| | | |
|---|---|---|
| **Department** | : | Data management and Biostatistics |
| **Information Type** | : | Statistical Analysis Plan (SAP) |

| | | |
|---|---|---|
| **Title** | : | A randomized, double-blinded, single-center, phase 2 efficacy, and safety study of allogeneic HB-adMSCs for the treatment of patients with Chronic Post-COVID-19 Syndrome |
| **Product** | : | HB-adMSCs – Hope Biosciences adipose-derived mesenchymal stem cells (Allogeneic) or Placebo - Sterile Saline Solution 0.9% |
| **Effective date** | : | 05-May-2022 |

**Description:**

- The purpose of this SAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol HBPCOVID02.
- This SAP is intended to describe the planned safety, efficacy and tolerability analyses required for the study.
- This SAP is to convey the content of the complete statistical analysis deliverables.

# 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 HBPCOVID02.

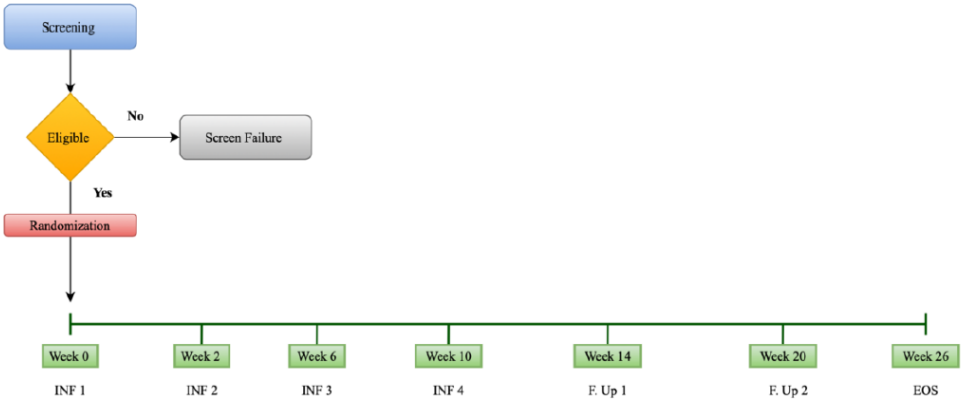
# 2. SUMMARY OF KEY PROTOCOL INFORMATION

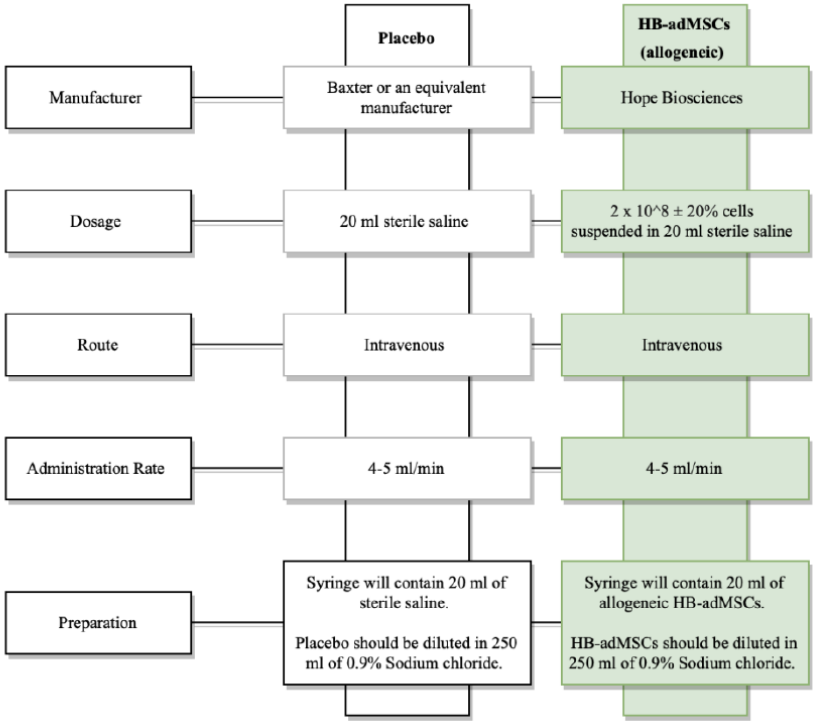
## 2.1. Study Objective(s) and Endpoint(s)

| Objectives | Endpoints |
|---|---|
| **Primary Objective** | **Primary Endpoint** |
| • To investigate the efficacy of intravenous infusions of HB-adMSCs (allogeneic) vs. Placebo in patients with Chronic Post-COVID-19 Syndrome as determined by improvements in individual symptom scores of Visual Analog Scale of Neurological Symptoms. (Time frame: Baseline to Week 26).<br><br>• To assess the safety of intravenous infusions of HB-adMSCs (allogeneic) vs. Placebo in patients with Chronic Post-COVID-19 Syndrome as determined by the incidence of adverse events or serious adverse events (Time frame: Baseline to Week 26). | The efficacy and safety primary endpoints of this study will be evaluated by assessing changes from Baseline to Weeks 26 in the following:<br>• Changes in the Visual Analog Scale of Neurological Symptoms.<br>VAS are psychometric measuring tools intended to document the characteristics of disease-related symptom severity in individuals. The neurological symptoms included in this scale are (1) extreme fatigue (2) 3 brain fog, (3) headache (4) sleep disturbances (5) loss of taste/smell.<br>• Incidence of treatment-emergent Adverse Events (TEAEs) and serious Adverse Events (SAEs).<br>• Incidence of AEs of special interest (serious or nonserious), including thromboembolic events, infections, and hypersensitivities<br>• Changes in laboratory values, vital signs, weight, physical exam results, and medications used to treat Chronic Post-COVID-19 Syndrome. |
| **Secondary Objective** | **Secondary Endpoint** |
| • To investigate the efficacy of intravenous infusions of HB-adMSCs (allogeneic) vs. Placebo in patients with Chronic Post-COVID-Syndrome as determined by | The efficacy and safety secondary endpoints of this study will be evaluated by assessing changes from Baseline to Weeks 26 in the following: |

| Objectives | Endpoints |
|---|---|
| improvements in individual symptom scores of Visual Analog Scale of Non-Neurological Symptoms. (Time frame: Baseline to Week 26).<br>• To evaluate the efficacy of intravenous infusions of HB-adMSCs (allogeneic) vs. Placebo in patients with Chronic Post-COVID-Syndrome as determined by changes in Fatigue Scale (Time frame: Baseline to Week 26).<br>• To assess the efficacy of intravenous infusions of HB-adMSCs (allogeneic) vs. Placebo in patients with Chronic Post-COVID-19 Syndrome as determined by changes in SF-36 Quality of life self-assessment. (Time frame: Baseline to Week 26).<br>• To identify the safety of intravenous infusions of HB-adMSCs vs. Placebo in patients with Chronic Post-COVID-19 Syndrome as determined by changes in Patient Health Questionnaire (PHQ-9). | • Changes in Subject's energy and stamina as evidenced on the Fatigue Assessment form.<br>• Changes in Visual Analog Scale of non -Neurological Symptoms. The symptoms included in this scale are (1) dyspnea a rest and with activity, (2) cough, (3) body aches, and (4) joint pain.<br>• Changes in Subject's quality of life as evidenced by the Short Form 36 Health Survey Questionnaire.<br>• Changes in Subject's level of depression as evidenced by the PHQ 9 scale. |

## 2.2. Study Design

| **Overview of Study Design and Key Features** | |
|---|---|
|  | |
| **Design Features** | This study is a randomized, double-blind, single-center, phase 2 clinical trial to assess the efficacy and safety of multiple HB-adMSCs (allogeneic) vs. Placebo for treating Chronic Post- COVID-19 Syndrome. The trial includes,<br>• A screening period of up to 4 weeks<br>• A 10-week treatment period while on randomized study treatment<br>▪ Infusion 1 (Week 0), Infusion 2 (Week 2), Infusion 3 (Week 6) and Infusion 4 (Week 10)<br>• A safety Follow-up period after the last investigational product administration.<br>▪ Follow up 1 at week 14, Follow up 2 at week of 20 and end of study (EOS) at Week 26<br>• 80 Subjects<br>• 2 Treatment groups<br>▪ Group 1 → HB-adMSCs<br>▪ Group 2 → Placebo |
| **Study Intervention** | • Active Product: allogeneic HB-adMSCs (allogeneic Hope Biosciences adipose derived mesenchymal stem cells)<br>▪ Dose: 2x10^8 ± 20% cells suspended in 20ml sterile saline<br>▪ Route: Intravenous<br>▪ Regimen: Weeks 0, 2, 6, and 10. |

| **Overview of Study Design and Key Features** | |
|---|---|
| | • Placebo: 20ml sterile saline<br>▪ Dose: N/A<br>▪ Route: Intravenous<br>▪ Regimen: Weeks 0, 2, 6, and 10.<br>• Duration of administration: 1 hour<br>• Study treatment details,<br>  <br> |
| **Study Intervention Assignment** | • Participants will be randomised 1:1 to receive HB-adMSCs active treatment or Placebo. |
| **Interim Analysis** | No interim analysis planned |

# 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 to Weeks 26 in Visual Analog Scale of Neurological Symptoms score between treatment groups (HB-adMSCs – Placebo) is equal to zero.

**Alternative hypothesis H1**: The difference in change from baseline to Weeks 26 in Visual Analog Scale of Neurological Symptoms score 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 26 for efficacy endpoints for both treatment groups,

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

### 3.1. Multiplicity Adjustment

The Bonferroni-Holm method for adjustment of multiplicity adjustment is performed for all secondary efficacy endpoint of interest.

Bonferroni-Holm method starts with ordering the p-values in increasing order and starts with testing the hypothesis with the lowest p-value on the 2.5/k% level (one-sided), where k is the number of hypotheses in the procedure. If significant, the testing proceeds to comparing the next lowest p-value with 2.5/(k-1) %.

### 3.2. Interim Analysis

No interim analysis planned.

## 4. ANALYSIS SETS

| Population | Definition / Criteria | Analyses Evaluated |
|---|---|---|
| Safety analysis set | • All randomized subjects who received at least one dose of HB-adMSCs infusion or placebo.<br>• If participants receive a treatment different to their randomized treatment, they will be analysed according to the treatment actually received. | • Safety<br>• Study Population |
| Efficacy analysis set | • All randomized participants who received all 4 infusions of HB-adMSCs or placebo.<br>• 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.<br>• 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.

As a primary analysis, a standard Analysis of Covariance (ANCOVA) will be applied for primary and secondary endpoint to test the significance of the effects of the treatment at Week 26. The model includes treatment as fixed factor and the corresponding baseline value as a covariate.

A parametric Repeated Measures Analysis (RMA) Model will be applied as a secondary analysis to test the significance of the effects of the treatment at Week 2, Week 6, Week 10, Week 14, Week 20 and Week 26 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 26 (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, appropriate non-parametric 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 26 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 change in Visual Analog Scale of Neurological Symptoms 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 efficacy of intravenous infusions of HB-adMSCs (allogeneic) vs. Placebo in patients with Chronic Post-COVID-19 Syndrome as determined by improvements in individual symptom scores of Visual Analog Scale of Neurological Symptoms. (Time frame: Baseline to Week 26). | Changes in the Visual Analog Scale of Neurological Symptoms. VAS are psychometric measuring tools intended to document the characteristics of disease-related symptom severity in individuals. The neurological symptoms included in this scale are (1) extreme fatigue (2) brain fog, (3) headache (4) sleep disturbances (5) loss of taste/smell. |

### 5.2.2. Main analytical approach

| **Endpoint/Variables** |
|---|
| • Change from baseline in Visual Analog Scale of Neurological Symptoms score following treatment with HB-adMSCs or Placebo at Week 26. |
| **Primary analysis** |
| **ANCOVA Model Specification** |
| • To compare the HB-adMSCs to Placebo on Change from baseline to Week 26, a standard Analysis of Covariance (ANCOVA) model will be fitted<br>• Terms fitted in the mixed effect model will include: |

- Primary endpoint efficacy measurements available at - Week 26 will be response variable in a linear mixed model using a variance-covariance residual matrix.
- The model will include:
  - Fixed factors: treatment
  - Covariate: baseline
  - Stratification: pre-existing condition prior to COVID-19 (Y/N), average VAS score of Neurological Symptoms (<5cm/>=5cm) and age group (<43/>=43)

**Model Checking and Diagnostics**

For the ANCOVA 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 does not hold.

**Results presentation**

Presentation of results from a statistical analysis model will include the estimated mean treatment effects (Least Square Means (LSMeans)) and estimated mean treatment differences will be presented together with two-sided 95% confidence intervals standard error for mean difference and p-value.

**Endpoint/Variables**

Change from baseline in Visual Analog Scale of Neurological Symptoms score following treatment with HB-adMSCs or Placebo at Week 2, Week 6, Week 10, Week 14, Week 20 and Week 26.

**Secondary 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: pre-existing condition to COVID-19 (Y/N), average VAS score of Neurological Symptoms (<5cm/>=5cm), and age group (<43/>=43)
- 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

**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 does not hold.

**Results presentation**

Presentation of results from a statistical analysis model will include the estimated mean treatment effects (Least Square Means (LSMeans)) and estimated mean treatment differences will be presented together with two-sided 95% confidence intervals standard error for mean difference and p-value.

**Additional analysis**

**Summary analysis method**

To compare difference between baseline to Week 2, Week 6, Week 10, Week 14, Week 20 and Week 26, a paired t-test will be used for primary endpoint change from baseline VAS to check the statistical significance. Clinical significance will be determined using the established (published) MCID value for the VAS change from baseline. The available MCID value for Change from baseline VAS measure is provided in the Table 1 which will be used as a threshold to evaluate/identify clinically relevant changes.

To further evaluate if the improvements are clinically relevant, effect size of the treatment difference at Week 2, Week 6, Week 10, Week 14, Week 20 and Week 26 will also be calculated for the efficacy endpoint VAS score 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 HB-adMSCs mean score and Placebo mean scores divided by the standard deviations of the scores. An absolute 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 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 |
|---|---|
| VAS (Pain) | −1.9 [2] |

MCID will be calculated as the mean change from baseline, to compare the result with the reference values established in the literature (provided in Table 1) for ΔVAS Score. Clinically important improvements for VAS score will be defined as mean 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.

**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.

## 5.3. Secondary Endpoint(s) Analyses

### 5.3.1. Efficacy Endpoints / Variables

- Changes in Subject's energy and stamina as evidenced on the Fatigue Assessment form.
- Changes in Visual Analog Scale of non -Neurological Symptoms. The symptoms included in this scale are (1) dyspnea a rest and with activity, (2) cough, (3) body aches, and (4) joint pain.
- Changes in Subject's quality of life as evidenced by the Short Form 36 Health Survey Questionnaire.
- Changes in Subject's level of depression as evidenced by the PHQ 9 scale.

**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 ANCOVA model will be perfomed to test the significance of treatment difference for secondary efficacy endpoints above as given in the Section 5.2.2.

**Additional analysis**

Additional 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.

### 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 last day of infusion treatment. Here the first day of exposure is defined as the first day of exposure to infusion treatment.

Treatment Adverse events (TAES) are summarised descriptively, whereas non-TEAEs are presented in listings. TAE 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 TAEs 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, 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 CBC- complete blood count, CMP- comprehensive metabolic panel and Coagulation Panel. 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. Changes to Protocol Defined Analyses

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

# 6. SAMPLE SIZE DETERMINATION

The sample size consists of 80 subjects who have been diagnosed with Chronic Post-COVID-19 - Syndrome.

# 7. SUPPORTING DOCUMENTATION

## 7.1. 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.

### 7.1.1. 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 26, 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.

### 7.1.2. 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.

### 7.1.3. 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.

## 7.2. Appendix 2 Data Derivation Rule

### 7.2.1. 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.

### 7.2.2. 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 |

### 7.2.3. Study Day and Reference Dates

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

### 7.2.4. 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.

### 7.2.5. 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.

### 7.2.6. 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.<br><br>Else if study intervention start date is not missing:<br><br>• If month and year of start date = month and year of study intervention start date, then<br>o If stop date contains a full date and stop date is earlier than study intervention start date, then set start = 1st of month.<br>o Else set start date = study intervention start date.<br><br>• 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.<br><br>• Else if study intervention start date is not missing:<br>o If year of start date = year of study intervention start date, then<br>▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.<br>o Else set start date = study intervention start date.<br>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>
<ul>
<li>Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:</li>
</ul>
<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.<br><br>Else if study intervention start date is not missing:<br><br>• If month and year of start date = month and year of study intervention start date, then<br>o If stop date contains a full date and stop date is earlier than study intervention start date, then set start = 1st of month.<br>o Else set start date = study intervention start date.<br><br>• 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.<br><br>• Else if study intervention start date is not missing:<br>o If year of start date = year of study intervention start date, then<br>▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.<br>o Else set start date = study intervention start date.<br>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 |

# 8. REFERENCES

[1]Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed ed. Hillsdale, N.J.: L. Erlbaum Associates Hillsdale, N.J.; 1988.

[2]Randall DJ, Zhang Y, Li H, Hubbard JC, Kazmers NH. Establishing the Minimal Clinically Important Difference and Substantial Clinical Benefit for the Pain Visual Analog Scale in a Postoperative Hand Surgery Population. J Hand Surg Am. 2022;47(7):645-53.