STATISTICAL ANALYSIS PLAN

IND 27536

HBPD04

"A Randomized, Double-Blind, Single Center, Phase 2, Efficacy and Safety Study of allogeneic HB-adMSCs vs Placebo for the Treatment of Patients with Parkinson's Disease"

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Protocol Title	:	A Randomized, Double-Blind, Single Center, Phase 2, Efficacy and Safety Study of allogeneic HB-adMSCs vs Placebo for the Treatment of Patients with Parkinson's Disease
Short Title	:	Allogeneic HB-adMSCs vs Placebo for the treatment of Patients with Parkinson's disease
Study Number	:	HBPD04
Phase	:	2
Product	:	HB-adMSCs–Hope Biosciences adipose derived mesenchymal stem cells
Indication	:	Parkinson's disease
Sponsor name	:	Hope Biosciences Research Foundation
Effective date	:	24-Jun-2021

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1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the analyses to be included in the Clinical Study Report for Protocol HBPD04. Details of the planned final analysis provided.

Additional details with regards to data handling conversions and the specification of the data displays will be provided in the Programming Specifications (PS) document.

2. SUMMARY OF KEY PROTOCOL INFORMATION

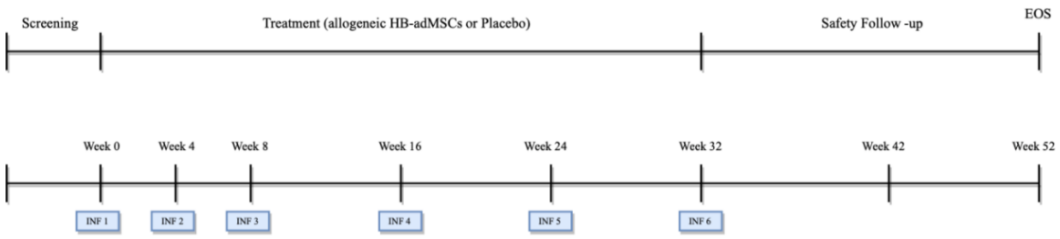
2.1. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objective	**Primary Endpoints**
• To investigate the safety and efficacy of intravenous infusions of allogeneic HB-adMSCs vs Placebo in patients with Parkinson's disease as determined by improvements in quality of life as measured by the MDS-UPDRS assessment. (Time frame: Baseline to Weeks 4, 8, 12, 16, 20, 24, 32 and 52).	• Changes in the total score MDS-UPDRS Part II (Motor Aspects of Experiences of Daily Living (M-EDL) from Baseline to Weeks 52. • Changes in MDS-UPDRS Part III Motor Examination from Baseline to Weeks 52. Incidence of treatment-emergent Adverse Event (TEAEs) and serious Adverse Events (SAEs). Incidence and risk of AEs of special interest (serious or nonserious), including thromboembolic events, peripheral events defined as, thromboembolism of the extremities, also infections and hypersensitivities. Clinically significant changes in laboratory values, vital signs, weight, and physical examination results.
Secondary Objective	**Secondary Endpoints**
• To evaluate the safety and efficacy of intravenous infusions of allogeneic HB-adMSCs vs Placebo in patients with Parkinson's disease as, determined by changes in disease assessments and dosage of medications. (Time frame: Baseline	The safety and efficacy endpoints of this study will be evaluated by identifying changes from Baseline to Weeks 4, 8, 12, 16, 20, 24, 32 and 52 in the following:

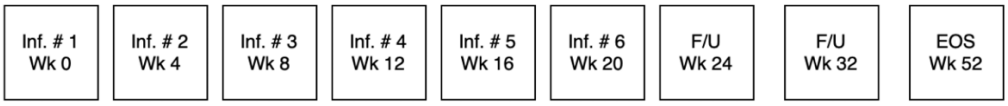
Objectives	Endpoints
to Weeks 4, 8, 12, 16, 20, 24, 32 and 52).	• Changes in MDS-UPDRS Part I. Non-Motor Aspects of Experiences of Daily Living (nM-EDL). • Changes in the total score MDS-UPDRS Part II (Motor Aspects of Experiences of Daily Living (M-EDL) and Part III (Motor Examination) • Changes in MDS-UPDRS Part IV. Motor Complications. • Changes in SF-36. • Changes in Parkinson's disease fatigue scale (PFS-16). Score of ≥8 indicates the presence of significant fatigue. • Changes in Parkinson's disease Questionnaire (PDQ-39), assessing how often patients experience difficulties across the 8 quality of life dimensions of functioning of wellbeing. • Changes in Visual Analog Scale for Pain and muscle spasms. • Changes in Dosage of medications taken to treat Parkinson's disease.

2.2. Study Design

Overview of Study Design and Key Features



Updated Study Design (Version 1.1)



Design Features	This study is a randomized, double-blind, single center, phase 2 study to assess efficacy and safety of multiple infusions of allogeneic HB-adMSCs vs. Placebo for the treatment of Parkinson's disease. The trial includes, • There is a screening period of up to 4 weeks • Based on an updated study design (monthly infusions), there is a 20-week treatment period while on randomized study treatment ▪ Infusion 1 (Week 0), Infusion 2 (Week 4), Infusion 3 (Week 8), Infusion 4 (Week 12), Infusion 5 (Week 16) and Infusion 6 (Week 20) • A safety Follow-up period after the last investigational product administration. ▪ Follow up 1 at week 24, Follow up 2 at week of 32 and end of study at Week 52 • 60 Subjects • 2 Treatment groups ▪ Group 1 → HB-adMSCs ▪ Group 2 → Placebo
Study Intervention	• Active Product: allogeneic HB- adMSCs (allogeneic Hope Biosciences adipose derived mesenchymal stem cells) ▪ Dose: 200 million ▪ Route: Intravenous

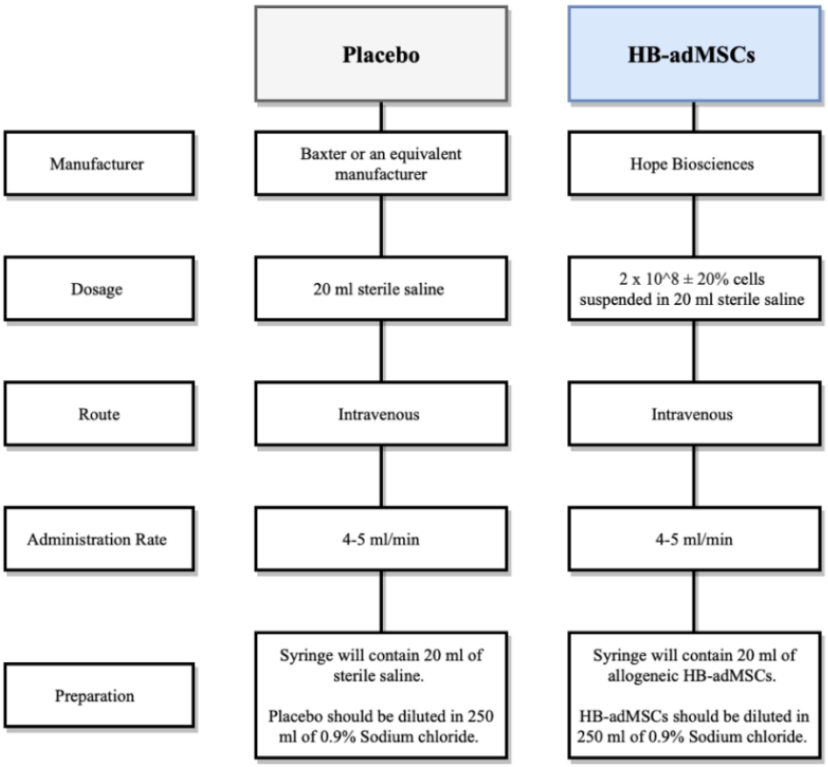
<table>
<tr><th colspan="2">Overview of Study Design and Key Features</th></tr>
<tr><td></td><td>

Regimen: Weeks 0, 4, 8, 12, 16 and 20.

Placebo: Saline Solution 0.9%

Dose: N/A
Route: Intravenous
Regimen: Weeks 0, 4, 8, 12, 16 and 20.

Duration of administration 1 hour
Study treatment details,



</td></tr>
<tr><td>Study Intervention Assignment</td><td>

Participants will be randomized 1:1 to receive HB-adMSCs active treatment or Placebo.

</td></tr>
<tr><td>Interim Analysis</td><td>Interim analysis of all safety and efficacy data may be performed at any time deemed appropriate by the Sponsor. Although, the subject's data may be analyzed at any time, a data analysis of all available data will be conducted when a least 20 subjects have completed all 6 infusions. Data may be analyzed for internal informational purposes, reports, presentations, and manuscripts.</td></tr>
</table>

3. STATISTICAL HYPOTHESES

The primary analysis will test whether HB-adMSCs is superior to Placebo according to the following statistical hypotheses:

Null hypothesis H0: The difference in change from baseline at Weeks 52 in MDS-UPDRS Part II and Part III between treatment groups (HB-adMSCs – Placebo) is equal to zero.

Alternative hypothesis H1: The difference in change from baseline at Weeks 52 in MDS-UPDRS Part II and Part III scores between treatment groups (HB-adMSCs – Placebo) is not equal to zero.

Secondary analysis will be tested for mean difference for change from Baseline to Week 52 for efficacy endpoints for both treatment groups,

Null hypothesis H0: $\Delta = 0$
Alternative hypothesis H1: $\Delta \neq 0$

Additionally, clinically significant differences are tested based on established (published) MCID,

Null hypothesis H0: $\Delta <$ MCID
Alternative Hypothesis H1: $\Delta \geq$ MCID (hypothesis for the effect of the treatment that improves (or reduces) the signs and symptoms of PD by an established MCID (e.g., for PDQ-39, established MCID value is 4.72 points).

3.1. Multiplicity Adjustment

The Bonferroni-Holm method for adjustment of multiplicity will be performed for all efficacy endpoints of interest.

3.2. Interim Analysis

An interim analysis of all efficacy endpoint data will be conducted when a least 20 subjects have completed 6 infusions (Week 20). Interim efficacy endpoint tables will include data till end of Week 20.

4. ANALYSIS SETS

Population	Definition / Criteria	Analyses Evaluated
Safety analysis set	• All randomised subjects who received at least one dose of HB-adMSCs infusion or placebo. • If participants receive a treatment different to their randomized treatment, they will be analysed according to the treatment actually received.	• Safety • Study Population
Efficacy analysis set	• All randomized participants who received all 6 infusions of HB-adMSCs or placebo. • Participants will be analysed according to their randomized treatment.	• Efficacy
Screened Population	• This population consists of all subjects who signed an ICF to participate in the clinical trial. • This population will be used for summarizing screening failures and reasons for screening failures.	• Study Population

5. STATISTICAL ANALYSES

5.1. General Considerations

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All participants have completed (or withdrawn from) the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release and database lock has been declared by Data Management.

5.1.1. General Methodology

Unless otherwise stated, all hypotheses will be tested at a 2-sided significance level of 0.05 and 95% confidence interval. All continuous measurements will be summarised descriptively at each visit by treatment using observed data.

Summary of continuous variables will be presented using N, Mean, 95% confidence interval of mean, Standard Error of mean (SE), Standard Deviation (SD), Median and Range (Minimum and Maximum). The categorical variables will be presented using number and percentage based on N.

For measurements over time mean values will be plotted to explore the trajectory over time. Observed data will be used as the basis for plotting data along with bars as +/- SE, not otherwise specified.

A parametric Repeated Measures Analysis (RMA) Model will be applied as a primary analysis to test the significance of the effects of the treatment including baseline as covariate.

Presentation of results from a statistical analysis model will include the estimated mean treatment effects (Least Square Means (LSMeans)). For all endpoints analysed statistically, estimated mean treatment differences will be presented together with two-sided 95% confidence intervals and p-values,

HB-adMSCs - Placebo

Pairwise t-test will be performed on the efficacy endpoints to test the difference between baseline and week 52 (EOS) as secondary analysis. Data for all the efficacy outcomes will be checked for normality (Shapiro-Wilk Test). When there is a larger deviation of data distribution from normality, non-parametric Wilcoxon signed rank test will be used.

Study population analyses including analyses of subject disposition, demographic and baseline characteristics, medical history, prior and concomitant medications.

Disposition summary includes, subject screened, randomized and disposition at end of study – Week 52 along with reasons for withdrawals. Subjects in different analysis populations also will be presented.

The screen failure table includes total number of screened subjects and reasons. The percentage in the screen failure table will be calculated based on total number of screened subjects as denominator.

5.1.2. Baseline Definitions

For all endpoints, the baseline value will be the latest pre-treatment assessment visit with a non-missing value. i.e., If an assessment has been made both at screening visit (Visit 1) and Week 0 infusion 1 visit (Visit 2, Week 0), the value from the Week 0 visit is used as the baseline value. If the value measured at the Week 0 visit is missing and

the assessment also has been made at screening, then the screening value is used as the baseline value.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.2. Primary Endpoint(s) Analyses

The primary objective of this study is to compare HB-adMSCs to Placebo on Total MDS-UPDRS Part II and III scores. Efficacy analysis set will be used for this analysis. The details of the planned displays are in programming specification document.

5.2.1. Definition of endpoint(s)

Objectives	**Endpoints**
Primary Objective	**Primary Endpoint**
To investigate the safety and efficacy of intravenous infusions of allogeneic HB-adMSCs vs Placebo in patients with Parkinson's disease as determined by improvements in quality of life as measured by the MDS-UPDRS assessment. (Time frame: Baseline to Weeks 4, 8, 12, 16, 20, 24, 32 and 52).	Changes in the total score MDS-UPDRS Part II (Motor Aspects of Experiences of Daily Living (M-EDL) and Part III from Baseline to Weeks 52. Changes in MDS-UPDRS Part III Motor Examination from Baseline to Weeks 52.

5.2.2. Main analytical approach

Endpoint/Variables
• Change from baseline at Weeks 52 in total score MDS-UPDRS Part II following treatment with HB-adMSCs or Placebo. • Change from baseline at Weeks 52 in MDS-UPDRS Part III Motor Examination.
Primary analysis
Repeated Measures Model Specification

• To compare the HB-adMSCs to Placebo on Change from baseline, a Repeated measures analysis (RMA) model will be fitted
• Terms fitted in the mixed effect model will include:
  • All primary endpoint efficacy measurements available at post-baseline at scheduled measurements will be response variable in a linear mixed model using an unstructured residual covariance matrix.
• The model will include:
  • Fixed factors: treatment and visit
  • Covariate: baseline
  • Stratification: disease severity, sex, age

- Furthermore, the model will include:
  - Interaction terms between treatment and visit
  - And Interaction terms between baseline and visit
  - Subject will be included as a random factor
- Due to updated study design (monthly infusions; see 2.2 Study Design): All subjects on the new protocol with updated study design (infusions at six timepoints: weeks 0, 4, 8, 12, 16, 20) will be included in model as primary analysis predicting outcome values as a function of the interaction of group and time, controlling for constituent main effects and stratification variables.
- As sensitivity analyses:
  - All subjects with available data at the timepoints Infusion 1 (Weeks 0), Infusion 2 (Week 4), Infusion 3 (Week 8), Infusion 4 (Week 12/16), Infusion 5 (Week 16/24) and Infusion 6 (Week 20/32) regardless of protocol (prior to or following the updated study design) will be included in models predicting outcome values as a function of the interaction of group and time, controlling for constituent main effects and stratification variables.

Model Checking and Diagnostics

For the Repeated Measures Analysis (RMA) Model assumptions will be checked, and appropriate adjustments may be applied based on the data.

Distribution assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residual and a plot of the residuals versus the fitted values (i.e., checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

Non-parametric analyses, Mann-Whitney U (or Wilcoxon Rank-Sum) Test will be conducted if the normality assumptions do not hold.

Secondary analysis

Summary analysis method

To compare difference between baseline and Week 52 for all the secondary endpoints, a paired comparison will be perfomed using paired t-test to check for statistical significance. Clinical significance will be determined using the established (published) MCID values for each of the efficacy outcomes. The available MCID values for each outcome measure are provided in the Table 1 which will be used as a threshold to evaluate/identify clinically relevant changes (improvements).

To further evaluate if the improvements are clinically relevant, effect size of the difference (improvement) between baseline to week 52 will also be calculated for all the secondary efficacy outcomes using cohen's d calculation. Cohen's d is a standardized measure of effect size (ES) that provides information on the amount of change in the outcome meaure relative to the variation within the measure. Cohen's d is calculated as the difference between the baseline mean score and post-baseline mean scores divided by the standard deviation of the scores. A positive value of ES represents improvement while a negative value indicates

worsening. An effect size of <0.2 will be considered trivial, ≥ 0.2 as small, ≥0.5 as medium and >0.8 as large [1].

Cohen's d $= \frac{M1-M2}{(sd1+sd2)/2}$, where M1 and M2 are the Mean scores a for HB-adMSCs and Placebo respectively, and SD1 and SD2 are the corresponding standard deviations.

Table 1 Established MCID values for the outcome measures.

Outcome measure	MCID
PDQ-39 SI	–4.72 [2]
PHQ-9	–1.7 [3]
PFS-16	N.E.
MDS-UPDRS I	–2.64 [2]
MDS-UPDRS II	–3.05 [2]
MDS-UPDRS III	–3.25 [4]
MDS-UPDRS IV	–0.9 [5]
VAS (Pain)	–1.9 [6]

N.E.: Not Established

MCID will be calculated as the difference between the mean scores before and after intervention i.e., post-baseline mean score – baseline mean score, to compare the result with the reference values established in the literature (provided in Table 1) e.g., Δ (PDQ-39 SI) EOS = Week 52 – Week 0 Baseline. Clinically important improvements for each efficacy outcome measure will be defined as change from baseline ≥ established (published) MCID.

Results presentation

Secondary endpoints will be summarized using n, mean, confidence interval of mean, SD, median, minimum and maximum. And p-value for paired comparison will be displayed for all post-baseline visits, along with ES and MCIDs.

Normality checking

Distribution assumptions used for the statistical analysis will be examined by obtaining a normal plot and Shapiro-Wilk Test.

Non-parametric analyses, Wilcoxon signed-rank test will be conducted if the normality assumption does not hold.

Bayesian Method

Lastly, strength of evidence for any differential changes between treatment and placebo groups will be assessed via residual change and generalized linear mixed models with Bayesian inference. Bayesian methods will assess the probability that an effect of HB-adMSCs exists (relative to placebo). Our analytical plan is shaped by the limitations of conventional (Frequentist) methods for addressing this question and the advantages of a Bayesian approach for assessing the probability that a given strategy might successfully be expanded into a larger-scale program for the treatment of Parkinson's disease. This data,

valuable in its own right, can justify the commitment of resources needed for such an expansion.

The Bayesian approach addresses these questions: (1) "Among patients with Parkinson's disease, what is the probability that allogeneic HB-adMSC confers benefit relative to placebo on status on primary endpoints?" (2) "What is the best estimate of these effects?" and (3) "What is their precision?" By estimating the probability that such effects exist, we are assessing the probability that the alternative hypothesis is true; a probability that is, by definition, not accessible to Frequentist methods. The FDA has discussed the use of Bayesian statistical methods to make decisions regarding the efficacy of new treatments as an alternative to Frequentist methods in developing clinical applications [7-12]. The current proposal will provide the optimal, unbiased estimates for the benefit conferred by allogeneic HB-adMSCs, while also estimating the probability that such effects exist. Posterior distributions can then be used as informative priors for continued monitoring in expansions of treatments and treatment strategies exhibiting initial promise.

Residual change models will predict the effect of treatment group on endpoint values at week 52 for each outcome, controlling for baseline and including stratification variables as covariates. Generalized linear mixed models will predict each outcome as a function of the interaction between the fixed factors treatment group and time, controlling for lower order effects of time and treatment group. Generalized linear mixed models will control for stratification variables, and subject will be included as random effect.

Bayesian model specification

Construct a linear model for each visit in order to model within-subject observation covariance structures by multivariate normal (MVN) distribution in the MCM procedure.

Initial values of the MCMC chains will be selected at random via the "init=random" argument of brm() in the brms package. Seed for random number generation will be specified as "seed = 12345" argument in brm().

Models will use weakly informative priors (described above) to maximize the influence of the present data on posterior probabilities (PP). Models were evaluated via posterior probability guidelines in the literature, suggesting that PP = 75% to 90% indicates "moderate evidence," PP = 91% to 96% indicates "strong evidence," and PP ≥ 97% indicates "very strong to "extreme evidence." Consistent with prior research, a PP ≥75% (equivalent to a Bayes factor = 0.33 or 3.00) that an effect exists will be taken as a minimum threshold of evidence in favor of the alternative hypothesis. This probability was chosen to emphasize the value in identifying a signal for the effects of treatment group, time, and their interaction.

Estimation will utilize three MCMC chains of 8000 total iterations each (with 4000 of these discarded as burn-in iterations). The median, standard deviation, and 95% credible intervals (CrI) of the posterior distribution will be used to provide a point estimate and corresponding range of uncertainty for the magnitude of each predictor effect, including treatment group.

Evaluation of posterior distributions will permit statements regarding the probability that effects of varying magnitudes exist, given the data. Specification of diffuse, neutral priors will reflect the initial uncertainty regarding effect sizes. For all generalized linear models,

priors for regression coefficients will be specified as ~Normal (μ=0, σ2=1 x 10), and priors for the levels one and two error variances will be specified as ~Half- Normal (μ=0, σ2=1 x 103). The choice of prior distribution for level two variances will follow Gelman's recommendations from the literature.

Model Checking and Diagnostics

Convergence diagnostics via scale reduction factors (Rhat), effective sample size, and posterior predictive distributions will be examined to ensure satisfaction of Bayesian modeiling assumptions, including Rhat < 1.01, sufficiently large effective sample size, and graphical inspection that the observed distribution of each outcome fell within the range of distributions produced by 1000 replications drawn from the posterior predictive distributions of the outcome.

Adequate values for the number of MCM samples/thinning/number of burn-in samples should be chosen to ensure that the ratio Monte Carlo Standard Errors (MCSE) and standard deviation of the posterior distribution for all the parameters in the model as small as possible, typically close to 0.01.

In addition, if possible, the number of tuning units and maximum number of tuning iterations may be increased to find a better proposal distribution for the model parameters, which in turn may reduce the MCSE/SD ratio.

The Geweke diagnostics test checks whether the mean estimates have converged by comparing means from the early and latter part of the Markov chain using a z score t-test. Large absolute values of the z-score statistic indicate rejection of the null hypothesis of no difference between the mean estimates obtained from the early and latter parts of the chain.

The convergence diagnostics for all parameters in the Bayesian analysis will be visually checked by the trace plots.

If the trace plots show apparent trend or the autocorrection plots show significant positive or negative correlation, number of iterations will be increased or reparameterization might be explored.

Results presentation

Presentation of results from the Bayesian statistical models will include the estimated conditional/marginal mean treatment effects and standard deviation. For all endpoints analysed statistically, estimated mean treatment differences will be presented together with 95% credible intervals and posterior probabilities.

Subgroup

No Subgroup analysis performed.

5.2.3. Additional analysis

Addtional analysis for the secondary endpoints will not be performed, unless it is specified.

Endpoint/Variables
• Subjects achieving an improvement (reduction) in outcome measure ≥ MCID (established/published) from baseline to week 52 in total score MDS-UPDRS Part II and Part III following treatment with HB-adMSCs or Placebo.
Statistical analysis method
Number of the treatment responders for each outcome measure will also be determined at week 52: Clinical responder being defined as a patient whose motor or non-motor outcome measure score improved from baseline to week 52 by equal to or beyond the established (published) MCID threshold, Table 1 for the given outcome. Proportion of subjects (N and Percentage) achieving an improvement (reduction) in outcome measure ≥ MCID (established/published) from baseline to week 52 will be provided.
Results presentation
Presentation of results include Number of Percentage of subjects in the tables.
Normality checking
Not applicable.
Subgroup
No Subgroup analysis performed.

5.3. Secondary Endpoint(s) Analyses

5.3.1. Efficacy Endpoints / Variables

- Change from baseline at Week 52 in total MDS-UPDRS Part I. Non-Motor Aspects of Experiences of Daily Living (nM-EDL).
- Change from baseline at Week 52 in the total score MDS-UPDRS Part II (Motor Aspects of Experiences of Daily Living (M-EDL) and total Part III (Motor Examination)
- Change from baseline at Week 52 in total MDS-UPDRS Part IV. Motor Complications.
- Change from baseline at Week 52 in SF-36 questionnaire domain scores.
- Change from baseline at Week 52 in Parkinson's disease fatigue scale (PFS-16).
- Changes in Parkinson's disease Questionnaire (PDQ-39) Summary Index (SI) score.

- Change from baseline at Week 52 in Visual Analog Scale for Pain and muscle spasms.

Primary analysis

Primary analysis of Repeated Measures Analysis (RMA) Model will be performed for above secondary efficacy endpoints above as given in the Section 5.2.2.

Secondary analysis

Secondary analysis of paired comparison will be perfomed using paired t-test to check for statistical significance will be performed for above secondary efficacy endpoints above as given in the Section 5.2.2.

Additional analysis

Endpoints:

- Subjects achieving an improvement (reduction) in outcome measure ≥ MCID (established/published) from baseline to week 52 in total MDS-UPDRS Part I. Non-Motor Aspects of Experiences of Daily Living (nM-EDL).
- Subjects achieving an improvement (reduction) in outcome measure ≥ MCID (established/published) from baseline to week 52 in total MDS-UPDRS Part III. Motor Examination.
- Subjects achieving an improvement (reduction) in outcome measure ≥ MCID (established/published) from baseline to week 52 in total MDS-UPDRS Part IV. Motor Complications.
- Subjects achieving an improvement (reduction) in outcome measure ≥ MCID (established/published) from baseline to week 52 in Parkinson's disease Questionnaire (PDQ-39) Summary Index (SI) score.

Additional analysis of Proportion of subjects (N and Percentage) achieving an improvement (reduction) in outcome measure ≥ MCID (established/published) from baseline to week 52 will be performed as given in the Section 0.

Other Secondary efficacy endpoints:

- Proportion of subjects requiring reinstatement of PD medication dose

Patients are defined as having reinstated with PD medication if, at any time during the study, their medication dose reinstated up to, or above, their baseline level after it has been reduced. Number of subjects reinstated PD dose will be summarised using count and percentage.

Reinstatement is not applicable for patients who did not reduce their dose during the study.

5.3.2. Safety Analyses

The safety analyses will be based on the Safety analysis set, unless otherwise specified.

5.3.2.1. Extent of Exposure

- Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Weeks = (Treatment stop date – Treatment start date)/7**

- Duration will be summarized by treatment group. Each subject will contribute duration of exposure to the treatment taken.

- Participants who were randomized but not report a treatment start date will be categorised as having zero days of exposure.

A listing and summary table of exposure will be created.

The details of the planned displays are in programming specification document.

5.3.2.2. Adverse Events

AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA).

A treatment emergent adverse event (TEAE) is defined as an event that has onset date on or after the first day of exposure to infusion treatment and on or before the first safety follow-up (week 24). Here the first day of exposure is defined as the first day of exposure to infusion treatment.

Treatment Emergent Adverse events (TEAEs) are summarised descriptively, whereas non-TEAEs are presented in listings. TEAE data will be displayed in terms of the number of subjects with at least one event (N), percentage of subjects with at least one event (%) and the number of events (E).

Summaries of TEAEs and of serious AEs will be presented as an overview including all AEs, serious AEs, AEs by severity, AEs by relation to treatment, action to AEs and treatment advised, and outcome of AEs.

Furthermore, summary tables based on system organ class and preferred terms are made for:

- All TAEs
- Serious AEs
- AEs leading to withdrawal of study

Incidence and risk of AEs of special interest (includes serious or nonserious), including thromboembolic events, peripheral events defined as, thromboembolism of the

extremities, also infections and hypersensitivities will be summarized based on system organ class and preferred terms.

Individual adverse events will be listed.

The details of the planned displays are in programming specification document.

5.3.2.3. Clinical Laboratory data

Laboratory evaluations including the analyses of Biochemistry laboratory tests (includes Comprehensive Metabolic Profile), Hematology laboratory tests (Complete Blood Count (CBC) and Coagulation Panel) and Urinalysis. The details of the planned displays are in programming specification document.

All laboratory parameters, including numerical urine analysis parameters will be summarised descriptively. Categorical urine analysis results will be summarized using count and percentage based on subjects.

Results of urine pregnancy test will be listed in individual subject data listings only.

Individual laboratory evaluations will be listed. In addition, a listing containing individual subject laboratory values outside the normal reference ranges will be provided.

Data recorded at unscheduled assessments will not be included in tables and figures but will be listed.

5.3.3. Additional Safety Assessments

The analyses of non-laboratory safety test results including physical examination and vital signs.

Physical Examination and Vital signs will be summarized using count and percentage based on subjects. The vital signs based on visit and change from baseline will be summarized using descriptive statistics.

Individual Vital signs, Physical Examination evaluations will be listed.

The details of the planned displays are in programming specification document.

5.4. Interim Analyses

An interim analysis of all efficacy endpoint data will be conducted when a least 20 randomized subjects have completed 6 infusions (Week 20). Interim efficacy endpoint tables will include data till end of Week 20.

5.4.1. Definition of endpoint(s)

Objectives	Endpoints
To investigate the efficacy of intravenous infusions of allogeneic HB-adMSCs vs Placebo in patients with Parkinson's disease as determined by improvements in quality of life as measured by the MDS UPDRS, SF-36, PFS-16, and PDQ-39 assessments (Time frame: Baseline to Weeks 4, 8, 12, 16, 20, 24, 32 and 52).	**Primary Endpoint** Changes in the total score MDS-UPDRS Part II (Motor Aspects of Experiences of Daily Living (M-EDL) and Part III (Motor Examination) from Baseline to Weeks 20.
	Secondary Endpoints • Change from baseline at Week 52 in total MDS-UPDRS Part I. Non-Motor Aspects of Experiences of Daily Living (nM-EDL). • Change from baseline at Week 52 in the total score MDS-UPDRS Part II (Motor Aspects of Experiences of Daily Living (M-EDL) and total Part III (Motor Examination) • Change from baseline at Week 20 in total MDS-UPDRS Part III. Motor Examination. • Change from baseline at Week 20 in total MDS-UPDRS Part IV. Motor Complications. • Change from baseline at Week 20 in SF-36 questionnaire domain scores. • Change from baseline at Week 20 in Parkinson's disease fatigue scale (PFS-16). • Changes in Parkinson's disease Questionnaire (PDQ-39) Summary Index (SI) score.

5.4.2. Main analytical approach

Endpoint/Variables

- Change from baseline at Weeks 20 in total score MDS-UPDRS Part II and Part III following treatment with HB-adMSCs or Placebo.

Primary analysis

Repeated Measures Model Specification

- To compare the HB-adMSCs to Placebo on Change from baseline, a Repeated measures analysis (RMA) model will be fitted
- Terms fitted in the mixed effect model will include:
  - All primary endpoint efficacy measurements available at post-baseline at scheduled measurements will be response variable in a linear mixed model using an unstructured residual covariance matrix.
- The model will include:
  - Fixed factors: treatment and visit
  - Covariate: baseline
  - Stratification: disease severity, sex, age
- Furthermore, the model will include:
  - Interaction terms between treatment and visit
  - And Interaction terms between baseline and visit
  - Subject will be included as a random factor
- Due to updated study design (monthly infusions; see 2.2 Study Design): All subjects on the new protocol with updated study design (infusions at six timepoints: weeks 0, 4, 8, 12, 16, 20) will be included in model as primary analysis predicting outcome values as a function of the interaction of group and time, controlling for constituent main effects and stratification variables.
- As sensitivity analyses:
  - All subjects with available data at the timepoints Infusion 1 (Weeks 0), Infusion 2 (Week 4), Infusion 3 (Week 8), Infusion 4 (Week 12/16), Infusion 5 (Week 16/24) and Infusion 6 (Week 20/32) regardless of protocol (prior to or following the updated study design) will be included in models predicting outcome values as a function of the interaction of group and time, controlling for constituent main effects and stratification variables.

Model Checking and Diagnostics

For the Repeated Measures Analysis (RMA) Model assumptions will be checked, and appropriate adjustments may be applied based on the data.

Distribution assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residual and a plot of the residuals versus the fitted values (i.e., checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

Non-parametric analyses, Mann-Whitney U (or Wilcoxon Rank-Sum) Test will be conducted if the normality assumptions do not hold.

Secondary analysis

Summary analysis method

To compare difference between baseline and Week 20 for all the secondary endpoints, a paired comparison will be perfomed using paired t-test to check for statistical significance. Clinical significance will be determined using the established (published) MCID values for each of the efficacy outcomes. The available MCID values for each outcome measure are provided in the Table 1 which will be used as a threshold to evaluate/identify clinically relevant changes (improvements).

To further evaluate if the improvements are clinically relevant, effect size of the difference (improvement) between baseline to week 20 will also be calculated for all the secondary efficacy outcomes using cohen's d calculation. Cohen's d is a standardized measure of effect size (ES) that provides information on the amount of change in the outcome meaure relative to the variation within the measure. Cohen's d is calculated as the difference between the baseline mean score and post-baseline mean scores divided by the standard deviation of the scores. A positive value of ES represents improvement while a negative value indicates worsening. An effect size of <0.2 will be considered trivial, ≥ 0.2 as small, ≥0.5 as medium and >0.8 as large [1].

Cohen's d $= \frac{M1-M2}{(sd1+sd2)/2}$, where M1 and M2 are the Mean scores at aHB-adMSCs and Placebo respectively, and SD1 and SD2 are the corresponding standard deviations.

Table 2 Established MCID values for the outcome measures.

Outcome measure	MCID
PDQ-39 SI	–4.72 [2]
PHQ-9	–1.7 [3]
PFS-16	N.E.
MDS-UPDRS I	–2.64 [2]
MDS-UPDRS II	–3.05 [2]
MDS-UPDRS III	–3.25 [4]
MDS-UPDRS IV	–0.9 [5]
VAS (Pain)	–1.9 [6]

N.E.: Not Established

MCID will be calculated as the difference between the mean scores before and after intervention i.e., post-baseline mean score – baseline mean score, to compare the result with the reference values established in the literature (provided in Table 1) e.g., Δ (PDQ-39 SI) EOS = Week 20 – Week 0 Baseline. Clinically important improvements for each efficacy outcome measure will be defined as change from baseline ≥ established (published) MCID.

Results presentation
Secondary endpoints will be summarized using n, mean, confidence interval of mean, SD, median, minimum and maximum. And p-value for paired comparison will be displayed for all post-baseline visits, along with ES and MCIDs.
Normality checking
Distribution assumptions used for the statistical analysis will be examined by obtaining a normal plot and Shapiro-Wilk Test. Non-parametric analyses, Wilcoxon signed-rank test will be conducted if the normality assumption does not hold.
Bayesian Method
Lastly, strength of evidence for any differential changes between treatment and placebo groups will be assessed via residual change and generalized linear mixed models with Bayesian inference. Bayesian methods will assess the probability that an effect of HB-adMSCs exists (relative to placebo). Our analytical plan is shaped by the limitations of conventional (Frequentist) methods for addressing this question and the advantages of a Bayesian approach for assessing the probability that a given strategy might successfully be expanded into a larger-scale program for the treatment of Parkinson's disease. This data, valuable in its own right, can justify the commitment of resources needed for such an expansion. The Bayesian approach addresses these questions: (1) "Among patients with Parkinson's disease, what is the probability that allogeneic HB-adMSCs confers benefit relative to placebo on status on primary endpoints?" (2) "What is the best estimate of these effects?" and (3) "What is their precision?" By estimating the probability that such effects exist, we are assessing the probability that the alternative hypothesis is true; a probability that is, by definition, not accessible to Frequentist methods. The FDA has discussed the use of Bayesian statistical methods to make decisions regarding the efficacy of new treatments as an alternative to Frequentist methods in developing clinical applications [7-12]. The current proposal will provide the optimal, unbiased estimates for the benefit conferred by allogeneic HB-adMSCs, while also estimating the probability that such effects exist. Posterior distributions can then be used as informative priors for continued monitoring in expansions of treatments and treatment strategies exhibiting initial promise. Residual change models will predict the effect of treatment group on endpoint values at week 20 for each outcome, controlling for baseline and including stratification variables as covariates. Generalized linear mixed models will predict each outcome as a function of the interaction between the fixed factors treatment group and time, controlling for lower order effects of time and treatment group. Generalized linear mixed models will control for stratification variables, and subject will be included as random effect.

Bayesian model specification

Construct a linear model for each visit in order to model within-subject observation covariance structures by multivariate normal (MVN) distribution in the MCM procedure.

Initial values of the MCMC chains will be selected at random via the "init=random" argument of brm() in the brms package. Seed for random number generation will be specified as "seed = 12345" argument in brm().

Models will use weakly informative priors (described above) to maximize the influence of the present data on posterior probabilities (PP). Models were evaluated via posterior probability guidelines in the literature, suggesting that PP = 75% to 90% indicates "moderate evidence," PP = 91% to 96% indicates "strong evidence," and PP ≥ 97% indicates "very strong to "extreme evidence." Consistent with prior research, a PP ≥75% (equivalent to a Bayes factor = 0.33 or 3.00) that an effect exists will be taken as a minimum threshold of evidence in favor of the alternative hypothesis. This probability was chosen to emphasize the value in identifying a signal for the effects of treatment group, time, and their interaction.

Estimation will utilize three MCMC chains of 8000 total iterations each (with 4000 of these discarded as burn-in iterations). The median, standard deviation, and 95% credible intervals (CrI) of the posterior distribution will be used to provide a point estimate and corresponding range of uncertainty for the magnitude of each predictor effect, including treatment group.

Evaluation of posterior distributions will permit statements regarding the probability that effects of varying magnitudes exist, given the data. Specification of diffuse, neutral priors will reflect the initial uncertainty regarding effect sizes. For all generalized linear models, priors for regression coefficients will be specified as ~Normal (μ=0, σ2=1 x 10), and priors for the levels one and two error variances will be specified as ~Half- Normal (μ=0, σ2=1 x 103). The choice of prior distribution for level two variances will follow Gelman's recommendations from the literature.

Model Checking and Diagnostics

Convergence diagnostics via scale reduction factors (Rhat), effective sample size, and posterior predictive distributions will be examined to ensure satisfaction of Bayesian modeiling assumptions, including Rhat < 1.01, sufficiently large effective sample size, and graphical inspection that the observed distribution of each outcome fell within the range of distributions produced by 1000 replications drawn from the posterior predictive distributions of the outcome.

Adequate values for the number of MCM samples/thinning/number of burn-in samples should be chosen to ensure that the ratio Monte Carlo Standard Errors (MCSE) and standard deviation of the posterior distribution for all the parameters in the model as small as possible, typically close to 0.01.

In addition, if possible, the number of tuning units and maximum number of tuning iterations may be increased to find a better proposal distribution for the model parameters, which in turn may reduce the MCSE/SD ratio.

The Geweke diagnostics test checks whether the mean estimates have converged by comparing means from the early and latter part of the Markov chain using a z score t-test. Large absolute values of the z-score statistic indicate rejection of the null hypothesis of no difference between the mean estimates obtained from the early and latter parts of the chain. The convergence diagnostics for all parameters in the Bayesian analysis will be visually checked by the trace plots. If the trace plots show apparent trend or the autocorrection plots show significant positive or negative correlation, number of iterations will be increased or reparameterization might be explored.
Results presentation
Presentation of results from the Bayesian statistical models will include the estimated conditional/marginal mean treatment effects and standard deviation. For all endpoints analysed statistically, estimated mean treatment differences will be presented together with 95% credible intervals and posterior probabilities.
Subgroup
No Subgroup analysis performed.

5.5. Changes to Protocol Defined Analyses

Analysis is planned as per protocol. No deviation from the planned protocol specified analysis.

6. SAMPLE SIZE DETERMINATION

Sample size consists of up to 60 subjects who have been diagnosed with Parkinson's disease.

The sample size of N=60 (30 per group) was determined based on a prospective power analysis using an effect size of 0.34 (mean difference of 5.4 points) for MDS-UPDRS Part III, observed from our previous expanded access clinical study, "An intermediate-size patient population expanded access protocol to evaluate the safety of autologous HB-adMSCs for the treatment of patients with Parkinson's Disease", which included N=10 subjects and demonstrated a moderate treatment effect based on clinical relevance. The sample size was selected based on feasibility constraints, with the understanding that it provides adequate power to detect a minimal clinically important difference of 3.25 points [4] in MDS-UPDRS Part III between groups, assuming moderate effect sizes. This sample size is appropriate for this early phase trial, which aims to detect clinically meaningful treatment effects and provide preliminary data on the efficacy and safety of the treatment.

SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the "Safety" population. Screen failures will be summarized or listed based on the "Screened"

population. A summary of the number of participants in each of the participant level analysis set will be provided.

6.1.1. Subject Disposition

A summary of the number and percentage of subjects who completed the study as well as those who withdrawn from the study will be provided by treatment. Reason of study withdrawn will be summarized by treatment.

A summary of the study intervention status will be provided. This display will show the number and percentage of subjects who have completed the Week 52, as well as primary reasons for withdrawn.

The study analysis set will be summarised in the subject disposition table.

The details of the planned displays are in programming specification document.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics including, age, sex, ethnicity, race, height at baseline, weight at baseline, BMI at baseline will be summarized with descriptive statistics. In addition, the following categories will be summarized: 18-64, 65-84 and >=85 based on the randomised analysis set.

Listings of demographic characteristics will also be produced.

The details of the planned displays are in programming specification document.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized.

Protocol deviations will be tracked by the study team throughout the conduct of the study.

The details of the planned displays are in programming specification document.

6.1.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using WHO Drug Dictionary. Concomitant medications will be summarized as number and percentage of subjects.

For classifying study phase for concomitant medications, use the following definition.

Study Phase	Definition
Prior	If medication end date is not missing and is before date of first dose of study medication.
Concomitant	Any medication that is not a prior

Please refer to Section 6.2.6 for handling of missing and partial dates for concomitant medication.

The details of the planned displays are in programming specification document.

6.1.5. Study Intervention Exposure and Compliance

A summary of Overall cumulative exposure to HB-adMSCs will be produced.

The details of the planned displays are in programming specification document.

6.2. Appendix 2 Data Derivation Rule

6.2.1. Criteria for Potential Clinical Importance

The potential clinical importance criteria are not defined this trial. A laboratory value that is outside the reference range is considered either high abnormal or low abnormal will be displayed based on lab normal range data.

6.2.2. Study Period

Adverse events will be classified according to the time of occurrence relative to the study intervention period.

Treatment emergent	Definition
Y	If event start date is not missing and is before date of first dose of study medication.
N	Any event started on or after date of first dose of study medication or event date is missing or partial

6.2.3. Study Day and Reference Dates

Study Day

• Study Day 1 is defined as the day the first dose was taken.
• Study day >1 is calculated as the number of days from the date of the Study Day 1:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Date of Study Day 1 → Study Day = Ref Date – Date of Study Day 1
  • Ref Data ≥ Date of Study Day 1 → Study Day = Ref Date – (Date of Study Day 1) + 1

6.2.4. Assessment Window

For data summaries by visit, scheduled visits with nominal visit description will be displayed. Unscheduled visits will not be displayed or slotted into a visit window. While

in the baseline derivation or post-baseline worst scenarios are derived, unscheduled visits are considered. All unscheduled visits will be displayed in listings, as appropriate.

6.2.5. Multiple measurements at One Analysis Time Point

For lab tests on a study day, if more than one assessment is taken on the same day, the test from the latest non-missing lab measurements will be used for the analysis. All lab measurements will be displayed in the listings, as appropriate.

6.2.6. Handling of Missing and Partial Dates

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>• Partial dates will be displayed as captured in participant listing displays.</td></tr>
<tr><td>Adverse Events</td><td>• Partial dates for AE recorded in the CRF will be imputed using the following conventions:
<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e, subject did not start the study medication), then set start date = 1st of month.

Else if study intervention start date is not missing:

• If month and year of start date = month and year of study intervention start date, then
o If stop date contains a full date and stop date is earlier than study intervention start date, then set start = 1st of month.
o Else set start date = study intervention start date.

• Else set start date = 1st of month</td></tr>
</table></td></tr>
</table>

Element	Reporting Detail		
		Missing start day and month	If study intervention start date is missing (ie., subject did not start study medication), then set start date = January 1. • Else if study intervention start date is not missing: o If year of start date = year of study intervention start date, then ▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1. o Else set start date = study intervention start date. Else set start date = January 1.
		Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year)
		Missing end day and month	No imputation
		Completely missing start/end date	No imputation

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>Concomitant Medications</td><td>
Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e, subject did not start the study medication), then set start date = 1st of month.

Else if study intervention start date is not missing:

• If month and year of start date = month and year of study intervention start date, then
o If stop date contains a full date and stop date is earlier than study intervention start date, then set start = 1st of month.
o Else set start date = study intervention start date.

• Else set start date = 1st of month</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (ie., subject did not start study medication), then set start date = January 1.

• Else if study intervention start date is not missing:
o If year of start date = year of study intervention start date, then
▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
o Else set start date = study intervention start date.
Else set start date = January 1.</td></tr>
</table>
</td></tr>
</table>

Element	Reporting Detail		
		Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year)
		Missing end day and month	A '31' will be used for the day and 'Dec' will be ised for the month
		Completely missing start/end date	No imputation

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7. REVISIONS TO STATISTICAL ANALYSIS PLAN (VERSION HISTORY)

SAP version	Purpose	Comments
1.0	Interim analysis	Version used for Interim Analysis
2.0	Final analysis with updated as new protocol subjects in main analysis and all subjects including old and new protocol infusion data for sensitivity analysis	Version used for Final analysis

Certificate Of Completion

Envelope Id: A84E6B35-E006-499C-95E5-256674F00BFA
Status: Completed
Subject: Complete with Docusign: HBPD04-Statistical-Analysis-Plan-v2_0.pdf
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Initials: 0
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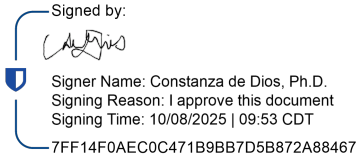
Constanza de Dios, Ph.D. Constanza.Inez.C.deDios@uth.tmc.edu Security Level: Email, Account Authentication (Required), Login with SSO	 Signed by: Signer Name: Constanza de Dios, Ph.D. Signing Reason: I approve this document Signing Time: 10/08/2025 | 09:53 CDT 7FF14F0AEC0C471B9BB7D5B872A88467 Signature Adoption: Drawn on Device Signature ID: 7FF14F0A-EC0C-471B-9BB7-D5B872A88467 Using IP Address: 73.166.88.185 With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document	Sent: 8/10/2025 | 09:33 Viewed: 8/10/2025 | 09:53 Signed: 8/10/2025 | 09:53
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Signer Events	Signature	Timestamp
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Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
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Certified Delivered	Security Checked	22/10/2025 I 09:26
Signing Complete	Security Checked	22/10/2025 I 09:27
Completed	Security Checked	22/10/2025 I 09:27

Payment Events	Status	Timestamps

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