeks

Period	**Blinded Extension Beyond 53 Weeks**											
Visit Name	**Wk 57**	**Wk 61**	**Wk 65**	**Wk 69**	**Wk 73**	**Wk 77**	**Wk 81**	**Wk 85**	**Wk 89**	**Wk 93**	**Wk 97**	**Wk 101**
Days	**393**	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**617**	**645**	**673**	**701**
Weeks	**57**	**61**	**65**	**69**	**73**	**77**	**81**	**85**	**89**	**93**	**97**	**101**
Physical Examination[1]	S	S	S	S	S	S	S	S	S	S	S	S
Neurological Examination	X	X	X	X	X	X	X	X	X	X	X	X
Body Weight[2]	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	X
Thyroid Function		X		X		X		X		X		X
NTproBNP, Troponin	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Panel	X	X	X	X	X	X	X	X	X	X	X	X
Follicle stimulating hormone - FSH[3]			X			X			X			X
Columbia-Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test - Serum	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X
Echocardiogram[4]		X			X			X			X	X
Nerve Conduction Studies (tibial nerve CMAP/sural nerve SNAP)	Only performed if positive findings on neurologic exam or per Investigator judgement											
Ophthalmologic examination[5]						X						X
[redacted]												
Brain MRI[6]				X				X				X
UHDRS - TFC, TMS, IS, [redacted]				X				X				X
[redacted]												

Period	**Blinded Extension Beyond 53 Weeks**											
Visit Name	**Wk 57**	**Wk 61**	**Wk 65**	**Wk 69**	**Wk 73**	**Wk 77**	**Wk 81**	**Wk 85**	**Wk 89**	**Wk 93**	**Wk 97**	**Wk 101**
Days	**393**	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**617**	**645**	**673**	**701**
Weeks	**57**	**61**	**65**	**69**	**73**	**77**	**81**	**85**	**89**	**93**	**97**	**101**
[redacted]												
Serum Biomarkers (NfL and others)[7, 11]	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]												
PK blood collection[11]		X		X		X		X		X		X
mRNA[8, 11]		X		X		X		X		X		X
Lumbar puncture ([redacted] NfL, [redacted])[11]				X				X				X
Lumbar puncture – PK[11]				X				X				X
[redacted]												
Drug dispensation[9]	X	X	X	X	X	X	X	X	X	X	X	X
Drug administration record[10]	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medications	Update as necessary											
Adverse Events	Update as necessary											
Serious Adverse Events	Update as necessary											

[X] Assessment to be recorded in the clinical database or received electronically from a vendor

[S] Assessment to be recorded in the source documentation only

[1] Findings must be recorded on the appropriate Medical History or Adverse Events eCRF

[2] In indoor clothing, but without shoes

Period	Blinded Extension Beyond 53 Weeks											
Visit Name	Wk 57	Wk 61	Wk 65	Wk 69	Wk 73	Wk 77	Wk 81	Wk 85	Wk 89	Wk 93	Wk 97	Wk 101
Days	393	421	449	477	505	533	561	589	617	645	673	701
Weeks	57	61	65	69	73	77	81	85	89	93	97	101

[3] Male patients only
[4] Echocardiogram with GLS
[5] Indirect with indentation (if necessary) and direct ophthalmoscopy
[6] To minimize burden to patients, it is recommended that Post-baseline MRI and UHDRS assessments are done up to 1 day prior to the planned study drug dosing date at any given visit. If done same day as Lumbar Puncture, MRI and UHDRS should be done first.
[7] Serum Biomarkers, including NFL. See Biomarkers Assessments in Blood and CSF, Section 8.5.3
[8] For visits where samples are collected only once a day, they must always be collected at approximately the same time of the day
[9] IRT call and drug preparation by site personnel
[10] Weekly dosing, not reflected on the VES, should be confirmed with weekly telephone calls to the participant and will be collected on the eCRF

Table 8-4 Assessment Schedule, Part 3 - Open Label Extension

Period	Open Label Extension														
Visit Name	Baseline-Ext[1]	Wk 5-Ext	Wk 9-Ext	Wk 13-Ext	Wk 17-Ext	Wk 21-Ext	Wk 25-Ext	Wk 29-Ext	Wk 33-Ext	Wk 37-Ext	Wk 41-Ext	Wk 45-Ext	Wk 49-Ext	EOT open-label[2]	EOS
Days	1	29	57	85	113	141	169	197	225	253	281	309	337	365	999
Weeks	1	5	9	13	17	21	25	29	33	37	41	45	49	53	143
Physical Examination[3]	S	S	S	S	S	S	S	S	S	S	S	S	S	S	
Neurological Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Electrocardiogram (ECG)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Thyroid Function	X		X		X		X		X		X		X	X	
NTproBNP, Troponin	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Period	**Open Label Extension**														
Visit Name	**Baseline-Ext[1]**	**Wk 5-Ext**	**Wk 9-Ext**	**Wk 13-Ext**	**Wk 17-Ext**	**Wk 21-Ext**	**Wk 25-Ext**	**Wk 29-Ext**	**Wk 33-Ext**	**Wk 37-Ext**	**Wk 41-Ext**	**Wk 45-Ext**	**Wk 49-Ext**	**EOT open-label[2]**	**EOS**
Days	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**999**
Weeks	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**	**53**	**143**
Coagulation Panel	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Follicle stimulating hormone - FSH[4]	X			X			X			X				X	
Pregnancy Test - Serum[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Columbia-Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Echocardiogram[7]	X			X			X			X				X	
Nerve Conduction Studies (tibial nerve CMAP/sural nerve SNAP)	Only performed in case of positive findings on neurologic exam or per Investigator judgement														
Ophthalmologic examination	X						X							X	
[redacted]															
Brain MRI[15]	X				X				X					X	
UHDRS - TFC, TMS, IS, [redacted]	X				X				X					X	

[redacted]

Period	**Open Label Extension**														
Visit Name	**Baseline-Ext[1]**	**Wk 5-Ext**	**Wk 9-Ext**	**Wk 13-Ext**	**Wk 17-Ext**	**Wk 21-Ext**	**Wk 25-Ext**	**Wk 29-Ext**	**Wk 33-Ext**	**Wk 37-Ext**	**Wk 41-Ext**	**Wk 45-Ext**	**Wk 49-Ext**	**EOT open-label[2]**	**EOS**
Days	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**999**
Weeks	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**	**53**	**143**
[redacted]															
Plasma (mHTT/total HTT)[8, 10]	X		X		X		X		X		X			X	
Serum Biomarkers (NfL and others)[9, 10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK blood collection[10]	X		X		X		X		X		X			X	
mRNA[8, 10]	X		X		X		X		X		X			X	
Lumbar puncture ([redacted] NfL[redacted])[10]	X				X				X					X	
Lumbar puncture - PK[10]	X				X				X					X	
Randomization[11]	X														
Study completion information											X			X	
[redacted]															
Drug dispensation[12]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Drug administration record[13]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Prior and concomitant medications[14]	X														
Serious Adverse Events[14]	X	Update as necessary													
Adverse Events[14]	X	Update as necessary													
End of Study Disposition															X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] The Baseline visit in the OLE is equivalent to the EOT-Blinded Extension visit for participants who are still ongoing at the time the End of the Blinded Extension is declared. Investigators will be notified ahead of time in preparation for transition to OLE. Since the duration of the BE may be different for individual participants, and in order to minimize participant burden, guidance will be provided to Investigators to clarify which BE assessments may be deferred at the final regular BE visit to ensure

Period	Open Label Extension														
Visit Name	**Baseline-Ext[1]**	**Wk 5-Ext**	**Wk 9-Ext**	**Wk 13-Ext**	**Wk 17-Ext**	**Wk 21-Ext**	**Wk 25-Ext**	**Wk 29-Ext**	**Wk 33-Ext**	**Wk 37-Ext**	**Wk 41-Ext**	**Wk 45-Ext**	**Wk 49-Ext**	**EOT open-label[2]**	**EOS**
Days	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**999**
Weeks	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**	**53**	**143**

that they are performed only once as part of the OLE baseline visit, such as LP and MRI.
[2] Participants who discontinue study treatment should be scheduled for an EOT Open-label visit at which time all of the assessments listed for the EOT open-label visit will be performed. A 30-day safety follow up period after the last open label study treatment dose was taken must be observed.
[3] Findings must be recorded on the appropriate Adverse Events eCRF
[4] Male patients only
[5] Serum pregnancy test is collected as part of the blood chemistry. Refer to Section 8.4.3 for positive result follow up action
[6] Urine dipstick done at site; if findings then send urine to central lab for microanalysis
[7] Echocardiogram with GLS
[8] For visits where samples are collected only once a day, they must always be collected at approximately the same time of the day
[9] Serum Biomarkers, including NFL. See Biomarkers Assessments in Blood and CSF, Section 8.5.3
[10] Pre-dose
[11] Randomization will be done if there is more than one dose chosen
[12] IRT call and drug preparation by site personnel
[13] Weekly dosing, not reflected on the VES, should be confirmed with weekly telephone calls to the participant and will be collected on the eCRF.
[14] Update as necessary
[15] To minimize burden to patients, it is recommended that Post-baseline MRI and UHDRS assessments are done up to 1 day prior to the planned study drug dosing date at any given visit. If done same day as Lumbar Puncture, MRI and UHDRS should be done first

The table below (see Table 8-5) reflects the changes in the USM follow-up notification dated 06-Dec-2022.

Participants randomized to placebo do not require additional safety assessments and can be discontinued from the study at the Week 33 visit or immediately if this visit was already completed. The End of Treatment and End of Study (EOS) dispositions can be declared. Participants that had already permanently discontinued study treatment and had scheduled an EOT and/or follow up assessments at the time of the USM follow-up notification dated 06-Dec-2022 should have follow up (FU) assessments as closely as possible to Assessment Table 8-5.

Table 8-5 Assessment Schedule Urgent Safety Measure

Period	Revised follow-up assessment schedule[3]			
Visit Name	Wk 33	Wk 53	Week 69	EOS
Days	225	365	477	477
Weeks	33	53	69	69
Physical Examination	S	S	S	
Neurological Examination	X	X	X	
Vital signs (including body weight)	X	X	X	
Electrocardiogram (ECG)	X			
Hematology	X	X[1]	X[1]	
Clinical Chemistry	X	X[1]	X[1]	
Thyroid Function	X	X[1]	X[1]	
NTproBNP, Troponin	X	X[1]	X[1]	
Pregnancy Test - Serum	X	X	X	
Urinalysis	X	X[1]	X[1]	
Columbia- Suicide Severity Rating Scale (C-SSRS)	X	X	X	
Serum Biomarkers (NfL)	X	X	X	
Nerve Conduction Studies (tibial CMAP/sural nerve SNAP)[2]	X	X	X	
Brain MRI	X	X	X	
[redacted]				
UHDRS – TFC, TMS, IS, [redacted]	X		X	
[redacted]				
Adverse Events	X	X	X	
Serious Adverse Events	X	X	X	
Prior and concomitant medications or therapies	X	X	X	
End of Study Disposition				X

Period	Revised follow-up assessment schedule[3]			
Visit Name	Wk 33	Wk 53	Week 69	EOS
Days	225	365	477	477
Weeks	33	53	69	69

[1] To minimize burden to participants, it is recommended that safety labs/urinalysis are performed only if required for Adverse Events or follow up of an AE.

[2] NCS must be performed in triplicate and recommended bilaterally. However, if performed unilaterally, then it should be conducted on the same side as per the screening visit

[3] Visit window for Week 33 onwards is ±2 weeks.

8.1 Screening

As per the USM, no further enrollment is allowed.

Written Informed Consent must be obtained before any study specific procedures are performed. During the screening assessment period, inclusion and exclusion criteria will be evaluated and all screening assessments to confirm eligibility must be performed prior to randomization.

For details of assessments required during screening please refer to Table 8-2.

Participants will be required to have all screening assessments within 42 days of randomization with the exception of CAG repeat and height. However, participants may remain in screening for greater than 42 days in the following cases:

- If recruitment (i.e. randomization) is paused (e.g. enrollment is complete for open treatment arms and pending opening of additional treatment arms following the cohort gating assessment),
- In cases where a switch in concomitant medication is considered by the Investigator following the guidance in Table 6-2, participants should be on a stable dose and regimen of permitted chronic concomitant medications for at least 6 weeks prior to receiving the first dose of study drug which in the medical judgement of the Investigator is not anticipated to change during the study. If new medications are initiated during Screening, laboratory evaluations must meet eligibility criteria before first dose of study drug.
- In order to minimize patient burden and upon consultation with the Novartis, the screening period may also be extended beyond 42 days to accommodate the scheduling of baseline assessments.

A participant who has laboratory test results that do not satisfy the entrance criteria may have the tests repeated. These tests may be repeated as soon as the Investigator believes the re-test results are likely to be within the acceptable range to satisfy the entrance criteria, but should be completed within the screening period. In this instance, the participant will not be required to sign another Informed Consent Form (ICF), and the original Participant Number assigned by the Investigator will be used. In the event that the laboratory tests cannot be performed within the screening visit window, or the re-tests do not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the participant is considered a screen failure, and must be discontinued from the study.

At this time, participants will be eligible to randomize into any open Treatment Arm if it has not yet been completed.

At that time, and depending on the overall recruitment rate and number of participants in active screening, guidance will be provided to Investigators regarding screening new potential patients.

All visits are to be scheduled according to the appropriate number of calendar days from Day 1 of study drug administration, and not from the previous visit date.

It is permissible to re-screen a participant if she/he fails the initial screening; however, each case must be discussed and agreed with the Novartis on a case-by-case basis.

8.1.1 Information to be collected on screening failures

Participants who sign an informed consent form and are subsequently found to be ineligible, for any reason, prior to randomization will be considered as screen failures. The reason for screen failure should be recorded on the appropriate eCRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening period (Section 10.1.3). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized. Data and samples collected from participants prior to screen failure may still be analyzed.

Participants who are randomized and fail to start treatment, e.g. participants randomized in error, will be considered an early terminator. The reason should be recorded on the appropriate eCRF.

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with eCRF.

Participant demographics and baseline characteristics collected will include the following: age of participant, gender (and childbearing potential for female), education level, race and ethnicity, height, weight, smoking and alcohol history, all relevant medical history including HD history, CAG repeat length, (for participants with previously existing source documentation, prior and current concomitant medication. For full list of assessments at screening and BL, please refer to Table 8-2.

BL assessments may be completed over a 6-day period.

Patients should not be randomized and receive study drug treatment until the baseline MRI scan has passed quality control (QC) at central vendor (expected turnaround time 3 days).

The LP should be performed on a different day than both the MRI and HD assessments; however if it cannot be, then the MRI and/or HD assessments must be completed prior to the LP.

8.3 Efficacy/Pharmacodynamics

Efficacy assessments include the following:

- Unified Huntington's Disease Rating Scales (UHDRS) components:
  - Total Functional Capacity (TFC)
  - Total Motor Scale (TMS)
  - Independence Scale (IS)
  - [redacted]

8.3.1 Unified Huntington's Disease Rating Scales (UHDRS)

The UHDRS is a research tool developed by the Huntington Study Group (HSG) to provide a uniform assessment of the clinical features and course of HD. It has undergone extensive reliability and validity testing (Huntington Study 1996). For this study, the UHDRS components collected will be for total functional capacity, total motor score, independence scale, and the functional assessment score. These components are clinician-guided assessments based on participant interview, physical exam and observation during motor activities.

8.3.1.1 UHDRS Total Functional Capacity (TFC)

The TFC focuses on the Investigator's assessment of the participant's capacity to perform a range of activities of daily living including occupation, finances, self-care, domestic chores and activities of daily living. The responses are derived from interview with the participant and/or companion, if applicable. Scores range from 0 to 13, with higher scores representing better functioning.

8.3.1.2 UHDRS Independence Scale (IS)

The IS represents the Investigator's assessment of the participant's level of independence, including topics of employment, finances, self-care and feeding. The scale has 19 discrete scores, from 10 (tube fed, total bed care) to 100 (no special care needed) with 5 point increments in between.

8.3.1.3 UHDRS Total Motor Scale (TMS)

The TMS is the cumulative sum of the individual motor ratings obtained during the administration of the motor assessment portion of the UHDRS. Scores range from 0 to 124; the higher score represents more significant impairment.

[redacted]

[redacted]

8.3.4 Imaging

Changes in volumetric MRI will be measured in regions of interests. Patients with HD have progressive reduction in volume in brain structures such as, but not limited to, the caudate, putamen, and cerebral cortex and increased ventricular volume (Johnson and Gregory 2019). Striatal atrophy has been the most consistent and sensitive finding in several observational imaging studies and is indicated as the earliest region to show volume loss. Studies have shown significant cross-sectional reductions in caudate and putamen volume up to 15 years prior to disease onset (Paulsen et al 2010) with longitudinal atrophy rates of 3-4% per year (Georgiou-Karistianis et al 2013). In addition, a combination of volume changes significantly correlate with clinical scales and provides an increased effect size and reduced required sample size for detecting a treatment effect based on one-year longitudinal MRI imaging data in patients with HD (Frost et al 2017). Ventricular volume will also be monitored from a safety perspective, to assess if similar increases in lateral ventricular volume occur as was seen with a HTT lowering antisense oligonucleotide (Tabrizi et al 2019b).

Imaging data will be collected, checked for quality, and read centrally as specified in the Imaging Review Charter by an imaging vendor designated by Novartis. Lateral ventricular volume will be assessed and monitored to detect if changes occur during the course of the study. A longitudinal increase in lateral ventricular volume is known to occur with age (~0.4ml/y, ~ 0.26%/y) and is increased approximately 4-fold in Huntington's disease (~1.5ml/y, ~1%/y) (Hobbs et al 2010).

Patients should not be randomized and receive study drug treatment until the baseline MRI scan has passed quality control (QC) at central vendor (expected turnaround time 3 days).

Three-dimensional MRI data will be acquired and used to measure brain volume at each time point and changes in brain volume longitudinally. Brain MRI scans will be performed at each time point without gadolinium contrast. Additional scan sequences, if feasible at the site, may include diffusion imaging to assess motion features of water and metrics of white matter integrity. Details regarding the MRI scan sequences, methods for assessment and recording are defined in the Imaging Vendor Manuals.

The LP should be performed on a different day than both the MRI and HD assessments; however if it cannot be, then the MRI and/or HD assessments must be completed **prior** to the LP. In the instance that a repeat MRI is needed due to QC issues, the MRI rescan should be acquired 48 h post-LP if there are no associated complication risks noted by the site physician. If there are LP associated complications, it is at the site physicians' discretion to delay the MRI rescan until side-effects resolve.

In the event an MRI cannot be performed after randomization, a local CT may be collected under exceptional circumstances for safety evaluations only, using the site's local imaging

protocol and standard procedures. If no new MRIs can be performed for the remainder of the study, such cases should be discussed with the Novartis on a case by case basis and participant's discontinuation from the study should be considered by the Investigator.

The coded medical images will be used for analysis as described in the imaging review charter; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

Sites will not receive any central read reports nor volumetric data from the central vendor during the study. Images should be locally reviewed by the Investigator for incidental findings. For the purpose of the study only clinically relevant abnormalities noted should be recorded as AE. MRI data will be archived as source documents according to local site practice and regulations.

[redacted]

8.3.5 Biomarkers/Pharmacodynamics

As per the USM, PK [redacted] including mHTT/HTT (plasma [redacted]) [redacted] should only be collected in all randomized participants up to 6 weeks after the last dose of study drug.

Mutant Huntingtin (mHTT) protein will be measured in CSF at time points specified in Table 8-2, Table 8-3 and Table 8-4, to evaluate the dose-response relationship between branaplam doses and mHTT in CSF. This relationship will be determined by statistical modelling based on the percent reduction of mHTT observed from BL levels. Total HTT protein will also be measured in CSF at time points specified in Table 8-2, Table 8-3 and Table 8-4. To assess the pharmacodynamic effect of branaplam administered once weekly, mHTT and total HTT will also be measured in plasma [redacted] at time points specified in Table 8-2, Table 8-3 and Table 8-4. [redacted]

For visits where [redacted] plasma samples are collected only once a day, they must always be collected at approximately the same time of the day.

[redacted]

For CSF samples, standard safety assessments performed by the site according to local standard practice may include, but are not limited to, the measurement of cells, glucose and protein. NfL [redacted] biomarkers may also be investigated centrally (Section 8.5.3). [redacted]

Refer to Section 8.5.4.1 for considerations regarding the LP.

8.3.6 Appropriateness of efficacy assessments

Efficacy/PD assessments chosen are standard in HD and the relevance noted in each Section 8.3.5 above.

8.4 Safety/Tolerability

To minimize burden to participants, it is recommended that safety labs/urinalysis are for performed only if required for Adverse Events or follow up of an AE. See VES Table 8-5 for list of safety assessments to be performed following the USM.

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.
For details on AE/SAE collection and reporting, refer to Section 10.

Table 8-6 Assessments & Specifications

Assessment	Specification
Physical examination	A complete physical examination including the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological will be performed at Screening and Baseline visits. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A short physical exam will include vital signs (temperature, blood pressure [SBP and DBP] and pulse) examination of general appearance, head, eyes, ears, nose, throat, neck, skin, lungs, heart and abdomen. Evidence of possible bleeding tendency such as bruises or petechial rash should be noted. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include temperature (method of body temperature (i.e. oral) is up to site local practices), BP and pulse measurements. After the participant has been supine for ten minutes, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat measurements will be made at 1 - 2 minute intervals. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.
Height and weight	Height and body weight (in indoor clothing, but without shoes) will be measured
Neurological	Neurological examination includes at a minimum the following: mental status, cranial nerves I- XII, motor system, deep tendon reflexes, sensory system including touch and vibration, coordination, gait. In addition, a detailed motor, deep tendon reflexes and sensory system examination will be completed and recorded on the appropriate eCRF at screening and at each visit to monitor for any abnormalities. Nerve conduction studies consisting of tibial CMAP and sural SNAP will be done at screening and during study if indicated clinically.
Cardiac	Full PK profile with digital standard 12-lead triplicate ECGs, PK samples and vital signs at the same time points (vital signs = pulse rate, supine systolic and diastolic blood pressure) will be performed. ECHO with GLS will be performed as per assessment schedule. Specific visits will require fasting prior to pre-dose ECGs as specified in the visit schedule and in Section 8.4.2.
Ophthalmologic	An ophthalmologic examination without sedation using dilated direct and indirect ophthalmoscopy with scleral indentation if necessary will be performed at the time points defined in the Assessment Schedule by an Ophthalmologist.

8.4.1 Laboratory evaluations

Central laboratories will be used for the analysis of scheduled hematology, biochemistry and other blood specimens collected as part of safety monitoring (as detailed Table 8-7). Dipstick urinalysis will be performed locally (unless local institution policies dictate otherwise), except

in the case of any out of range parameter on scheduled local urinalysis, when a urine sample will be sent to central laboratory for further analysis. Laboratory values obtained during the Screening phase will be used to assess patient's eligibility. The time windows granted for laboratory evaluations are identical to the corresponding visit time windows for each visit (refer to Table 8-1, Table 8-2, Table 8-3, Table 8-4, and Table 8-5 (post-USM).

The site does not need to wait for the results of centrally-analyzed laboratory assessments when an immediate clinical decision needs to be made and in those cases locally unscheduled testing may be performed.

Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to Investigators separately.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

Table 8-7 Laboratory evaluations

Test Category	Test Name
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Chloride, Sodium, Potassium, Phosphate, Creatinine, estimated Glomerular filtration rate (eGFR), Creatine kinase (CK), Total Bilirubin, Total Cholesterol, Low density lipoproteins (LDL), High density lipoproteins (HDL), Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose, (fasting and non-fasting), high sensitivity C-reactive protein (CRP), fasting bile acids; glycated hemoglobin (HbA1c) (screening visit only) If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated. In the event ALT/AST is above 3 times upper limit of normal, reflex testing will be performed by the central laboratory for GLDH (glutamate dehydrogenase) In the event CK is above ULN then reflex testing of isoenzymes will be performed by the central laboratory In case of severe amylase/lipase elevations (> 2x ULN), a reflex fractionation amylase test is recommended (local testing acceptable)
Hematology	Hematocrit, Hemoglobin, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), Platelets, Mean Platelet volume* (MPV), Red blood cells RBC), White blood cells, RBC Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other (absolute value preferred, %s are acceptable), reticulocytes * In event the platelet count is out of range (both upper and lower limits) MPV reflex testing will be performed by the central laboratory
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity) Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells); done only if findings on urine dipstick. In addition the central laboratory will perform analysis of the urine protein and blood.
Coagulation	Prothrombin time (PT), International normalized ratio [INR]), Activated partial thromboplastin time (APTT)
Additional tests	FSH, Troponin T, NTproBNP, T3 Triiodothyronine [free], T4 Thyroxine [free], Thyroid-Stimulating Hormone (TSH)
Pregnancy Test	Serum / Urine pregnancy test

8.4.2 Cardiac assessments

Electrocardiogram (ECG)

As per USM: Refer to Table 8-5 for schedule of ECG assessments. Participants do not require to be fasting prior to the ECG.

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable BL, according to the ECG Investigator Manual. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Triplicate 12-lead resting ECGs are to be collected, with ECG machines as supplied by central ECG vendor, at all timepoints pre-specified in the visit and assessment schedule and should be performed with a 2-4 minutes interval between each ECG. Details on the triplicate ECG collection procedure and its specific requirements and restrictions for the participant are provided in an ECG Investigator Manual. Specific visits will require fasting prior to pre-dose ECGs as specified in Table 8-8, and in Section 6.7.2. For PK sampling timepoints, please see Appendix 16.3.

Table 8-8 Central ECG Collection Plan

Period	Visit Name	Days	Timepoint	Timing of Triplicate ECGs
Screening	Screening	-42 to -7	-	Anytime
Baseline	Baseline	-6 to -1	-	Anytime
DRF	Wk 1	1	0 hr	Pre-dose after 4 hr fasting
DRF	Wk 1	1	4 hr	Post-dose
DRF	Wk 1	1	12 hr	Post-dose after 4 hr fasting
DRF	Wk 2	8	-	Pre-dose
DRF	Wk 3	15	-	Pre-dose
DRF	Wk 5	29	-	Pre-dose
DRF	Wk 9	57	0 hr	Pre-dose after 4 hr fasting
DRF	Wk 9	57	4 hr	Post-dose
DRF	Wk 9	57	12 hr	Post-dose after 4 hr fasting
DRF	Wk 13	85	-	Pre-dose
DRF	Wk 17	113	0	Pre-dose
BE & OLE	Wk 21 until EOT OLE	141 to EOT OLE	-	Pre-dose

For any ECGs with participant safety concerns, the Investigator should treat based on standard of care.

In the event that a clinically significant ECG abnormality is identified at the site at the time of ECG collection (e.g. severe arrhythmia, conduction abnormality of QTcF >500 msec), an expedited review by the central reader may be requested if applicable, and the ECG should be repeated to confirm the diagnosis. If the participant is hemodynamically compromised, the Investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

Clinically significant abnormalities must be recorded on the eCRF as either medical history/current medical conditions or adverse events as appropriate.

Echocardiogram with Global Longitudinal Strain (GLS)

Echocardiogram with GLS is no longer required per the USM follow-up notification dated 06-Dec-2022.

Pre-USM: Echocardiogram with GLS will be performed per the assessment schedule. An echocardiogram is a test that uses high frequency sound waves (ultrasound) to make a cardiac image and provides information regarding cardiac structure and function. GLS is an additional parameter used to assess myocardial contractility.

Two dimensional echocardiography measurements will be assessed during the study. The images will be transmitted to a central reading vendor for independent review. Sites will receive appropriate training as well as an Echocardiography Manual that includes detailed instructions and data transfer procedures.

A Left Ventricular Ejection Fraction (LVEF) <50% (calculated using the biplane Simpson method) is considered reduced and clinically relevant. Reductions in LVEF ≥10 % units and/or GLS ≥15 % units change from baseline are considered clinically relevant following consensus guidelines for abnormal cardiac response (Plana et al 2014).

Echocardiograms should be locally reviewed by the Investigator for incidental findings. For the purpose of the study only clinically relevant abnormalities noted should be recorded as AE. All other echocardiography assessments will be done by central reading vendor. The central reading vendor will only send alert notifications to sites when the LVEF and GLS thresholds defined above are met.

Eligibility at screening will be confirmed by the Investigator based on the local echocardiography assessment as reported by a cardiologist. Recordings at screening will be sent to the central reader to serve as reference measurement for future comparison. All recordings will be sent to the central reader.

Aligned with recommendations of the American Society of Echocardiography concerning the use of echocardiography in clinical trials (Gottdiener et al 2004), the following standard parameters - pertinent to the assessment of changes in cardiac muscle mass and/or contractile function - will be monitored during the study:

- Left ventricular wall (anterior and posterior) and septal thickness
- Left ventricular mass and mass index
- Left ventricular end-diastolic volume
- Left ventricular end-systolic volume
- Left ventricular ejection fraction
- Left ventricular diastolic and systolic diameter
- Left atrial size and volume
- Left Ventricular Global Longitudinal Strain

Cardiac Enzymes

Troponin and NTproBNP levels will be assessed at BL and timepoints outlined in the assessment schedule. These blood tests are to monitor cardiac injury and cardiac failure.

8.4.3 Pregnancy and assessments of fertility

As per the USM follow-up notification dated 06-Dec-2022, the study treatment has been permanently discontinued; oral contraception is now permitted as a highly effective contraception method given that there is no longer a potential for a Drug-Drug Interaction (DDI).

All pre-menopausal women who are not surgically sterile will have a serum pregnancy or urine pregnancy test at the visits specified in the assessment schedule (Table 8-2, Table 8-3 and Table 8-4). Additional serum pregnancy testing might be performed if required by local requirements or if urine pregnancy is positive. If the result of urine pregnancy test is positive: i) treatment should be put on hold and ii) confirmation is necessary by serum test.

A positive serum pregnancy test requires immediate discontinuation from the study drug. The patient must be followed to understand the outcome of the pregnancy.

A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants should not donate sperm for 120 days (4 months) after the last dose of study treatment. In addition, a condom is required by male partners of participants in the study in order to prevent exposure to the study drug.

If participants cannot visit the site to have serum pregnancy tests 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, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).

Assessments of Fertility

A woman is considered of childbearing potential from menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Medical documentation of bilateral oophorectomy, hysterectomy, or bilateral tubal ligation must be retained as source documents.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

In the absence of medical documentation, confirming permanent sterilization, or if the post-menopausal status at screening/baseline is not clear, the Investigator should use his medical

judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

8.4.4 Neurological assessments

Neurological Examination

In addition to a standard neurological examination (mental status, cranial nerves I- XII, motor system, deep tendon reflexes, sensory system including touch and vibration, coordination, gait), a more detailed neurological examination comprised of motor system, deep tendon reflexes and sensory system will be completed and reported on a corresponding eCRF at BL and any clinically significant abnormalities will be noted at each visit.

Nerve conduction study (NCS)

As per the USM of 05-Aug-2022, if a repeat NCS is required due to findings suggestive of peripheral neuropathy, it is recommended that this be performed bilaterally with three separate readings. If it is performed unilaterally then it must be the same side as it was performed at screening.

Nerve Conduction Studies (NCS) are medical diagnostic tests to evaluate the function, of motor and sensory nerves by measuring electrical conduction. NCSs will be conducted at screening and repeated in the event there are any new clinically significant findings during the neurological exam that might suggest peripheral neuropathy. The screening NCS results will be interpreted locally and should be normal without of any electrodiagnostic evidence of neuropathy.

This study will be assessing both the motor and sensory electrophysiological functions by testing the tibial and sural nerves respectively. The study will be performed unilaterally and the same side should always be assessed with three separate readings performed. The CMAP is recorded by electrical stimulation of a motor nerve. Its amplitude is measured in millivolts (mV). The SNAP is obtained by electrically stimulating a sensory nerve. Its amplitude is measured in microvolts (μV). In addition, nerve conduction velocity (NCV) is taken during both tests. NCV indicates how quickly electrical impulses move along a nerve. It is measure in meters per second (m/s).

These tests will be performed by medical specialists at the site such as clinical neurophysiologists, or neurologists who subspecialize in electrodiagnostic medicine and who will be responsible in providing the final results and their interpretation.

The following tests will be assessed as safety parameters:

Table 8-9 Nerve conduction study 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.

8.4.5 Other safety evaluations

8.4.5.1 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a questionnaire that prospectively assesses suicidal ideation and suicidal behavior. The scale is administered on site, at each visit, including unscheduled visits. However, the questionnaire can be administered to the participant by the Investigator over the phone, if needed.

The following constructs are assessed: severity of ideation, intensity of ideation, behavior and lethality of actual suicide attempts. Composite endpoints are followed over time to monitor participant safety (Posner et al 2011).

8.4.5.3 Ophthalmologic examination

Pre-USM: A complete ophthalmic examination will be performed by an ophthalmologist at Screening and at subsequent visits noted in the assessment table. The examination will include an eye history, visual acuity measurement, dilated ophthalmoscopy (may include contact lens biomicroscopy to examine the macula and optic disc) and direct and indirect ophthalmoscopy and if necessary perform with scleral indentation if the examiner needs to better visualize any peripheral retinal anomalies. Local anesthesia may be used following standard local practice. Following the ophthalmologic examination, further follow up such as OCT may be performed as part of normal clinical practice if required.

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.

Post-USM: **Complete ophthalmic examination is no longer required, per the USM follow-up notification dated 06-Dec-2022.**

8.4.5.4 Reproductive system/fertility assessments

Fertility hormones

The cell cycle arrest properties of branaplam may also have an effect on male and female fertility. The clinical Investigator will discuss fertility preservation measures (such as sperm banking, egg harvesting) with the patients during Screening. In order to monitor the potential effects of branaplam on testicular function, specifically spermatogenesis, FSH levels will be

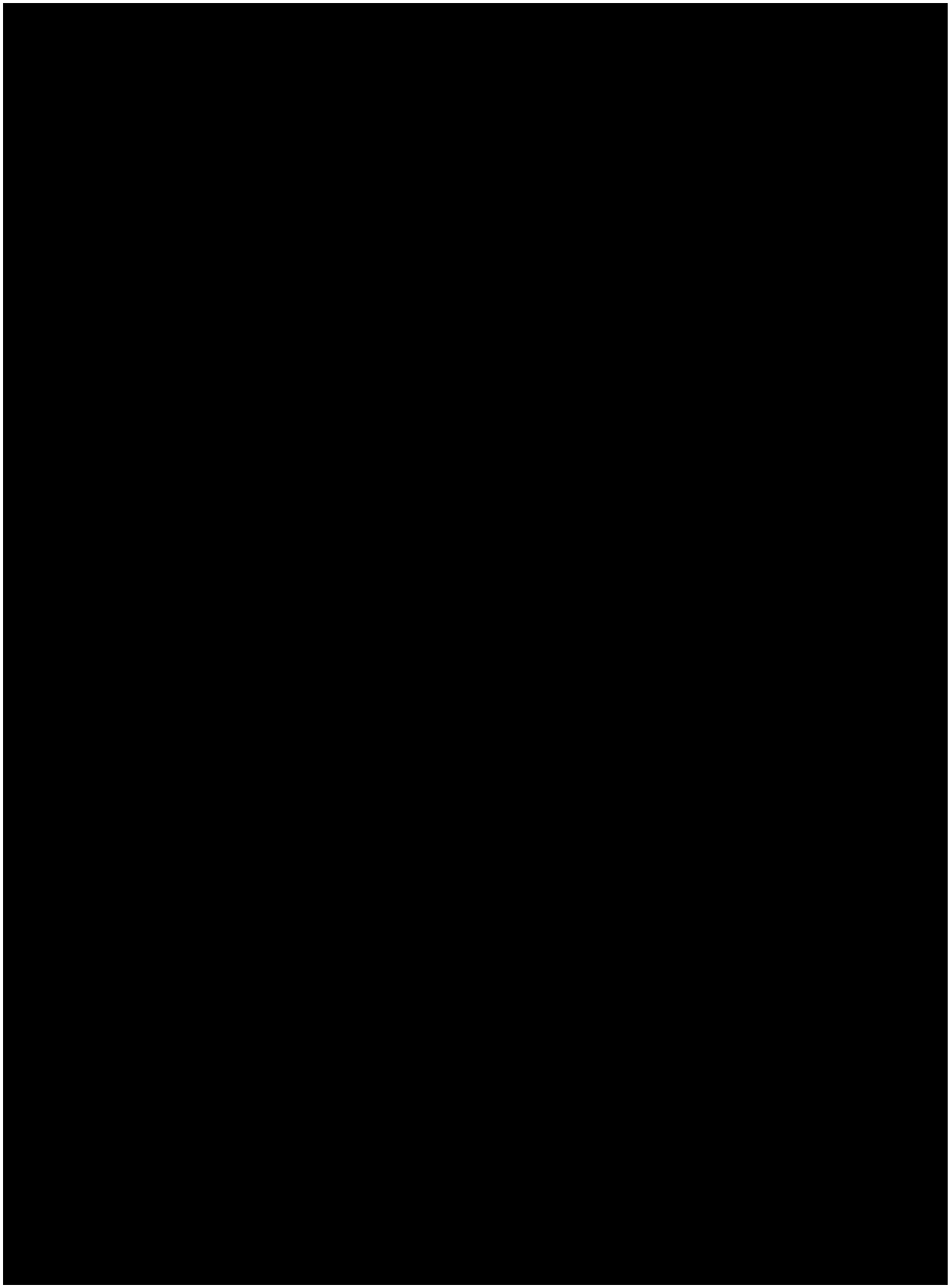
obtained at baseline and then at regular intervals during the course of the study. If FSH levels double from the patient's BL **and** is above 5 IU/mL consultation with an endocrinologist is recommended.

8.4.6 Appropriateness of safety measurements

The safety assessments selected are included due to potential risks associated with branaplam.

Neurological Investigations: Potential risk of neurotoxicity (axonal degeneration of peripheral nerves and spinal cord) was identified based on two dog studies. In order to assess this, a comprehensive neurologic exam will be conducted. In addition, nerve conduction evaluations with CMAP and sensory nerve action potential (SNAP) will be conducted at the Screening visit to ensure no existing peripheral neuropathy is present. These tests may be repeated if, in the opinion of the Investigator, there is potential peripheral neuropathy based on participant self-report, abnormal findings on neurological examination indicative of a potential peripheral neuropathy (see Section 8.4.4).

8.5 Additional assessments



8.5.2 Pharmacokinetics

As per the USM, PK and blood biomarkers including mHTT/HTT (plasma) should only be collected in all randomized participants up to 6 weeks after the last dose of study drug .

Pharmacokinetic (PK) samples will be collected at the visits defined in the assessment schedule. Follow instructions for fasting as outlined in Section 6.7.2.1 and sample collection, numbering, processing, and shipment in the Lab Manual. Refer to Appendix 16.3 for PK sample log. PK samples should be collected as close to the scheduled timepoints as feasible.

An additional blood sample will be collected in the event that a patient experiences an AE which requires premature termination from the study medication.

PK samples from plasma and CSF will be obtained from all participants at all dose levels. Bioanalytical analysis of PK samples will be executed if participant is treated with branaplam and no bioanalysis will be executed in plasma samples if participant is treated with placebo. Branaplam and its metabolite UFB112 will be determined in plasma and CSF by a validated LC-MS/MS method. The anticipated Lower Limit of Quantification (LLOQ) is 0.500 ng/mL. 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.

PK samples remaining after completion of the determination of parent and/or UFB112 may be used for exploratory assessment of metabolites, plasma protein binding or other bioanalytical purposes (e.g. cross check between different sites, stability assessment). Given the exploratory nature of the work, the analytical method used for those assessments will not be validated.

For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol. If feasible, the following pharmacokinetic parameters will be determined in plasma after first dosing and at the Week 17 visit using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 8 or higher): the maximum concentration (Cmax), the time it takes to reach Cmax (Tmax), AUClast,

AUCtau, AUCinf, T1/2, Vz/F (branaplam only) and CL/F (branaplam only) 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, if the observation period to estimate the T1/2 values is shorter than the estimated T1/2 value, and/or if the extrapolated AUC is greater than 20% of the estimated AUCinf, no values will be reported for T1/2, AUCinf, CL/F (branaplam only), and Vz/F (branaplam only).

For plasma samples collected at other times (Ctrough values) and CSF samples, mean concentrations will be calculated.

8.5.3 Biomarkers

Per USM, PK and blood biomarkers including mHTT/HTT (plasma [redacted]) [redacted] should only be collected up to 6 weeks after the last dose of study drug. The 0-Hour timepoint (pre-dose in the protocol pre-USM) is the only required timepoint for collection.

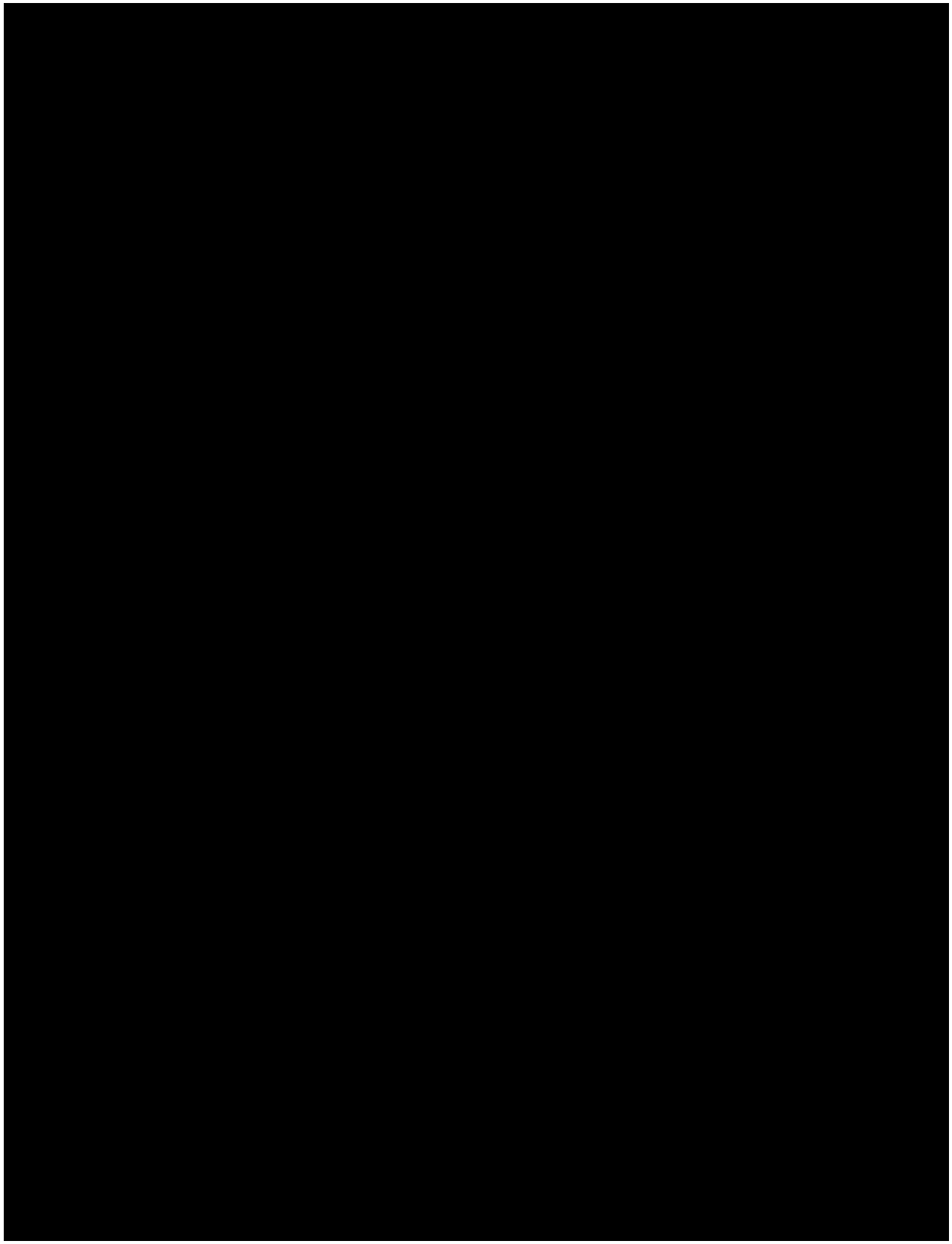
Biomarker analyses will be used to investigate the effect of branaplam at the molecular and cellular level as well as to determine how changes in these markers may relate to exposure and clinical outcomes. In addition, potential predictive markers of efficacy, as well as mechanisms of resistance to branaplam treatment will be explored. Additional markers related specifically to Huntington's disease may be assessed. Samples and data may be also used to support development of future companion diagnostic tests.

Sample(s) will be collected at the time point(s) defined in the Assessment Schedule (Table 8-2, Table 8-3 and Table 8-4).

Instructions for sample collection, processing and shipment will be provided in the Laboratory Manual.

Biomarker assessments in blood and CSF

Blood (serum, plasma, PBMC) and CSF will be collected as indicated in Table 8-2, Table 8-3 and Table 8-4 for soluble and/or cell-based markers. These will include [redacted] NfL [redacted]



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9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

As per the USM follow-up notification dated 06-Dec-2022 study treatment is permanently discontinued for all patients.

Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the participant or the Investigator.

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

Study treatment must be discontinued under the following circumstances:

- Participant (or legal representative, if needed) decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the participant
- Following emergency unblinding
- Emergence of the following adverse events: Consider any adverse events that in the judgment of the Investigator, taking into account the participant's overall status, prevent the participant from continuing participation in the study. Refer to Table 6-3 and protocol Section 6.5.2.1 Dose adjustments for QTcF prolongation.
- Any laboratory abnormalities that in the judgment of the Investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study.

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

Participants 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 'Withdrawal of Informed Consent' Section 9.1.2). Where possible,

participants in the DRF Treatment Period should return for the remaining DRF assessments (off study drug) indicated in the Assessment Schedule (Table 8-2, Table 8-3 and Table 8-4).

If participants fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, the participant should be followed for a period of 30 days. The following data should be collected at unscheduled site visits (if needed) or via telephone contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The Investigator must also contact the IRT to register the participant's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section.

Premature discontinuation of study treatment during Core Period:

- If a participant prematurely discontinues study treatment before or at Week 17 visit during the DRF period (for reasons other than withdrawal of consent), all assessments corresponding to all visits during the DRF period should still be completed up to and including Week 17 as described in the visit evaluation schedule Table 8-2, Table 8-3 and Table 8-4).
- If a participant prematurely discontinues study treatment during the blinded extension after the Week 17 visit during the DRF period (for reasons other than withdrawal of consent) and therefore does not continue in the OLE, all assessments as described under the EOT/Week 53 visit in the VES should be completed during the last visit.

Any participant that discontinues study drug treatment at any given timepoint during the Core period should complete the EOT-Core Disposition CRF.

- Participants that prematurely discontinue blinded study treatment during the Core period and do not continue in the OLE study period must be followed up for safety for 30 days after the last dose of blinded study drug is administered.
- Participants that complete the blinded study treatment during the Core period and continue in the OLE study period, will be monitored for safety during the OLE while taking the selected open label dose.

9.1.2 Withdrawal of informed consent and exercise of participants' data privacy rights

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment
  and
- Does not want any further visits or assessments (including further study-related contact).

This request should be as per local regulations (e.g., in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs discontinuation based on the protocol definitions of these terms.

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 their consent/ exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

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.

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

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise data privacy rights should be made as detailed in the assessment table (refer to Section 8).

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. No new Personal Data (including biological samples) will be collected following withdrawal of consent.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other participants' data privacy rights), the Investigator must 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 considered as lost to follow-up until due diligence has been completed.

9.1.4 Early study termination by the Novartis

The study can be terminated by Novartis at any time.

This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible for the End of Treatment visit and treated as a prematurely withdrawn participant. 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 participant's interests. The Investigator or Novartis depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant 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.

In the event of an early study termination decision, a 30-day safety follow-up is required after the last administration of study treatment. Alternatively, if an umbrella extension study is opened, the study may be concluded early and participants rolled into the new study where they will receive continued treatment; in this case, the 30-day safety follow-up is not required.

All randomized and/or treated participants should have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All serious adverse events (SAEs) reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the participant should be recorded in the source documentation.

Continuing care should be provided by the Investigator and/or referring physician based on participant availability for follow-up.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 10.1.1 and Section 10.1.2.

AEs will be reported by the participant (or, when appropriate, by a companion/caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs and SAEs.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.1.3 SAE reporting.

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant 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 Investigator has the responsibility for managing the safety of individual participants and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade:
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Drug interrupted/increased
- Dose interrupted/permanently discontinued

6. Its outcome

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be not recovered/not resolved (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

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 must 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 participants with the underlying disease.

10.1.2 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:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant 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 it were more severe (please refer to the ICH-E2D Guidelines).

- 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 signing the informed consent

- social reasons and respite care in the absence of any deterioration in the participant's general condition
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

- Is medically significant, e.g., defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment 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 participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." 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).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

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

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site. Information about all SAEs is collected and recorded on the electronic Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

SAE reporting timeframes

1. Screen Failures: SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.
2. Randomized OR Treated participants: SAEs collected between time participant signs ICF until 30 days after the participant has discontinued or stopped study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances that than within 24 hours of the Investigator receiving the follow-up information. (Note: If more stringent, local regulations

regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

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 study treatment, a CMO & PS 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 study 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 European Union (EU) Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30-day period following the last administration of study treatment should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

If a female participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the Investigator to the Novartis Chief Medical Officer and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

If a female partner of a male trial participant who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

After consent is provided the pregnancy reporting will occur up to one year after the estimated date of delivery.

10.1.5 Reporting of study treatment errors including misuse/abuse

Misuse/Abuse

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.

All reports of misuse and abuse of the product are also considered serious adverse events irrespective of whether a clinical event has occurred and should be reported in the safety database within 24 hours of Investigator's awareness.

Medication errors

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

- Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE.
- In addition, study treatment errors and uses outside of what is foreseen in the protocol if associated with an AE/SAE and misuse or abuse will also be collected and reported in the safety database within 24 hours of Investigator's awareness.

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

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate eCRFs

Please refer to Table 16-1 in Section 16.1 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-1 should be followed up by the Investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Section 16.1. Repeat liver chemistry tests (i.e., ALT, AST, total

bilirubin (TBL), prothrombin time/international normalized ratio (PT/INR), alkaline Phosphatase (ALP) and GGT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate eCRF.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption or every other week dosing after discussion with Novartis if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment Section 9.1), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - These investigations can include based on Investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease
    - Obtaining a more detailed history of symptoms and prior or concurrent diseases
    - Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
    - Exclusion of underlying liver disease, as specified in Section 5.2
    - Imaging such as abdominal ultrasound, CT or MRI, as appropriate
    - Obtaining a history of exposure to environmental chemical agents
    - Considering gastroenterology or hepatology consultations

All follow-up information and procedures performed must be recorded as appropriate in the eCRF.

Follow up on potential drug-induced liver injury (DILI) cases

An increase in transaminase combined with total bilirubin increase may be indicative of potentially severe DILI, and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities. The threshold for potential DILI may depend on the participant's baseline AST/ALT and total bilirubin value; participants meeting any of the following criteria will require further follow-up as outlined below

For participants with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed to be the cause of liver injury. A detailed history, including relevant information such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, and history of any pre-existing liver conditions or risk factors should be collected. Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR, alkaline phosphatase, albumin, and creatine kinase. If available, testing of Glutamate Dehydrogenase (GLDH) is additionally recommended. (In the event ALT/AST is above 3 times upper limit of normal, reflex testing will be performed by the central laboratory for GLDH).

Perform relevant examinations (Ultrasound or MRI, Endoscopic retrograde cholangiopancreatography (ERCP)) as appropriate, to rule-out an extrahepatic cause of cholestasis. Cholestasis (is defined as an ALP elevation > 2.0 x ULN with R value < 2 in participants without bone metastasis, or elevation of the liver-specific ALP isoenzyme in participants with bone metastasis). Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury. For children, there are caveats to calculating the R-ratio as normal levels of ALP are higher than in adults with standard ranges varying by developmental age. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury. Table 10-2 Table 10-1 provides guidance on specific clinical and diagnostic assessments which can be performed to rule -out possible alternative causes of observed LFT abnormalities. These labs may be done locally.

Table 10-1 Guidance on specific clinical and diagnostic assessments

Disease	Assessment
Hepatitis A, B, C, E	IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	Antinuclear Antibodies (ANA) & Anti-Smooth Muscle Antibody (ASMA) titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic congestive heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	Caeruloplasmin
Hemochromatosis	Ferritin, transferrin

Other causes should also be considered based upon participant's medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; cardiovascular disease / ischemic hepatitis – ECG, prior hypotensive episodes; Type 1 diabetes mellitus / glycogenic hepatitis).

Following appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" (i.e., >50% likely,), if it appears greater than all other possible causes of liver injury combined. The term "treatment-induced" indicates probably caused by the treatment, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant," and thus, meet the definition of SAE and should be reported as a SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented.

10.2.2 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

- Serum creatinine increase ≥ 25% compared to baseline during normal hydration status
- Urine protein-creatinine ratio (PCR) ≥1 g/g or ≥113 mg/mmol, OR new onset dipstick proteinuria ≥ 3+ OR new onset dipstick hematuria ≥ 3+ (after excluding menstruation, urinary tract infection (UTI), extreme exercise, or trauma)

Abnormal renal event findings must be confirmed within 24-48 hours after the first assessment.

Every renal laboratory trigger or renal event as defined in Table 10-2 should be followed up by the Investigator or designated personnel at the trial site as summarized in Section 16.2.

Since this is an early phase study baseline serum creatinine is determined as the mean of two serum creatinine measurements (e.g. at screening and pretreatment).

Table 10-2 Renal Events and Definition and Diagnosis

A renal event is defined as the presence of any of the following	Confirm Finding
GFR Event Serum creatinine increase ≥ 25% versus baseline **Note: Dependent on NORMAL hydration status, see the list below**	Confirm assessment 24 - 48 h after first assessment
Urine Event Protein-creatinine ratio > or = 1 g/g Cr or ≥113 mg/mmol New onset dipstick proteinuria ≥ 3+New onset dipstick hematuria ≥ 3+*	
*Exclude menstruation, urinary tract infection (UTI), extreme exercise or trauma, and bleeding from the distal urinary tract/bladder	

When assessing (Drug Induced Nephrotoxicity (DIN) renal events, also consider other causes of renal events and/or altered serum creatinine and BUN:

- Hypovolemia
- Major operations
- Severe infections and sepsis
- Co-medications affecting creatinine secretion (e.g., trimethoprim, cimetidine)
- Change of antihypertensive treatment regimens
- Acute or worsening heart failure
- Rhabdomyolysis (monitor for increase in CPK)

10.2.3 Prospective suicidality assessment

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.

The C-SSRS, which uses a semi-structured interview to probe participant responses, will be administered by an individual who has received training and certification in its administration. 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

If, at any time after screening and/or baseline, the score is “yes” on item 4 or item 5 of the suicidal ideation section of the C-SSRS or “yes” on any item of the suicidal behavior section, the participant must be referred to a mental health care professional for further assessment and/or treatment. The decision on whether the study treatment should be discontinued is to be taken by the Investigator in consultation with the mental health professional to whom the participant is referred.

In addition, all life-threatening events must be reported as SAEs. For example, if a participant answers “yes” to one of the questions in the suicidal behavior section, an SAE must be reported if the event was life-threatening. All events of “Non-Suicidal Self-Injurious Behavior”

(question also included in the suicidal behavior section) should be reported as AEs and assigned the appropriate severity grade.

10.2.4 Data Monitoring Committee

As per the USM follow-up notification dated 06-Dec-2022, after DMC recommendation to permanently discontinue study drug administration, Novartis will continue to engage with the DMC, until conclusion of the study or as mutually agreed by the DMC and Novartis.

This study will include an external Data Monitoring Committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site Investigators participating in the study. The primary goal of the DMC is to perform an ongoing review of safety and tolerability data, and critical efficacy variables during the course of the clinical study, and recommend to Novartis whether to continue, modify, or terminate the trial.

The DMC will consist of external experts, with experience in management and monitoring of clinical trials and/or disease area expertise but without direct involvement in any activities related to branaplam studies. The DMC will be assisted by an independent statistician and statistical programmer provided by Novartis; however Novartis study personnel will not have access to treatment codes or any unblinded data or data summaries prepared for the DMC.

The DMC is responsible for monitoring the safety of the trial participants, ensuring that the branaplam studies are being conducted with the high scientific and ethical standards and making appropriate recommendations based on data reviewed. The DMC will conduct full unblinded safety reviews of cumulative safety and tolerability data, as well as participant narratives for deaths and SAEs, discontinuations due to AEs and cases of special interest at regular intervals. In addition, unblinded safety review by the DMC will be implemented to stagger participant exposure to cohorts with higher doses. The DMC will be updated on an ongoing basis regarding any new preclinical safety data as well.

The DMC may also assess any potential relationship between CSF and/or PBMC mHTT data and dose/dose regimen with respect to signs and signals of safety concerns.

The DMC could make the following recommendations:

- Requesting changes or adjustments that may be required to ensuring participant safety and preserve trial integrity.
- Suggesting modification to protocol, including but not limited to changes in eligibility criteria, alteration of dosing regimen frequency of visits/safety assessments, or discontinuation of one or more Treatment Arms.
- Recommending continuation of the trial according to current version of the protocol OR to discontinue trial

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the Novartis and the DMC.

At the time of the CGAs, all available data will be reviewed from a safety and dose finding perspective by an independent Novartis team to support the decision to open the next cohort.

The independent Data Monitoring Committee (DMC) will review the data separately. The decision to open a new cohort will be made by the Novartis in consultation with the DMC.

10.2.5 Steering Committee

A Steering Committee (SC) comprised of Investigators or experts in HD management will be formed prior to initiation of the trial. The purpose of the SC is to provide overall guidance regarding design, conduct and execution of the trial to include (but not limited to) safety, accrual and contribution to scientific input for publications. Responsibilities of the SC and communication flow between SC and Novartis will be included in the SC charter document.

11 Data Collection and Database management

11.1 Data collection

Data not requiring a separate written record will be defined in the protocol and the Assessment Schedule (Table 8-2, Table 8-3 , Table 8-4 and Table 8-5 (post-USM)) and can be recorded directly on the eCRFs. All other data captured for this study will have an external originating source (either written or electronic) with the eCRF not being considered as source.

Designated Investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 Code of Federal Regulations (CFR) Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the Investigator staff.

The Investigator/designee is responsible for assuring that the data (recorded on eCRFs) (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 instructions for generating copies of the participant's 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.

11.2 Database management and quality control

Novartis personnel (or designated contract research organization (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.

Randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) with the Investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/Clinical Research Associate (CRA) organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The Investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the participant's file. The Investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

As per the USM, the original planned analyses of primary, secondary and exploratory endpoints to demonstrate efficacy are no longer applicable. No statistical modelling will be done. As specified earlier, the primary IA will take place once the majority of participants in cohort 1 complete their Week 33 visit Efficacy and safety endpoints will be summarized descriptively in an unblinded way as all the parties have been unblinded. More details will be documented in the Statistical Analysis Plan.

As per the USM, there is only one Cohort initiated and the OLE period is no longer applicable. No analysis based on OLE will be performed.

This section will mainly describe the IA that will take place once all randomized participants have completed their assessments at Week 17.

Data will be reported by treatment group and by visit as applicable. This study will include 3 treatment arms A, B, and C (or X or Y), which consists of 6 treatment groups (3 active dose groups and 3 matching placebo groups that are embedded within each treatment arm with a ratio of 4:1 active vs. placebo). Note that, in the analysis all participants assigned to placebo in different treatment arms will be pooled together as one placebo group. Hence, there are 4 treatment groups in total (3 active, 1 placebo). Assessment of potential bias due to pooling of placebo from different Cohorts will be described in the SAP.

Unless specified differently, descriptive analysis for categorical data will be summarized as frequencies and percentages and continuous data will be summarized with the mean, standard deviation (SD), median, minimum, and maximum.

Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

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 will consist of all randomized participants who received at least one dose of study drug. Efficacy analysis will be conducted on the Full Analysis Set.

The Safety Set (SAF) will consist of all participants who received at least one dose of study drug. Participants will be analyzed according to the treatment received. Safety analyses for the Core Period will be conducted on participants from SAF.

Pre-USM: Open Label Analysis Set (OLS) will consist of all participants who received at least one dose of study drug in OLE. The OLS will NOT be used for IA and will be used after OLE is completed.

Open label Safety Analysis Set (OLSAF) will consist of all participants who received at least one dose of study drug in OLE. Participants will be analyzed according to the treatment received. Safety analyses on OLE data will be conducted on participants from OLSAF.

12.2 Participant demographics and other baseline characteristics

Demographic variables and other baseline data including disease characteristics will be summarized for each treatment group and for all participants (total) for the Full Analysis Set. In addition, all relevant medical history at baseline will be summarized following the same strategy.

12.3 Treatments

The SAF will be used for the below analyses for Core Period (and cumulatively: Core + OLE). The OLSAF will be used for analyses for OLE Period.

The duration of exposure in days to each treatment group will be summarized by means of descriptive statistics. Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system. The number of participants who permanently discontinued from randomized treatment and the reasons will be summarized.

In addition, the number of participants whose dose interruption/discontinuation is within the acceptable limits as described in Section 2.1 primary estimand (i.e., missed dose less than 25% in the first 16 week and not missed 2 or more consecutive weeks prior to LP at week 17) will be summarized.

12.4 Analysis of the primary endpoint(s)/estimand(s)

As per the USM, the primary estimand and statistical modelling for dose-response relationship are no longer applicable. Primary endpoint of mHTT in CSF will be summarized descriptively.

The primary data analysis, so called the IA, will be performed at the end of DRF, when all randomized participants have completed their last assessment of this DRF period (Week 17, after 16 weeks on treatment). The analysis may include 4 treatment groups (3 active, 1 placebo).

There are two primary objectives in this study:

1. To assess the dose-response relationship of branaplam administered over 16 weeks on mHTT protein change from baseline in CSF.
2. To evaluate the safety and tolerability of various doses of branaplam over 16 weeks or longer in patients with HD.

The second primary objective safety and tolerability evaluation of the study drug will be addressed in safety Section 12.5.2. No inferential and model based statistical analyses are planned for any safety or tolerability endpoints. Hence, the rest of Section 12.4 mainly outlines the analysis plans for the first primary endpoint: reduction of mHTT in CSF for dose finding purpose.

The dose finding objective is associated with the two goals below:

- To confirm an overall dose response (DR) signal, versus placebo, based on data of 16 weeks of treatment
- To identify the dose(s) that correspond(s) to the optimal treatment effect based on the estimated DR relationship

12.4.1 Definition of primary endpoint(s)/estimand(s)

The primary estimand is defined in Section 2.1 of this protocol.

The efficacy primary endpoint is the % change from baseline of mHTT concentrations in CSF after 16 weeks of treatment, which is expressed as:
$(mHTT_{wk17} - mHTT_{baseline})/mHTT_{baseline}*100\%$.

The primary endpoints of the safety and tolerability objective will comprise main safety data, including but not limited to AEs/SAEs, physical exam (including neurological examination) findings, clinical laboratory assessments, and HTT lowering.

12.4.2 Statistical model, hypothesis, and method of analysis

The Multiple Comparison Procedure - Modelling (MCP-Mod) methodology (Bretz et al 2005, Pinheiro et al 2014) will be employed to test for an overall DR signal and to estimate the DR curve. MCP-Mod method is able to utilize all available data from the continuum of active doses and placebo to estimate a parametric DR curve which allows for interpolation of treatment effect across a range of doses. It is a hybrid approach that combines hypothesis testing and modeling to analyze Phase IIb dose-ranging studies with the purpose of finding suitable dose(s) for future trials. The first step of the procedure (MCP-step) is to assess presence of a DR signal using a trend test deducted from a set of pre-specified candidate dose-response shapes. The second step (Mod-step) relies on parametric modeling to estimate the DR curve and target doses of interest. An overview of the steps for the MCP-Mod methodology is outlined below. Details will be provided in the Statistical Analysis Plan (SAP).

MCP-Mod is a two-step procedure:

Step 1 (Testing an overall dose-response signal - MCP part):

The (covariate) adjusted mean responses at each individual dose at week 17 will be obtained from a mixed-effect linear model for repeated measures (MMRM) with the following baseline covariates considered, as appropriate: treatment, visit, age, CAG repeat length (the large allele), education level, baseline TFC, baseline CSF mHTT, treatment-by-visit interaction. To allow adjustment for correlations between time-points within participants, an unstructured variance-covariance structure will be used, if applicable.

The generalized MCP-Mod procedure (Pinheiro et al 2014) will be performed based on the adjusted treatment means obtained from the MMRM analysis for Week 17 data. The null hypothesis of a flat DR relationship for the mHTT lowering at a one-sided significance level of 5% will be tested against the alternative hypothesis of a non-constant DR curve. The testing will be performed with a multiple contrast test.

A wide range of possible DR relationships will be pre-specified to take model uncertainty into account based on the range of the doses.

A set of candidate models with five candidate sigmoid maximum effect (Emax) DR curves will be used to derive the optimal model contrasts for the multiple contrast tests assuming a monotonic DR relation. The parameters of the five candidate sigmoidal maximum effect (Emax) models (median effect dose (ED50), h) will be (5, 1), (20, 2), (50, 1), (50, 3), and (80, 6), where ED50 are the values the dose at which half of the maximum effect is reached, and h is the Hill

parameter that determines the steepness of the dose-response shape. For each of the five candidate DR curves, a contrast test statistic will be derived (Bretz et al 2005). The overall null hypothesis of no DR relationship is rejected if the multiplicity adjusted p-value for at least one contrast test is < 0.05 (one sided).

Step 2 (Estimation of the dose-response curve and target dose – Mod part):

A Sigmoid Emax model will be used to estimate the DR relationship in the Mod step. The dose-response curve will be estimated using bootstrap. A large number of bootstrap samples from the multivariate normal distribution will be drawn with adjusted means from the MMRM and corresponding covariance matrix. For each draw generalized least squares is used to fit the draws from the multivariate normal distribution. The final DR curve estimate is the median of these predictions while confidence intervals will be calculated from the quantiles. The final DR curve estimate with the model-based two-sided 90% confidence interval will be presented graphically.

Step 2 might be skipped and replaced by ANOVA if data is not sufficient to support the modelling step.

All data related to safety, efficacy and other assessments including PK exposure will be taken into consideration to propose a dose for further studies.

12.4.3 Handling of remaining intercurrent events of primary estimand

Intercurrent events of primary estimand will be addressed with hypothetical strategy:

- Treatment discontinuations for any reason or interruptions of dosing beyond acceptable limits: the treatment effect will be imputed as if the treatment had continued or dosing had not been interrupted and participant behaved like other participants from the same treatment group whose treatment discontinuation/interruption is within the acceptable limits. The limits are reached if one or both of the criteria below are met:
  1. >25% missed doses (i.e., >4 doses missed during DRF)
  2. 2 or more consecutive weeks off treatment prior to the Week 17 visit (LP)
- Intake of prohibited medications without discontinuation of study drug: the treatment effect will be imputed as if the prohibited medications had not been taken and participant behaved like other participants from the same treatment group who did not take prohibited medications
- AE/SAE/Death or any other intercurrent events leading to endpoint missing: the treatment effect will be imputed as if the intercurrent events had not occurred and participant behaved like other participants from the same treatment group who did not experience such intercurrent events.

12.4.4 Handling of missing values not related to intercurrent event

As stated in the primary estimand, the question of interest is the treatment effect in participants who, had treatment continued over 16 weeks with limited dose interruption/discontinuation. Participants with primary endpoint missing for any other reason not related to intercurrent event, will have the value(s) imputed using multiple imputation (MI) methods under a missing at random (MAR) assumption. The proportion of participants with missing primary endpoint at

week 17 will be compared among different doses and placebo. More implementation details of the multiple imputation (MI) will be specified in the SAP.

12.4.5 Supportive analyses

- Modelling of DR relationship will be repeated by including additional covariate CAG age product (CAP) score which is derived from age and CAG length
- Modelling of DR relationship will be performed as an additional primary supportive analysis by Disease stage (1 and 2).

12.4.6 Sensitivity analyses for primary endpoint/estimand

Sensitivity analyses will be specified in the SAP.

12.4.7 Supplementary analysis

Supplementary analysis will be specified in the SAP (including investigating the robustness of the MCP-Mod).

12.5 Analysis of secondary endpoints/estimands

Safety endpoints as one of the primary endpoints will be described in Section 12.5.2.

Secondary variables are:

- Clinical endpoints: Unified Huntington's Disease Rating Scale (UHDRS) Total Functional Capacity (TFC), UHDRS Total Motor Score (TMS), UHDRS Independence Scale (IS)
- Volumetric MRI (vMRI): Ventricular, Caudate and Total Brain Volume

Other biomarkers: total HTT and mHTT protein in CSF and plasma.

In addition to the above listed efficacy and biomarker outcomes, the following are secondary PK outcome parameters:

- PK parameters (e.g. AUClast, AUCtau, Cmax, Tmax, Ctrough) of branaplam and its metabolite UFB112 in plasma across the study duration
- Concentrations of branaplam and its metabolite UFB112 in CSF and concentration ratio CSF/plasma of the analytes

No multiplicity adjustment will be carried out for secondary analyses.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

As per the USM, the original planned statistical modelling and OLE period are no longer applicable. Secondary efficacy endpoints will be summarized descriptively.

UHDRS Total Functional Capacity (TFC). The TFC consists of five items and ranges from 0 to 13. A higher TFC score indicates better functional capacity.

UHDRS Total Motor Score (TMS). The range of TMS is 0 to 124, with higher scores indicating more severe motor impairment.

UHDRS Independence Scale (IS). The IS measures the level of independence by one single score between 10 and 100.

For the three efficacy secondary endpoints, data will be reported over three periods as follows:

1. DRF: An analysis of change from baseline to week 17 will be performed using ANCOVA model with treatment group as factor and adjusting for important covariates for DRF period at the time of IA (based on Full Analysis Set).
2. Core: descriptive statistics of the change from baseline to the end of Core will be presented by treatment group and compared to placebo (based on Full Analysis Set)
3. Core + OLE: descriptive statistics of the change from baseline and baseline-extension (EXT) to week 53-EXT will be presented by treatment group originally assigned during core and by selected dose(s) for OLE (based on OLS)

12.5.2 Safety endpoints

As per the USM, the OLE period is no longer applicable. Safety analyses will be carried out based on the SAF cumulatively.

As one of the primary endpoint, safety analyses will be carried out based on the SAF for summaries including Core Period data, OLSAF for summaries using only OLE data:

- IA: all safety data from baseline to a cut-off date (a date pre-specified for iDBL) will be reviewed by treatment group.
- End of study: all safety data will be reported cumulatively (Core + OLE) and by two periods separately:
    1. Core period (DRF + BE: this would partially overlap with IA, plus the data from BE that were not reported at IA) by treatment group
    2. OLE period by treatment group (only if more than one dose is selected for OLE) and by treatment group originally assigned in the core period

Adverse events

The number (and percentage) of participants with treatment emergent AEs will be summarized in the following ways:

- By primary system organ class and preferred term.
- By primary system organ class, preferred term and maximum severity.
- By Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for SAEs, deaths, and study medication related AEs, AEs leading to study discontinuation and AEs leading to study drug interruption/discontinuation.

Vital signs

Number and percentage of participants with clinically notable vital signs will be presented. Participants with clinically notable vital signs will be defined in the SAP.

Cardiac assessments

Cardiac assessments will include 12-lead ECG, Echocardiogram (ECHO) with GLS, and cardiac enzymes (Troponin and NTproBNP). For each assessment, summary statistics will be

provided for each individual parameter, as appropriate. Number and percentage of participants with clinically significant abnormalities will be calculated.

Clinical laboratory evaluations

The number and percentage of patients with newly occurring or worsening laboratory abnormalities meeting the clinically notable criteria (to be defined in the SAP) will be summarized by laboratory parameter. The most extreme post-dose value is considered. For selected laboratory tests (e.g., liver enzyme abnormalities), summary statistics of change from BL laboratory results will be presented by laboratory test category, visit and treatment group.

12.5.3 Pharmacokinetics

As per the USM, dosing in the study includes only for the 56 mg/week branaplam dose. All planned activities will be executed as described below with exception of the dose linearity of branaplam for PK plasma parameters. The latter cannot be executed since only one dose was tested and, therefore, the analysis is deleted from the analysis plan.

Branaplam and UFB112 concentrations will be expressed in mass per volume. The plasma and CSF concentrations of both analytes will be listed by analyte, treatment, participant, and visit/sampling time point. Descriptive summary statistics will be provided by analyte, treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics of plasma and CSF concentrations of branaplam and UFB112 will include mean (arithmetic and geometric), SD, coefficient of variation (CV) (arithmetic and geometric), median, minimum, and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values.

Pharmacokinetic parameters will be calculated as described in Section 8.5.2. Pharmacokinetic parameters will be listed by analyte, treatment and participant. Descriptive summary statistics of pharmacokinetic parameters will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented. The dose linearity of branaplam for PK plasma parameters such as Cmax and AUClast/AUCtau will be explored after first and last treatment within the DRF part of the study if data allows. Accumulation ratios of branaplam will be assessed for PK plasma parameters such as Cmax and AUClast/AUCtau by comparison of PK parameters determined after first and last treatment within the DRF if data allows.

12.5.4 Biomarkers

As per the USM notifications of 05-Aug-2022 and 06-Dec-2022, the original planned statistical modelling and OLE period are no longer applicable. Secondary endpoint vMRI will be summarized descriptively. Due to the limitation of the assay, biomarker data may be reported separately except primary endpoint mHTT in CSF.

The following biomarkers are secondary variables: changes in brain volume as measured by volumetric MRI in selected brain regions of interest, total HTT protein in CSF and plasma, and mHTT in plasma. Biomarker data will be reported over three periods:

1. DRF: An analysis of change from BL to week 17 will be performed using longitudinal MMRM model (ANCOVA model for volumetric MRI variables) with treatment as factor and adjusting for important covariates for DRF period at the time of IA (based on Full Analysis Set).
2. Core: descriptive statistics of the change from BL to the end of Core will be presented by treatment group and compare to placebo (based on Full Analysis Set)
3. Core + OLE: descriptive statistics of the change from BL and BL-EXT to week 53-EXT will be presented by treatment group originally assigned during core and by selected dose(s) for OLE(based on OLS)

Volumetric MRI

For each period, analysis will be performed by brain regions of interest (ROIs): Ventricular, Caudate and Total Brain Volume.

Absolute and relative changes in brain volume will be summarized by visit.

[redacted]

12.5.5 PK/PD relationships

The relationship between branaplam plasma/CSF concentration/PK and efficacy/PD/biomarkers will be explored graphically, and further analysis will be conducted if warranted. This will likely be reported in a separate report.

[redacted]

12.6 Analysis of exploratory endpoints

[redacted]

12.6.2 Other exploratory endpoints

Exploratory endpoints will be evaluated descriptively over three periods as applicable and appropriate statistical models may be used.

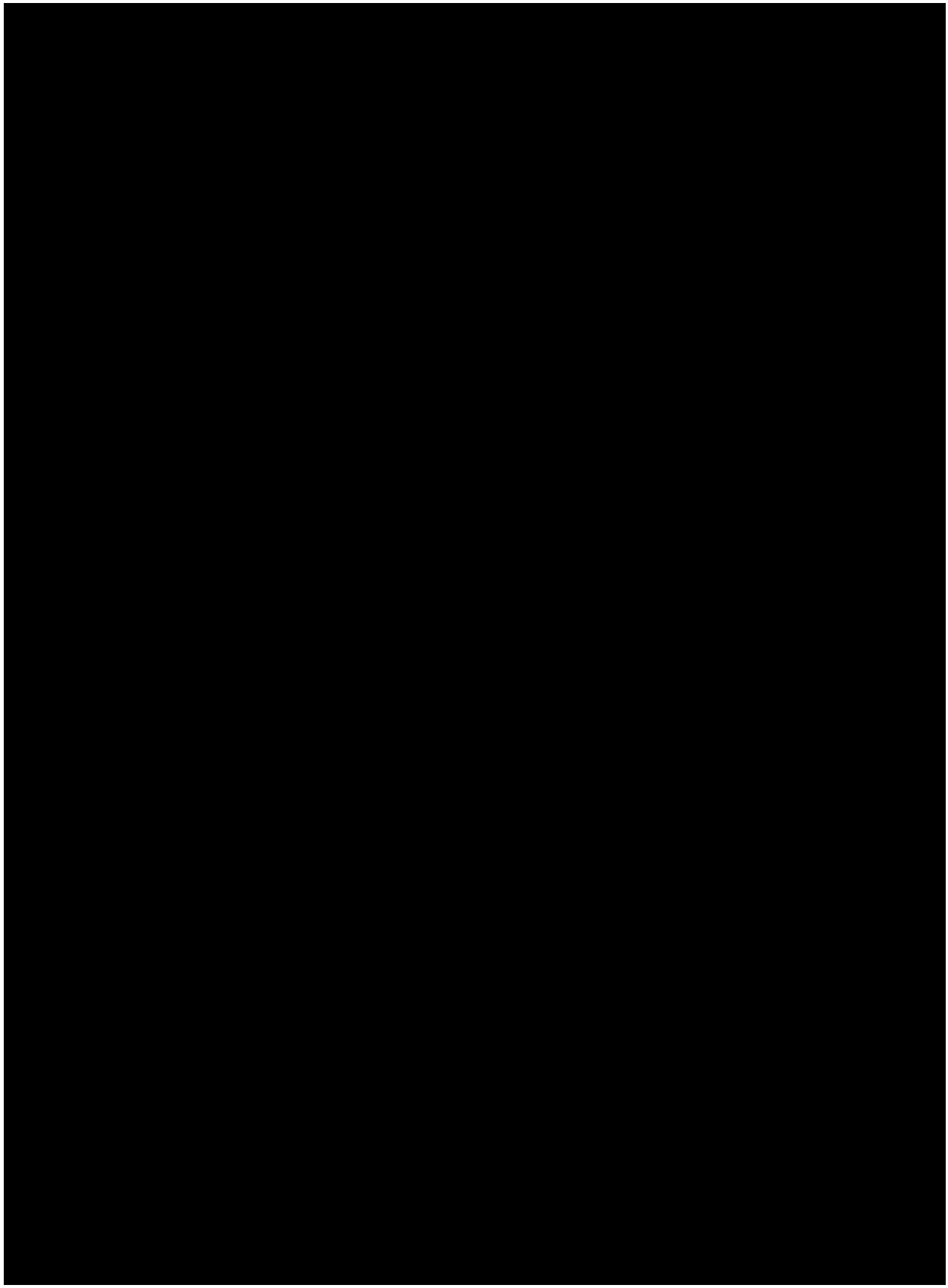
1. DRF: descriptive statistics of the change from BL to week 17 will be presented by treatment group and compare to placebo (based on Full Analysis Set)
2. Core: descriptive statistics of the change from BL to the end of Core will be presented by treatment group and compare to placebo (based on Full Analysis Set)
3. Core + OLE: descriptive statistics of the change from BL and BL-EXT to week 53-EXT will be presented by treatment group originally assigned during core and by selected dose(s) for OLE (based on OLS)

The following endpoints will be considered as exploratory:

[redacted]

- Neurofilament light chain (NfL) in serum and CSF

[redacted]



[redacted]

12.7 Interim analyses

Cohort Gating Assessments (CGAs)

Prior to the IA (primary analysis) to select the dose for the OLE and future studies, there will be up to two CGAs during the Core Period to determine whether to initiate additional dose Cohorts. As described in Section 3, additional Cohorts will be opened up sequentially based on safety data review in consultation with the DMC. No inferential and model based statistical analyses are planned for CGAs.

12.8 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.

12.8.1 Primary endpoint(s)

In the analysis, all participants assigned to matching placebo in different treatment arms will be pooled together as one placebo group. Bias because of pooling is not expected due to the nature of the biomarker endpoint.

The Multiple Comparison Procedure – Modelling (MCP-Mod) methodology (Bretz et al 2005 and Pinheiro et al 2014 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 (80, 6).

For the primary endpoint of mHTT reduction in CSF, the planned 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%. The calculations are based on assumption of 35% mHTT lowering in CSF (for the highest dose) and 0% mHTT lowering for placebo. The assumptions on SD were based on Tabrizi et al 2019a. 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 approximately. 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 12-1 presents the likelihood to identify AEs/SAEs at different timing of the cohort gating assessments and interim analysis.

Table 12-1 Likelihood of Identifying AEs/SAEs with Hypothetical Incidence Rate

Time of Assessment	Expected # in active group	Incidence rate	Likelihood to observe at least one AE/SAE
Cohort Gating Assessment 1	minimum 8	1%	8%
		5%	34%
		10%	57%
Cohort Gating Assessment 2	minimum 16	1%	15%
		5%	56%
		10%	81%
Interim analysis	60	1%	45%
		5%	95%
		10%	99%

12.8.2 Secondary endpoint(s)

The study is not powered for secondary endpoint.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Council on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC,, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis/Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, or EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial IInvestigator meetings.

Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

Summary results of primary and secondary endpoints will be disclosed based upon the global Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

13.3 Quality Control and Quality Assurance

Novartis/Novartis 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 IInvestigator 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 standard operating procedures (SOPs), and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an IInvestigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the IInvestigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an 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 and Health Authorities, where required, it cannot be implemented.

14.1 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 required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the IInvestigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

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16 Appendices

16.1 Appendix 1: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-1 Liver event and laboratory trigger definitions

-	**Definition/ threshold**
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN
-	• ALP > 2 × ULN (in the absence of known bone pathology)
-	• TBL > 2 × ULN (in the absence of known Gilbert syndrome)
-	• ALT or AST > 3 × ULN and INR > 1.5
-	• Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)
-	• Any clinical event of jaundice (or equivalent term)
-	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
-	• Any adverse event potentially indicative of a liver toxicity*
*These events cover the following: Hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal	

Table 16-2 Follow up requirements for liver events and laboratory triggers

Criteria	**Actions required**	**Follow-up monitoring**
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at IInvestigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at IInvestigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at IInvestigator discretion)

Criteria	Actions required	Follow-up monitoring
	• Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate eCRF	
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at IInvestigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at IInvestigator discretion)
> 3 to ≤ 5 × ULN (participant is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the participant and hold study drug until ULN < 3 • Consider every other week dosing if ULN <3 after discussion with Novartis	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)	-	-
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate eCRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)	-	-
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at IInvestigator discretion) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)

Criteria	Actions required	Follow-up monitoring
> 1.5 to ≤ 2 × ULN (participant is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the participant	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the participant • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at IInvestigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption, every other week dosing after discussion with Novartis or discontinuation of study drug • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate eCRF	Investigator discretion
[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN [b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia [c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.		

Based on IInvestigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.2 Appendix 2: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-3 Specific Renal Alert Criteria and Actions

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase 50 % [+]	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider participant hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3[+] OR Protein-creatinine **ratio** (PCR) ≥ 1g/g Cr (or ≥ 113 mg/mmol equivalent as converted by the measuring laboratory)	• Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3[+] on urine dipstick	• Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude UTI, trauma, bleeding from the distal urinary tract/bladder, menstruation and extreme exercise • Consider bleeding disorder
[+] Corresponds to KDIGO criteria for Acute Kidney Injury	

Additional specialized assessments are available to assess renal function or renal pathology. (Note: In exceptional cases, when a nephrologist considers a renal biopsy, it is recommended to make slide specimen available for evaluation by the RSG to potentially identify project-wide patterns of nephrotoxicity.)

Whenever a renal event is identified, a detailed participant history and examination are indicated to identify and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5-minute rest, with an appropriate cuff size)
- Signs and symptoms like fever, headache, shortness of breath, back or abdominal pain, dysuria or hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other diseases or causes, e.g., dehydration due to delirium, tumor lysis

Table 16-4 Renal Event Follow Up

FOLLOW-UP OF RENAL EVENTS
• Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells • Blood pressure and body weight • Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the eCRF.
• Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr), **OR** • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months. • Analysis of urine markers in samples collected over the course of the DIN event

16.3 Appendix 3: PK sample log - Time schedule for blood and CSF sampling for PK assessments

Table 16-5 Plasma PK samples for Core DRF and Blinded Extension

Day	Time point	Dose reference ID#	PK sample # (LMI070+UFB112)	Blood volume (mL)
1	0 h (pre-dose)[a]	1[b]	101	3
1	4 h (±30 min) post-dose	1[c]	102	3
1	7 h (±30 min) post-dose	1[c]	103	3
1	12 h (±30 min) post-dose	1[c]	104	3
2	22 h (±60 min) post-dose	1[c]	105	3
4	72 h (±120 min) post-dose	1[c]	106	3
8	0 h (pre-dose)[a][g]	1[c]	107	3
15	0 h (pre-dose)[a]	2[b]	108	3
29	0 h (pre-dose)[a]	3[b]	109	3
57	0 h (pre-dose)[a]	4[b]	110	3
57	4 h (±30 min) post-dose	4[c]	111	3
57	12 h (±30 min) post-dose)	4(c)	112	3
58	22 h (±60 min) post-dose	4(c)	113	3
85	0 h (pre-dose)[a]	5[b]	114	3
113	0 h (pre-dose)[a]	6[b]	115	3
113	4 h (±30 min) post-dose	6[c]	116	3
113	7 h (±30 min) post-dose	6[c]	117	3

Day	Time point	Dose reference ID#	PK sample # (LMI070+UFB112)	Blood volume (mL)
113	12 h (±30 min) post-dose	6(c)	118	3
114	22 h (±60 min) post-dose	6[(c)]	119	3
116	72 h (±120 min) post-dose	6[(c)]	120	3
169	0 h (pre-dose)[(a)]	7[(b)]	121	3
225	0 h (pre-dose)[(a)]	8[(b)]	122	3
281	0 h (pre-dose)[(a)]	9[(b)]	123	3
365 [(e)]	0 h (pre-dose)[(a)]	10[(b)]	124	3
421 [(f)]	0 h (pre-dose)[(a)]	11[(b)]	125	3
477 [(f)]	0 h (pre-dose)[(a)]	12[(b)]	126	3
533 [(f)]	0 h (pre-dose)[(a)]	13[(b)]	127	3
589 (f)	0 h (pre-dose)[(a)]	14[(b)]	128	3
645 (f)	0 h (pre-dose)[(a)]	15[(b)]	129	3
701 (f)	0 h (pre-dose)[(a)]	16[(b)]	130	3
999 [(e)]	EOT 0 h (pre-dose)[(a)]	17[(b)]	149	3
Plasma PK samples for Open Label Extension				
Day	**Time point**	**Dose reference ID#**	**PK sample # (LMI070+UFB112)**	**Blood volume (mL)**
1	0 h (pre-dose)[(a)]	18[(b)]	151	3
57	0 h (pre-dose)[(a)]	19[(b)]	152	3
113	0 h (pre-dose)[(a)]	20[(b)]	153	3
169	0 h (pre-dose)[(a)]	21[(b)]	154	3
225	0 h (pre-dose)[(a)]	22[(b)]	155	3
281	0 h (pre-dose)[(a)]	23[(b)]	156	3
365	0 h (pre-dose)[(a)]	24[(b)]	157	3
-	Unscheduled[(d)]	-	1001+	3

(a) Take sample immediately prior to administration of study drug (within approximately 3 hours prior to dosing)

(b) For pre-dose PK samples, dose reference # refers to the first dose the subject received immediately after collection of the PK sample with exception of sample 107.

(c) For post-dose PK samples, dose reference # refers to the last dose the subject received prior to collection of the PK sample.

(d) PK samples to be uniquely, sequentially numbered as #001, #002, #003, etc.; the time of unscheduled sample has to be recorded accurately in the DRF, BE or OLE study parts.

(e) Day 365 corresponds to Week 53/EOT in the BE. In the event the BE for the participant is extended beyond 365 days, the last sample taken in the BE is described as day 999 and is defined as EOT.

(f) Days of sample collection are scheduled in the event the BE is extended beyond the planned EOT at day 365

(g) The sample equals to 168 h after first dosing and pre-dose to second dosing.

Table 16-6 Time schedule for CSF sampling for PK assessments (all patients)

CSF PK samples for Core DRF and Blinded Extension				
Day	**Time point**	**Dose reference ID#**	**PK sample # (LMI070+UFB112)**	**volume (mL)**
1	0 h (pre-dose)(a)	1(b)	301	2 x 0.6
57	0 h (pre-dose)(a)	4(b)	302	2 x 0.6
113	0 h (pre-dose)(a)	6(b)	303	2 x 0.6
225	0 h (pre-dose)(a)	8(b)	304	2 x 0.6
365 (d)	0 h (pre-dose)(a)	10(b)	305	2 x 0.6
477 (e)	0 h (pre-dose)(a)	12(b)	306	2 x 0.6
589 (e)	0 h (pre-dose)(a)	14(b)	307	2 x 0.6
701 (e)	0 h (pre-dose)(a)	16(b)	308	2 x 0.6
999	0 h (pre-dose)(a)	17(b)	349	2 x 0.6
CSF PK samples for Open Label Extension				
1	0 h (pre-dose)(a)	18(b)	351	2 x 0.6
113	0 h (pre-dose)(a	20(b)	353	2 x 0.6
225	0 h (pre-dose)(a	21(b)	355	2 x 0.6
365	0 h (pre-dose)(a	24(b)	357	2 x 0.6
-	Unscheduled(c)	-	3001+	2 x 0.6

(a) Take sample immediately prior to administration of study drug (within approximately 3 hours prior to dosing)

(b) For pre-dose PK samples, dose reference # refers to the first dose the subject received immediately after collection of the PK sample.

(c) PK samples to be uniquely, sequentially numbered as #001, #002, #003, etc.; the time of unscheduled sample has to be recorded accurately in the DRF, BE or OLE study parts

(d) *Day 365 corresponds to Week 53/EOT in the BE. In the event the BE for the participant is extended beyond 365 days, the last sample taken in the BE is described as day 999 and is defined as EOT. (e) Days of sample collection are scheduled in the event the BE is extended beyond the planned EOT at day 365

16.4 Appendix 4: Biomarker sample log - Time schedule for blood/CSF sampling for Biomarker assessments

Table 16-7 Blood and CSF Biomarkers

Core DRF and Blinded Extension						
Day	**Time point**	**Dose reference ID#**	**CSF (mHTT/tHTT)**	**CSF Biomarkers (NfL, others)**	[redacted]	**Plasma (mHTT /tHTT)**
Baseline	-	-	-	-		700
1	0 h (pre-dose)(a)	1(b)	201	401		701
1	4 h (±30 min) post-dose	1(c)	-	-		-
1	7 h (±30 min) post-dose	1(c)	-	-		-
1	12 h (±30 min) post-dose	1(c)	-	-		-

Core DRF and Blinded Extension							
Day	**Time point**	**Dose reference ID#**	**CSF (mHTT/tHTT)**	**CSF Biomarkers (NfL, others)**	[redacted]	[redacted]	**Plasma (mHTT/tHTT)**
2	22 h (±60 min) post-dose	1[(c)]	-	-			705
4	72 h (±120 min) post-dose	1[(c)]	-	-			706
8	0 h (pre-dose)[(a)(g)]	1[(c)]	-	-			707
15	0 h (pre-dose)[(a)]	2[(b)]	-	-			708
29	0 h (pre-dose)[(a)]	3[(b)]	-	-			709
57	0 h (pre-dose)[(a)]	4[(b)]	202	402			710
57	4 h (±30 min) post-dose	4[(c)]	-	-			-
57	12 h (±30 min) post-dose)	4(c)	-	-			-
58	22 h (±60 min) post-dose	4(c)	-	-			713
85	0 h (pre-dose)[(a)]	5[(b)]	-	-			714
113	0 h (pre-dose)[(a)]	6[(b)]	203	403			715
113	4 h (±30 min) post-dose	6[(c)]	-	-			-
113	7 h (±30 min) post-dose	6[(c)]	-	-			-
113	12 h (±30 min) post-dose	6(c)	-	-			-
114	22 h (±60 min) post-dose	6[(c)]	-	-			719
116	72 h (±120 min) post-dose	6[(c)]	-	-			720
169	0 h (pre-dose)[(a)]	7[(b)]	-	-			721
225	0 h (pre-dose)[(a)]	8[(b)]	204	404			722
281	0 h (pre-dose)[(a)]	9[(b)]	-	-			723
365 [(e)]	0 h (pre-dose)[(a)]	10[(b)]	205	405			724
421 [(f)]	0 h (pre-dose)[(a)]	11[(b)]	-	-			725
477 [(f)]	0 h (pre-dose)[(a)]	12[(b)]	206	406			726

Core DRF and Blinded Extension					[redacted]			
Day	**Time point**	**Dose reference ID#**	**CSF (mHTT/tHTT)**	**CSF Biomarkers (NfL, others)**				**Plasma (mHTT/tHTT)**
533 (f)	0 h (pre-dose)(a)	13(b)	-	-				727
589 (f)	0 h (pre-dose)(a)	14(b)	207	407				728
645 (f)	0 h (pre-dose)(a)	15(b)	-	-				729
701 (f)	0 h (pre-dose)(a)	16(b)	208	408				730
999 (e)	EOT 0 h (pre-dose)(a)	17(b)	249	449				749
Blood and CSF Biomarkers for **Open Label Extension**								
Day	**Time point**	**Dose reference ID#**	**CSF (mHTT/tHTT)**	**CSF Biomarkers (NfL, others)**				**Plasma (mHTT/tHTT)**
1	0h (pre-dose)(a)	18(b)	251	451				751
57	0 h (pre-dose)(a)	19(b)	-	-				752
113	0 h (pre-dose)(a)	20(b)	253	453				753
169	0 h (pre-dose)(a)	21(b)	-	-				754
225	0 h (pre-dose)(a)	22(b)	255	455				755
281	0 h (pre-dose)(a)	23(b)	-	-				756
365	0 h (pre-dose)(a)	24(b)	257	457				757
-	Unscheduled(d)	-	2001+	4001+				7001+

(a) Take sample immediately prior to administration of study drug (within approximately 3 hours prior to dosing)

(b) For pre-dose PK samples, dose reference # refers to the first dose the subject received immediately after collection of the PK sample with exception of sample 107.

(c) For post-dose PK samples, dose reference # refers to the last dose the subject received prior to collection of the PK sample.

(d) Unscheduled samples to be uniquely, sequentially numbered as #001, #002, #003, etc.; the time of unscheduled sample has to be recorded accurately in the DRF, BE or OLE study parts.

(e) Day 365 corresponds to Week 53/EOT in the BE. In the event the BE for the participant is extended beyond 365 days, the last sample taken in the BE is described as day 999 and is defined as EOT.

(f) Days of sample collection are scheduled in the event the BE is extended beyond the planned EOT at day 365

(g) The sample equals to 168 h after first dosing and pre-dose to second dosing.

Table 16-8 Blood Biomarkers continued

Core DRF and Blinded Extension			[redacted]
Day	**Timepoint**	**Serum biomarkers (NfL, Others)**	
Screening	-	800	
Baseline	-	801	
8	0 h (pre-dose)[(a)]	802	
15	0 h (pre-dose) [(a)]	803	
29	0 h (pre-dose) [(a)]	804	
57	0 h (pre-dose) [(a)]	805	
85	0 h (pre-dose) [(a)]	806	
113	0 h (pre-dose) [(a)]	807	
141	0 h (pre-dose) [(a)]	808	
169	0 h (pre-dose) [(a)]	809	
197	0 h (pre-dose) [(a)]	810	
225	0 h (pre-dose) [(a)]	811	
253	0 h (pre-dose) [(a)]	812	
281	0 h (pre-dose) [(a)]	813	
309	0 h (pre-dose) [(a)]	814	
337	0 h (pre-dose) [(a)]	815	
365	0 h (pre-dose) [(a)]	816	
393	0 h (pre-dose) [(a)]	817	
421	0 h (pre-dose) [(a)]	818	
449	0 h (pre-dose) [(a)]	819	
477	0 h (pre-dose) [(a)]	820	
505	0 h (pre-dose) [(a)]	821	
533	0 h (pre-dose) [(a)]	822	
561	0 h (pre-dose) [(a)]	823	
589	0 h (pre-dose) [(a)]	824	
617	0 h (pre-dose) [(a)]	825	
645	0 h (pre-dose) [(a)]	826	
673	0 h (pre-dose) [(a)]	827	
701	0 h (pre-dose) [(a)]	828	
999	0 h (pre-dose) [(a)]	849	
Open Label Extension			
Day	**Timepoint**	**Serum biomarkers (NfL, others)**	
1	0 h (pre-dose) [(a)]	851	
29	0 h (pre-dose) [(a)]	852	
57	0 h (pre-dose[(a)])	853	
85	0 h (pre-dose) [(a)]	854	
169	0 h (pre-dose) [(a)]	857	
197	0 h (pre-dose) [(a)]	858	
281	0 h (pre-dose) [(a)]	861	
309	0 h (pre-dose) [(a)]	862	
337	0 h (pre-dose) [(a)]	863	

Core DRF and Blinded Extension			[redacted]
Day	**Timepoint**	**Serum biomarkers (NfL, Others)**	
365	0 h (pre-dose) [(a)]	864	
Unscheduled	-	8001+	

[(a)] Take sample immediately prior to administration of study drug (within approximately 3 hours prior to dosing)