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EVALUATION OF THE DOSE-RESPONSE OF CELLAVITA HD INVESTIGATIONAL PRODUCT AFTER INTRAVENOUS APPLICATION IN PARTICIPANTS WITH HUNTINGTON'S DISEASE

ADORE-DH version Amendment 6 dated February 23, 2021

Statistical Analysis Plan
Final Analysis

Version: 1.0
Date: 16 March 2022

Sponsor Approval Page

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Modification History

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1.0	16 MARCH 2022	MUNISH MEHRA	ORIGINAL

Contents

Abbreviation

Abbreviation	Specification
AE	Adverse Events
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CIBIS	Clinician Interview Based Impression of Severity
CK	Creatine Kinase
CKmB	Creatine Kinase mB
CNS	Central Nervous System
CPK	Creatine phosphokinase
CRF	Case Report Form
CS	Clinically Significant
C-SSRS	Columbia Suicidal Severity Rating Scale
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FTA-ABS	Fluorescent Treponemal Antibody Test Absorption Test
Gamma-GT	Gamma-glutamyl transferase
HAM-D	Hamilton Depression Assessment Scale
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HD	Huntington's disease
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency
HTLV	Human T Cells of Lymphotropic Virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IL	Interleukins
INR	International normalized ratio
ITT	Intention to Treat
LDL	Low Density Lipoprotein
MAR	Missing at Random
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MI	Multiple Imputation
MMRM	Mixed Model Repeated Measures
MNAR	Missing Not At Random
MPV	Mean Platelet Volume
NCS	Non Clinically Significant

PP	Per Protocol
PT	Preferred Term
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
SOC	System Organ Class
TCS	Total Chorea Score
TEAE	Treatment Emergent Adverse Event
TFC	Total Functional Capacity
TMS	Total Motor Score
TNF-α	Tumor Necrosis alpha Factor
UHDRS	Unified Huntington's Disease Rating Scale
VLDL	Very Low-Density Lipoprotein
WBC	White Blood Cell Count
β-hCG	Beta-Human Chorionic Gonadotropins

1. Introduction

This statistical analysis plan was drafted for the ADORE-DH protocol for Cellavita Pesquisa Científica Ltda. In this document, the contents and methods of statistical analysis will be described in details.
This statistical analysis plan was based on protocol (version Amendment 6 dated February 23, 2021) and Case Report Form (CRF, version 03-FEB-22 20:47:51).

This statistical analysis plan reflects some changes from the statistical analysis section of the protocol as these were deemed more relevant and appropriate for analysis for this HD study based on analysis of other HD studies. The clinical study report will identify changes to planned analysis between the protocol and SAP.

2. Study Objective (s)

The primary objective of this clinical trial is to identify the dose of Cellavita-HD product that has the best clinical response (Total Motor Scale from UHDRS).

The secondary efficacy objectives of the study are:

- Clinical neurological evaluation throughout the study (Other domains from UHDRS and HAM-D)
- Overall assessment of Huntington's disease severity (CIBIS scale)
- BMI assessment
- Assess the incidence of suicide attempts during treatment
- Neurological evaluation by imaging

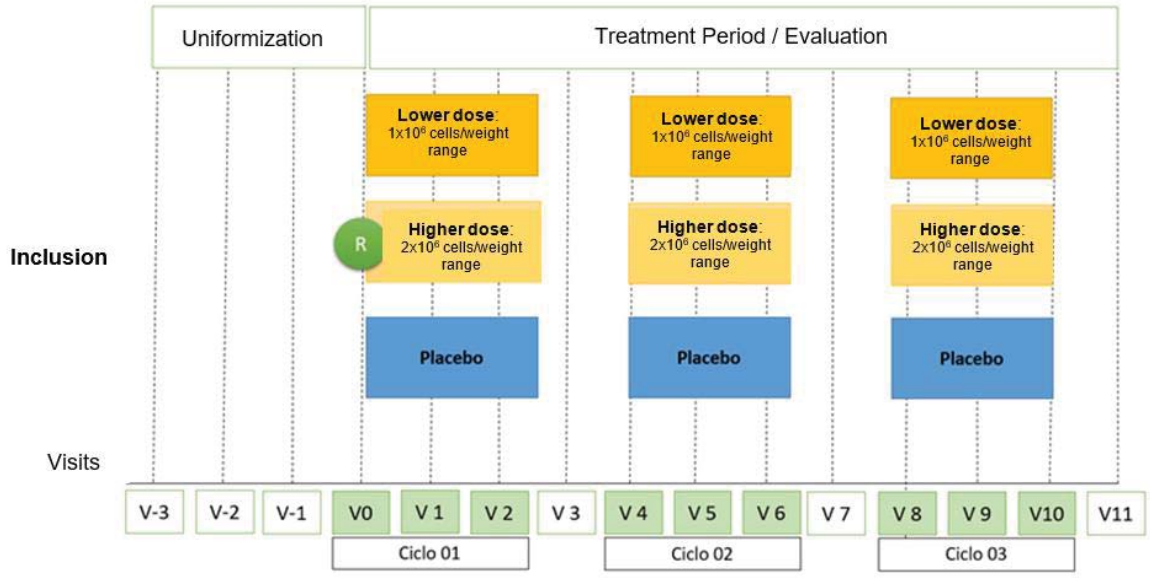
The safety objective of the study is to evaluate the incidence and classification of adverse events occurring between treatments regarding type, frequency and intensity as well as abnormalities in safety data such as ECGs, Vital Signs, Chemistry & Hematology laboratory assessments, etc.

3. Study Design

This study is a prospective, phase II, single-center, randomized, placebo controlled, triple-blind study evaluating two test doses vs placebo in 35 participants randomized 2:2:1 into the following treatment groups:

G1: (n = 14 participants) - Lower dose: dose of $1x10^6$ cells/by weight range per administration.
G2: (n = 14 participants) - Higher dose: dose of $2x10^6$ cells/by weight range per administration.
G3: (n = 7 participants) - Placebo: constituted by the vehicle of the investigational product.

After a 90 days screening period, participants will be included in the study and will begin treatment and follow-up phase that will last 330 days. The total period of participation in the study will be up to 420 days from the period of uniformization of the study; that is, about 14 months approximately (See figure below). Note: Ciclo below means Cycle.



Above visits take place as indicated below (for additonal details on windows around visits, see schedule of assessments)

- Visit -3 inclusion (V-3): -30 to -1 days before V-2;
- Visit -2 (V-2): up to 30 + 7 days after V-3
- Visit -1 (V-1): up to 30 + 7 days after V-2
- Visit 0 (V0): first administration of cycle 1; up to 30 days after V-1
- Visit 1 (V1): second administration of cycle 1 (30 days after Visit 0)
- Visit 2 (V2): third administration of cycle 1 (60 days after Visit 0)
- Visit 3 (V3): follow-up visit (90 days after Visit 0)
- Visit 4 (V4): first administration of cycle 2 (120 days after Visit 0)
- Visit 5 (V5): second administration of cycle 2 (150 days after Visit 0)

- Visit 6 (V6): third administration of cycle 2 (180 days after Visit 0)
- Visit 7 (V7): follow-up visit (210 days after Visit 0)
- Visit 8 (V8): first administration of cycle 3 (240 days after Visit 0)
- Visit 9 (V9): second administration of cycle 3 (270 days after Visit 0)
- Visit 10 (V10): third administration of cycle 3 (300 days after Visit 0)
- Visit 11 (V11): follow-up visit/final visit (330 days after Visit 0)

After the 11th Visit, participants will enter an extension protocol.

Subjects will be randomized and treatment initiated at V0.

The estimated number of participants was calculated considering clinical/regulatory and non-statistical assumptions. In this way, the document Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products - Guidance for Industry (FDA, 2015) predicts that a smaller sample size is considered appropriate for diseases considered fatal, where a major potential benefit may warrant an unknown risk. Additionally, considering conditions provided by the FDA document such as limited capacity of the investigational product manufacturing and the relatively rare prevalence of the target disease, Sponsor suggests the sample size of 35 participants, which is considered a feasible sample size and at the same time adequate to meet the proposed objective.

Schedule of Assessments: Framework of study activities - Inclusion and Uniformization Period

Activities	Inclusion	Uniformization	
	V-3	V-2	V-1
	-37 to -1 days before V-2	Up to 30 + 7 days after V-3	30 + 7 days after V-2
Consent form (ICF)	X		
Evaluation of inclusion/exclusion criteria	X	X[a]	X[a]
Medical evaluation: medical history, and physical examination/vital data	X	X	X
Demographic data (date of birth, gender and race)	X		
Confirmation or performance of laboratory diagnosis of Huntington's disease	X		
Evaluation of laboratory diagnosis of Huntington's disease, if applicable		X[b]	
Blood and urine collection for laboratory inclusion tests	X		
Evaluation of laboratory blood and urine tests		X	
Pregnancy urinary test for women	X	X	X
Blood collection for serology examination	X		
Evaluation of the serology examination		X	
ECG performance	X		
Evaluation of ECG result		X	
Performance of CNS MRI	X		
Assessment of the CNS MRI result		X	
UHDRS Scale	X	X	X
CIBIS Scale	X	X	X
Hamilton Depression Assessment Scale (HAM-D)	X	X	X
Activities	**Inclusion/uniformization**	**Uniformization**	
	V-3	**V-2**	**V-1**
	-37 to -1 days before V-2	**Up to 30 + 7 days after V-3**	**30 + 7 days after V-2**
Concomitant/prior medication registration	X	X	X
Evaluation of adverse events	X	X	X
Assessment of pregnancy risk and dispensation of contraceptive method, if applicable.	X	X	X
General guidelines	X	X	X

[a] Items **"d" and "e"** of the inclusion criteria will be evaluated only at the inclusion visit (V-3) due to the natural fluctuation of the disease
[b] For participants who need to carry out the laboratory diagnosis of Huntington's disease, the test will be performed at V-3 and evaluated at V-2

Inclusion criteria Item d) Obtaining 5 points or more in the motor evaluation of the UHDRS (Unified Huntington's Disease Rating Scale) at the time of inclusion; Item e) Obtaining 8 to 11 points in the functional capacity of the UHDRS scale at the time of inclusion.

Schedule of Assessments: Framework of study activities - Treatment and Follow-up Period

Activities	V0 Start of treatment - Up to 30 days after V-1	V1 30+5 days after V0	V2 60+5 days after V0	V3 90+5 days after V0	V4 120+5 days after V0	V5 150+5 days after V0	V6 180+5 days after V0	V7 210+5 days after V0	V8 240+5 days after V0	V9 270+5 days after V0	V11 300+5 days after V0	V11[c] 330+5 days after V0
	1st adm. Cycle 1	2nd adm. Cycle 1	3rd adm. Cycle 1	F-up.	1st adm. Cycle 2	2nd adm. Cycle 2	3rd adm. Cycle 2	F-up.	1st adm. Cycle 3	2nd adm. Cycle 3	3rd adm. Cycle 3	Final
Evaluation of inclusion criteria/ Exclusion (except criteria "d" and "e")	X											
Evaluation of discontinuation criteria		X	X	X	X	X	X	X	X	X	X	X
Medical evaluation: medical history and physical examination/vital data	X	X	X	X	X	X	X	X	X	X	X	X
Randomization	X											
Intravenous administration of Cellavita-HD or placebo (hospitalization for a period prior to administration and for another 06 hours)	X[a]	X[a]	X[a]		X[a]	X[a]	X[a]		X[a]	X[a]	X[a]	
Blood and urine collection for laboratory tests				X				X				X
Evaluation of laboratory test results					X				X			X
Pregnancy urinary test for women	X	X	X	X	X	X	X	X	X	X	X	X
Blood collection for serology												X
Evaluation of serology result												X
ECG performance				X				X				X
Evaluation of ECG result					X				X			X
ECG monitoring	X	X	X		X	X	X		X	X	X	

Activities	V0 Start of treatment - Up to 30 days after V-1	V1 30+5 days after V0	V2 60+5 days after V0	V3 90+5 days after V0	V4 120+5 days after V0	V5 150+5 days after V0	V6 180+5 days after V0	V7 210+5 days after V0	V8 240+5 days after V0	V9 270+5 days after V0	V11 300+5 days after V0	V11[c] 330+5 days after V0
	1st adm. Cycle 1	2nd adm. Cycle 1	3rd adm. Cycle 1	F-up.	1st adm. Cycle 2	2nd adm. Cycle 2	3rd adm. Cycle 2	F-up.	1st adm. Cycle 3	2nd adm. Cycle 3	3rd adm. Cycle 3	Final
UHDRS and HAM-D scale and CIBIS	X	X	X	X	X	X	X	X	X	X	X	X
MRI for CNS evaluation												X
Evaluation of CNS MRI result												X
Concomitant medication registration	X	X	X	X	X	X	X	X	X	X	X	X
Evaluation of adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of pregnancy risk and dispensation of contraceptive method, if applicable.	X	X	X	X	X	X	X	X	X	X	X	X[b]
General guidelines	X	X	X	X	X	X	X	X	X	X	X	X
Dispensation from the study												X

[a] Hospitalization for 06 hours: all procedures provided for in the protocol should be performed at the times determined, including evaluation of vital signs, clinical examination and ECG. The length of stay can be extended at the discretion of the principal investigator.

[b] In this visit, because it is the last visit of the study, there will be no dispensation of contraceptive method, only assessment of the risk of pregnancy.

[c] If any examination performed on this visit presents any clinically significant abnormality, the research participants will be invited to perform an extraordinary visit.

4. Endpoints

4.1. Efficacy Endpoints

4.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is rate of change (slope) per year from Baseline to V11 in total motor score (TMS) from the UHDRS.

Baseline is defined as the last non-missing value prior to first infusion at V0. If a value was not collected at V0 the nearest prior non-missing value is used as the Baseline value.

The TMS Score is the sum of the 31 items in the Motor Assessment portion of UHDRS with each item rated 0 to 4. The TMS is between 0 (Best) to 124 (Worst).

4.1.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints will include the following:

From UHDRS: TMS (at V7), Total Chorea Score (TCS), Total Functional Capacity (TFC), Functional Assessment (FA), Behavioral Assessment (BA), Independence Scale (IS), Cognitive assessments (CA) of (F, A and S combined, Digits Direct, Reversed and both combined and Stroop posters individually and all combined).

TCS is based on 7 items (eCRF items 12.1 through 12.7) from 12.1 Chorea (FACE) through 12.7 12.7 Chorea (LLE).

TFC is based on 5 items for a score between 0 (worst) to13 (best).

FA is based on 25 item with Yes (1), No (0) answers to get a score between 0 (worst) to 25 (best).

BA is based on 16 items with a score of 0 (best) to 93 (worst)

IS is a single assessment with scores from 10 (worst) to 100 (best)

Cognitive scores are based on 5 items that are added up with a score from 0 to > 300 with higher scores being better. The 5 items include SDMT, SWR.

In addition to the above scores derived from the UHDRS the following additional secondary endpoints will be derived:

CIBIS from 1 (Normal) to 7 (Among the most extremely ill patients). 0 is not assessed and will not be summed.

Body Mass Index (BMI) (Kg/m2)

The Hamilton Depression (HAM-D) Rating Score provides an indication of depression using 17 items rating symptoms from 0 (absent); 1 (mild); 2 (moderate); 3 (severe) to 4 (incapacitating)

- Rate of change (slope) per year from baseline to post baseline Visits V3, V7 and V11 with V11 being most important
- Responder analyses may be generated after review of initial results on changes from baseline described above.

For computation of rate of change (slope) each subject's value will be associated with number of days from Baseline when it was recorded. The rate of change (slope) per day will then be multiplied by 365.25 to be expressed as a rate of change (slope) per year to compare with published literature.

All participants performed CNS MRI (performed in 1.5T) at V-3 visit and at V11 (after the last infusion).

Select MRI Parameters analyzed will include from V-3 (Baseline for MRI) through V11:

Gray Matter

(a) Caudate Left Hemisphere(mm3)
(b) Caudate Right Hemisphere(mm3)
(c) Frontal Lobe Left MCT (mm)
(d) Frontal Lobe Left Vol (mm3)
(e) Frontal Lobe Right MCT(mm)
(f) Frontal Lobe Right Vol (mm3)
(g) Globus Pallidus Left Hemisphere(mm3)
(h) Globus Pallidus Right Hemisphere(mm3)
(i) Putamen Left Hemisphere(mm3)
(j) Putamen Right Hemisphere(mm3)
(k) Thalamus Left Hemisphere(mm3)
(l) Thalamus Right Hemisphere(mm3)

White Matter

(a) Genu of Corpus FAR
(b) Genu of Corpus ADR
(c) Genu of Corpus MDR
(d) Genu of Corpus RDR
(e) Genu of Corpus FAL
(f) Genu of Corpus ADL
(g) Genu of Corpus MDL
(h) Genu of Corpus RDL
(i) Body of Corpus FAR
(j) Body of Corpus ADR
(k) Body of Corpus MDR
(l) Body of Corpus RDR

(m) Body of Corpus FAL
(n) Body of Corpus ADL
(o) Body of Corpus MDL
(p) Body of Corpus RDL
(q) Splenium FAR
(r) Splenium ADR
(s) Splenium MDR
(t) Splenium RDR
(u) Splenium FAL
(v) Splenium ADL
(w) Splenium MDL
(x) Splenium RDL

4.2. Safety Endpoints

4.2.1. Exposure Duration and Summary of Dosing

Exposure duration will include durations between each treatment cycle and between first and last treatment cycles.

Dosing includes number of infusions and volumes infused in each visit.

4.2.2. Adverse Events

Adverse events are as defined in the protocol Section 9.1. Additional details on Serious Adverse Events (SAEs), classification of AEs according to expectation (unexpected, expected), Severity (Mild, Moderate, Severe,) and causality (Certain, Probable/Likely, Possible, Unlikely and Conditional/Unclassified) are defined in sections 9.1.1, 9.1.2, 9.1.3 and 9.1.4 respectively in the protocol.

Treatment Emergent Adverse Events (TEAEs) are all Adverse Events that started on or after the first administration of study drug.

4.2.3. Laboratory Test

Laboratory tests collected in the study and recorded in the eCRF are described in protocol Section 7.2.3 and indicated below.

- Hematology: RBC, Hemoglobin, Hematocrit, MCV, MCH, MCHC, RDW, WBC, Segmented, Typical Lymphocytes, Monocytes, Eosinophils, Basophils, Platelets, MPV.
- Chemistry: PT, INR, APTT, APTT Ratio, Glycated Hemoglobin, Amylase, Uric Acid, Total Bilirubin, Direct Bilirubin, Indirect Bilirubin, Triglycerides, Total Cholesterol, HDL, VLDL, LDL, Non-HDL, CKMB, CPK, Creatinine, Alkaline Phosphatase, Gamma GT, Potassium, Sodium, AST, ALT, Urea.
- Urinalysis as indicated on the eCRF.

- Other β-hCG urinary (women-only).
- Serology: HIV (1 + 2) (Anti-HIV-1.2), HTLV I and II, HBV (HbsAg and Anti-HBc), HCV (anti-HCV-Ab) and FTA-ABS (syphilis).

4.2.4. ECG

ECG data will be collected and recorded on the eCRF as indicated in the protocol Section 7.2.4 ECG data includes heart rate and whether the ECG was normal, abnormal (CS) or abnormal (NCS). Individual measurements of PR, RR, QRS, QT, etc. are not collected in this study.

4.2.5. Other

Vital Signs

Vital signs data recorded on the eCRF will include systolic and diastolic blood pressure, pulse and respiration rate, body temperature, and SpO2 measurements.

Physical Examination

Physical Examination assessments will be as indicated in Section 7.2.2.c of the protocol and summarized in a listing. A shift Table will summarize whether the measurement was normal, abnormal (CS) or abnormal (NCS) or not done.

4.3. Anti-Drug-Antibody

Not applicable

4.4. Pharmacokinetics Endpoints

Not applicable

4.5. Pharmacodynamics and Biomarker Endpoints

Not applicable

4.6. Pharmacogenomics Endpoints

Not applicable

4.7. Health Outcome Endpoints

Not applicable

4.8. Demographics and Disease Characteristics

Demographic and disease characteristics collected will include Age, Sex, Race, Dominant Hand, Education Level, Height, Weight, BMI, IMC Classification, Baseline primary and secondary efficacy variables as described in Sections 4.1.1 and 4.1.2

4.9. Prior and Concomitant Medication

Prior medications are those taken before V0 visit.

Concomitant medications are those taken starting V0 which is the day of initiation of treatment.

Prior and concomitant medications are collected on the Concomitant medications eCRF. For handling of missing or partial dates see Section 7.2.1

Prior and Concomitant medications will be grouped into categories such as Neuroleptics, Antidepressents, etc. and a Table generated for these.

4.10. Protocol Deviation and Treatment Compliance

Protocol deviation will be recorded by the clinical team. Any important deviations will be summarized in the clinical study report.

Study drug administration will be recorded on the eCRF with the start and stop time of the infusion, the volume infused, the Lot/Batch information and any comments if applicable.

5. Statistical Hypothesis

This study is a Phase II study to determine efficacy and safety of Cellavita HD. Hypothesis tests for efficacy will be conducted as described below. No hypothesis testing will be performed on any safety data.

All hypothesis tests will be at the two-sided 5% significance level (Two-sided Type I error of 0.05)

H_0：There is no difference in rate of change (slope) per year from Baseline through V11 in TMS between the two pooled active treatment groups and the placebo group

H_a：There is a difference in rate of change (slope) per year from Baseline through V11 in TMS between the two pooled active treatment groups and the placebo group

The following statistical tests will be performed:

1. Between the two active pooled treatment groups and placebo (primary)
   Participants receiving either 1 million or 2 million cells per kg (Treated) vs. Placebo

2. Between each of the two active treatment groups individually and placebo (to determine efficacy of each treatment group compared to placebo)
   Participants receiving 1 million cells per kg (Treated) vs. Placebo
   And Participants receiving 2 million cells per kg (Treated) vs. Placebo

3. Between the two active treatment groups to assess similarity between the two treatment groups.

Participants receiving 1 million vs. 2 million cells per kg.

The same tests performed for TMS will also be performed for other continuous endpoints.

6. Analysis Populations (Datasets)

According to the principles of intent to treat (ITT) analysis as defined in ICH E9, all participants who have been randomized will be considered as part of the ITT population... Participants will be tabulated based on treatment group to which they are randomized.

The Safety Population will include all participants who received at least one dose of study medication. Participants will be tabulated based on treatment group they actually received.

A Per Protocol (PP) population will be defined as all participants who received all 9 infusions. Participants will be tabulated based on treatment group they actually received.

7. Statistical Methods

7.1. General Statistical Consideration

All analysis (generation of Tables, Figures and Listings) will be performed using SAS 9.4 or newer.

All statistical Tables will summarize data by the following columns (or rows when summary Table is by treatment groups in rows) Low Dose, High Dose, Low & High Dose, Placebo, Total. If there are space limitations the Total column can be excluded. A footnote will clarify what Low and High Dose refer to.

All data collected on the eCRF will be included in the Listings. Some data will only be in Listings and no summary Tables or Figures will be created.

The eCRF collected participant initials and date of birth (The concatenation of these is variable SUBNUM in the dataset). For participant privacy this data will not be included in any Tables or Listings but will be retained in the analysis database. The Site ID and internal ID will be used to create a new unique Participant ID. In Listings this new Participant ID will be used as the unique identification of participants in this study.

Descriptive statistics for continuous data will include the mean, standard deviation, median, minimum, maximum, Q1, Q3.

Categorical data will be summarized by the frequency and percentages within each category. Unless otherwise specified the denominator for the %'s will be the number of participants randomized to the treatment group within the population summarized. Wherever applicable missing data will be summarized as a category.

All summary statistics will be displayed to 1 decimal place unless the data recorded is only at the decimal level in which case summary statistics will display data at one additional decimal place. Summary statistics such as minimum or maximum will be displayed as an integer or to the accuracy of data collected if it is only at the decimal level.

The p-value will be displayed up to 4 decimal places. If the p-value is less than 0.0001, it will be presented as' <.0001'; if the p-value is greater than 0.9999, it will be presented as ' >.9999'.

Baseline will be defined as the last non-missing measurement before a participant received first treatment of study drug (At baseline visit of V0).

All descriptive statistical summaries and statistical inferences will be performed based on nominal visits (visits at which data are collected).

Early termination visits will be allocated to the nearest scheduled visit where data was to be collected but is not recorded.

All analyses of changes, % changes, etc. will be by scheduled visits.

For analyses of abnormalities, data from both scheduled visits and unscheduled visits will be included.

7.2. Data Handling

7.2.1. Premature Withdrawal and Missing Data

The following imputation rules will be used for prior and concomitant medications.

Partial or missing start date for concomitant medication

1. Incomplete or partial start date will not be imputed if end date of concomitant medication is on or before treatment start date.
2. Incomplete or missing start date will be imputed as mentioned below if end date of concomitant medication falls after treatment start date (or if medication is ongoing at EoS for treated participants).

Handling of partial/missing dates for Medication

Partial/Missing Start Date

1. Missing day – Impute the 1st of the month unless month and year is same as month and year of first dose of study drug then impute first dose date.
2. Missing day and month – impute 1st January unless year is the same as first dose date then impute first dose date.

Partial/Missing End Date

1. Missing day – Impute the last day of the month unless month and year is same as month and year of last dose of study drug then impute last dose date.
2. Missing day and month – impute 31st December unless year is the same as last dose date then impute last dose date.

No other imputation of missing data for safety assessments will be made. Wherever possible missing data will be summarized as a category.

No imputation for missing data will be made as the mixed model repeated measures incorporates missing data.

Additional analyses may be conducted for FDA, EMA or other regulatory agencies if required and deemed appropriate under assumptions of MAR and MNAR using MI.

The eCRF did not allow entry of partial AE dates so no imputation of start or stop dates will be performed.

7.2.2. Derivation and Transformation on Data

Besides the calculation for some endpoints, which are based on data collected via eCRF, no derivation or transformation will be performed.

Age is auto calculated on the eCRF and the value will be used unless deemed inaccurate in which case Age will be computed as follows:

Age=（IC Signature Date-Date of Birth +1）/365.24, rounding to one decimal place

Duration of exposure will be defined as follows:

Exposure duration=Last dosing date - first dosing date +1

The CAP score refers to the term “-Age Product (CAP)”, which is an index calculated in relation to the age and length of the CAG repetition.

The CAP score formula is: CAP= 100 x Age x (CAG -L)/S

CAG is the number of repetitions on chromosome 4 (considering the allele with the highest number of these repetitions) (Section 2.6.7). L and S are constants (L=30 and S=627). “L” anchors the CAG length at the lower end of the distribution relevant to the pathology of HD. “S” is a normalization constant chosen so that the CAP score is approximately 100 at the participant's expected age of onset, as estimated by Langbehn et al. 2004. For the calculation in this study, the value of S will be 627, which is an estimate obtained by a reanalysis of data from Langbehn et al presented by Warner and Hayden 2012.

An additional derived variable of pre-treatment rate of change (slope) per year will be computed and summarized for select efficacy parameters such as TMS, TFC, etc.

For TMS this is computed as follows:

Pre-Treatment TMS rate of change (slope) per year = (Baseline TMS Score - 0 which is the best TMS score) / Duration since onset of symptoms in years.

Similarly for TFC the pre-treatment rate of change (slope) per year is as follows:

Pre-Treatment TFC rate of change (slope) per year = (Baseline TFC Score - 13 which is the best TFC score) / Duration since onset of symptoms in years.

Based on review of above pre-treatment slope additional analyses may be performed to see effect of pre-treatment slope on post-treatment slope by analyzing the post-treatment minus the pre-treatment slope.

7.3. Participants in Study

7.3.1. Subject Disposition and Analysis Populations (Datasets)

Subject disposition will be summarized by tabulating the number and % of subjects screened, randomized and treated in each of the above-mentioned analysis populations (if they are different).

The table will also summarize the number and % of subjects who completed the study through Visit 11, the number of participants who discontinued along with reasons for discontinuation.

An additional Table will summarize the number and % of participants completing each visit.

7.3.2. Protocol Deviation

Protocol deviations will only be included in the listings and no summary Table will be generated.

7.3.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics will summarize Age, Sex, Race, Dominant Hand, Education Level, Height, Weight, BMI, IMC Classification, CAP Score, Pre-Treatment TMS Slope, Pre-Treatment TFC Slope, Baseline primary and secondary efficacy assessments as described in Section 4.1.1 and 4.1.2.

7.3.4. Medical History and Concomitant Medication

Medical History, Prior and Concomitant Medications will be summarized.

7.4. Efficacy Analysis

Efficacy analysis will be based on the primary and secondary efficacy endpoints as described in Sections 4.1.1 and 4.1.2.

7.4.1. Analysis on Primary Efficacy Endpoint

The primary efficacy variable for this study is the rate of change (slope) per year from Baseline to Visit 11 in TMS.

The null hypothesis represents no difference between the two active treatment groups pooled together as compared to the placebo group:

H_0: $\mu_A = \mu_P$

H_A: $\mu_A \neq \mu_P$

Where μ_A is the mean rate of change (slope) per year from Baseline to Visit 11 in TMS for participants randomized to either of the two active doses and μ_P is the mean rate of change (slope) per year from Baseline to Visit 11in TMS for participants randomized to the placebo group.

Analysis will be performed on observed data using MMRM. The model will include the following effects: Treatment, Baseline TMS, Treatment * Day interaction. Due to the small sample size of the study and the study visits not conducted as per schedule of assessments due to COVID-19, the model may be changed or alternative models analyzed.

The unstructured covariance matrix for repeated observations within participants will be used. If the model does not converge, then a simpler covariance structure with less parameters will be used, according to the following order:

1. Toeplitz with heterogeneity (TOEPH)
2. ARH(1),
3. CSH,
4. Toeplitz (TOEP)
5. AR(1), and
6. CS.

The least square mean and standard error of the least square mean for each treatment group, and the 95% CI for the comparisons will be presented at each post-baseline visit.

In addition, actual observed values and rate of change (slope)s per year from Baseline to V3, V7 and V11 will be summarized using descriptive statistics for continuous data.

7.4.2. Analysis on Secondary Efficacy Endpoint

Continuous secondary efficacy endpoints will be analyzed as indicated above for the primary efficacy endpoint.

Categorical efficacy data will be analyzed using a Fisher's exact test.

Responder analysis may be performed using thresholds for responders using logistic regression. Covariates for logistic regression will include baseline value of the dependent variable

7.4.3. Subgroup Analysis of Efficacy Endpoints

Since this is a small Phase 2 study elect subgroup analyses may be done based on severity of disease as measured by TFC or other efficacy endpoints, CAG repeats (< 44 vs ≥ 44), Median CAP score, etc.

7.5. Safety Analysis

7.5.1. Treatment Compliance and Exposure

Exposure will be summarized by durations between each treatment and between first treatment and last treatment.

Dosing will be summarized by the number of syringes, duration of infusion and total volume at each visit.

7.5.2. Adverse Events

Analysis of Adverse Events will be performed based on the safety population. All Adverse events will be coded using MedDRA ver. 24.1 Sept 2021

Statistical summaries will be performed on general incidence rate of treatment emergent adverse event (TEAEs) including number of events and number of participants with the events. In summarizing the number of participants with adverse events, if a participant has more than one event within the SOC (or PT) they will only be counted once in that row.

The terms Treatment Emergent Adverse Events (TEAEs) and Adverse Events (AEs) are used interchangeably below and unless otherwise specified refer to TEAEs.

Adverse Events will be summarized in the following Tables:

- Overall one page summary of TEAEs.

- Summary of TEAE's by SOC & PT sorted by total number of participants with the TEAE within a SOC and within SOC by total number of participants within a PT. This sort order will also be used in other Tables by SOC and PT indicated below.

- Summary of Severe TEAE's by SOC & PT.

- Summary of TEAE's by SOC, PT and Maximum Severity within SOC or PT. The order for displaying severity will be: Mild, Moderate, Severe.

- Summary of TEAE's Related to Study Drug by SOC PT. For this Table any AE's classified as Certain, Probable/Likely, Possible will be included.

- Summary of TEAE's by SOC, PT and Maximum Relationship to Study Drug within SOC or PT. The order for displaying Relationship to Study Drug will be: Conditional/Unclassified, Unlikely, Possible, Probable/Likely, Certain,.

7.5.3. Laboratory Test Results

All Hematology and Chemistry laboratory data will be summarized by change and % change from Baseline to each post baseline scheduled visit. For Urinalysis change and % change will only be done for pH.

Analysis of hematology and chemistry abnormalities will include a summary of abnormalities between baseline and worst post baseline visits based on criteria indicated on eCRF (Abnormal CS, Abnormal NCS, Normal, Not Done).

In addition a shift Table will display changes in status from baseline to worst post-treatment value will be summarized. The order of determining worst will be abnormal clinically significant > abnormal not clinically significant>normal >not done.

A shift Table will summarize Serology Tests between Non-Reactive and Reactive.

7.5.4. 12 lead electrocardiogram

Analysis of ECG abnormalities will include a summary of abnormalities between baseline and at worst post baseline visits based on criteria indicated on eCRF (Abnormal CS, Abnormal NCS, Normal, Not Done).

In addition a shift Table will display changes in status from baseline to worst post-treatment value will be summarized. The order of determining worst will be abnormal clinically significant > abnormal not clinically significant>normal.

7.5.5. Vital Signs

Vital signs data will be summarized by change and % change from Baseline to each post baseline scheduled visit.

During visits when study drug was administered, Vital signs were performed Before drug administration, During drug administration and After drug administration and will be summarized as such.

Analysis of vital sign abnormalities will include a summary of CS and NCS abnormalities between baseline and worst post baseline visits visit.

7.5.6. Other Safety Results

A summary Table will include Physical Abnormalities at each visit.

7.6. Change from the Analysis Plan in Protocol

The analysis described in this SAP supersedes what was in the protocol as it was deemed more appropriate based on the data collected in the study and analysis methods for studies in Huntington's disease.

8. Reference

U. S. Food and Drug Administration. Center for Drug Evaluation and Research. (1996). ICH E3: Structure and Content of Clinical Study Reports.

U. S. Food and Drug Administration. Center for Drug Evaluation and Research. (1996). ICH E9: Statistical Principles for Clinical Trials.