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DEPARTMENT	:	Biostatistics and programming
Information Type	:	Statistical Analysis Plan (SAP)

Title	:	A Randomized, Double-Blind, Placebo-Controlled, Clinical Trial to Assess Efficacy and Safety of Allogeneic HB-adMSCs to Provide Immune Support Against COVID-19
Product	:	Allogeneic HB-adMSCs Hope Biosciences Adipose Derived Mesenchymal Stem Cells
Effective Date	:	25-JAN-2021

Description:

- The purpose of this SAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol HBCOVID02.
- 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.

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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 HBCOVID02:

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 HB-adMSCs in providing immune support against development of Coronavirus Disease by incidence of hospitalization for COVID-19, incidence of symptoms associated with COVID-19 (ie., fever, shortness of breath/difficulty breathing, and/or cough), and severity of COVID-19 associated symptoms (fever 38C or higher, cough, shortness of breath/difficulty breathing).	• Incidence of hospitalization for COVID-19. • Incidence of symptoms associated with COVID-19
Secondary Objectives	**Secondary Endpoints**
• To investigate the efficacy of HB-adMSCs in the prevention of upper and lower respiratory infections in a high-risk population.	• Absence of upper/lower respiratory infections (with hospitalization criteria) up to 3 months post infusions. • Change from baseline in leukocyte differential • Change from baseline in C-Reactive Protein • Change from baseline in TNF-alpha • Change from baseline in IL-6 • Change from baseline in IL-10 • Clinically significant changes in laboratory values, vital signs, weight and physical examination results. • Incidence of AEs (AEs) and serious AEs (SAEs) related to the drug

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2.2. Study Design

Overview of Study Design and Key Features	
Randomized, double-blind, placebo-controlled, parallel group study	
Design Features	• Randomized, double-blind, Placebo controlled, parallel group study. • 53 Subjects • 4 Treatment groups ▪ Group 1 → 2 x108 cells (allogeneic HB-adMSCs 200MM) ▪ Group 2 → 1 x108 cells (allogeneic HB-adMSCs 100MM) ▪ Group 3 → 5 x107 cells (allogeneic HB-adMSCs 50MM) ▪ Group 4 → Placebo • Duration of treatment: up to 26 weeks, and overall study includes screening (up to 45 Days prior to randomisation), and 5 treatment visits after randomisation includes Infusion 1 (Week 0), Infusion 2 (Week 2), Infusion 3 (Week 6), Infusion 4 (Week 10) and Infusion 5 (Week 14). And follow up weeks of 18, 22 and end of study at Week 26.
Dosing	• Allogeneic HB-adMSCs is to be administered as an IV infusion. Each 10-mL syringe contains 5 x 107 cells suspended in 5 mL of sterile saline to be diluted in 250 mL sterile saline.
Treatment Assignment	• Participants will be randomised 3:1 to receive HB-adMSCs treatments or Placebo.

2.3. Statistical Hypotheses

The null hypothesis for the primary endpoint of incidence of the hospitalizations due to COVID-19 symptoms at the end of the study is not different between the HB-adMSCs and Placebo treatment groups. The alternative hypothesis is that the treatments are different in the incidence of the hospitalizations due to COVID-19 at the end of the study. The hypothesis will be two-sided and tested at the 5% significance level.

The null hypothesis for the primary endpoint of incidence of the COVID-19 symptoms at the end of the study is not different between the HB-adMSCs and Placebo treatment groups. The alternative hypothesis is that the treatments are different in the incidence of the COVID-19 symptoms at the end of the study. The hypothesis will be two-sided and tested at the 5% significance level.

Additionally, a paired comparison will be made to compare the paired difference with placebo.

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3. PLANNED ANALYSES

3.1. Final Analyses

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.

4. ANALYSIS POPULATIONS

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 5 infusions of HB-adMSCs or placebo. • Participants will be analysed according to their randomized treatment.	• Efficacy

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5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1 Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions		
Protocol treatment arm	**Data Displays for Reporting**	
Treatment Arm	**Treatment Arm**	**Order in TLF**
Arm 1 (allogeneic HB-adMSCs 200MM)	aHB-adMSCs 200MM	1
Arm 2 (allogeneic HB-adMSCs 100MM)	aHB-adMSCs 100MM	2
Arm 3 (allogeneic HB-adMSCs 50MM)	aHB-adMSCs 50MM	3
Arm 4 (Placebo)	Placebo	4

Treatment comparisons will be displayed as follows using the descriptors as specified in the statistical analysis:

1. HB-adMSCs 200MM vs Placebo
2. HB-adMSCs 100MM vs Placebo
3. HB-adMSCs 50MM vs Placebo

5.2 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), the value from the Week 0 visit is used as the baseline value. If the value measured at the randomisation 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.

5.2.1 Change from Baseline

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]

NOTES:

- The baseline will be displayed along with Visit name on all summary displays.

5.3 Examination of Covariates, Other Strata and Subgroups

5.3.1 Covariates and Other Strata

Baseline will be included as a covariate in the efficacy analyses, wherever applicable.

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5.3.2 Examination of subgroups

No subgroup analysis planned.

5.4 Multiple Comparisons and Multiplicity

The primary comparison of interest is the overall comparison between HB-adMSCs treatments and Placebo for the primary endpoint, incidence of the hospitalizations due to COVID-19 symptoms and incidence of the COVID-19 symptoms, so multiplicity adjustment is not needed. However, for exploratory purposes we perform a pair-wise comparison will done and results from following paired comparisons will be displayed to find the paired wise differences,

1. HB-adMSCs 200MM vs Placebo
2. HB-adMSCs 100MM vs Placebo
3. HB-adMSCs 50MM vs Placebo

We do statistical analysis for the primary endpoints and secondary outcomes as exploratory and test the outcome using $\alpha = 0.05$.

5.5 General Considerations

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, 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. LOCF imputed data will be used as the basis for plotting data along with bars as standard error (SE) or Standard Deviation (SD), if not otherwise specified.

Primary endpoints of incidence of COVID-19 symptoms and Hospitalizations due to COVID-19 symptoms will be analysed based on binomial model and p-value will be displayed using two-sample binomial proportion test.

Additionally, time to first incidence of COVID-19 symptoms will analysed using Kaplan-Meir method.

A standard analysis of covariance (ANCOVA) model will be applied for secondary endpoints followed by Tukey's multiple comparison test to test the the significance of the effects of the treatment. The model includes treatment as fixed factor and the corresponding baseline value as a covariate.

Tukey's multiple comparison tests will be tested as two-sided hypotheses at a 5% level of significance. Treatment differences will be confirmed and considered significant if p-value reported is < 0.05.

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Presentation of results from a statistical analysis will include the estimated mean treatment effects (Least Square Means (LSMeans)) for absolute values and change from baseline. For all endpoints analysed statistically, estimated mean treatment differences will be presented together with two-sided 95% confidence intervals and p-values obtained using Tukey's method, and results from following paired comparisons will be displayed,

1. HB-adMSCs 200MM vs Placebo
2. HB-adMSCs 100MM vs Placebo
3. HB-adMSCs 50MM vs Placebo

All safety evaluations will be presented using Safety Analysis Set. The efficacy analysis will be presented using Efficacy analysis set.

Individual safety and efficacy parameters will be listed.

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the Safety analysis set.

Study population analyses including analyses of subject disposition, demographic and baseline characteristics, medical history, prior and concomitant medications. Additionally, including tobacco usage and alcoholic abuse.

A two sample binomial test will be applied for primary endpoints to calculate p-value comparing binimial proportions for incidence of COVID-19 symptoms and Hospitalizations due to COVID-19 symptoms.

p-value for treatment difference using one-way Analysis of variance (ANOVA) is displayed for baseline characteristics. A standard analysis of covariance (ANCOVA) model will be applied for secondary endpoints followed by Tukey's multiple comparison test to test the the significance of the effects of the treatment. The model includes treatment as fixed factor.

Details of the planned displays are presented in Appendix 5: List of Data Displays.

Categorical variables will be summarized by the number and percentage of subjects, and the continuous parameters will be summarized by n, mean, standard error of mean, median, sample standard deviation, minimum and maximum unless otherwise specified.

Disposition summary includes, subject screened, randomized and disposition at end of study – Week 26 along with reasons for withdrawals will be presented based on number of subjects and percentage. Subjects in different analysis populations also will be presented.

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7. EFFICACY ANALYSES

7.1. Primary Efficacy Analyses

7.1.1. Endpoint / Variables

The primary endpoints are incidence of COVID-19 symptoms and Hospitalizations due to COVID-19 symptoms after Week 26 end of study.

7.1.2. Summary Measure

Binomial proportions difference between treatments.

7.1.3. Population of Interest

The primary efficacy analyses will be based on the efficacy analysis set population, unless otherwise specified.

7.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 5: List of Data Displays.

7.1.4.1. Statistical Methodology Specification

Incidence of Hospitalizations due to COVID-19 symptoms:

The primary endpoint analysis is the comparison between HB-adMSCs treatments vs Placebo are described in this table.

Primary endpoint will be analysed using the two sample Binomial proportion model for the comparison of HB-adMSCs 200MM vs. Placebo, HB-adMSCs 100MM vs. Placebo and HB-adMSCs 50MM vs. Placebo to test the the significance of the effects of the treatment.

Incidence of COVID-19 symptoms:

The primary endpoint analysis is the comparison between HB-adMSCs treatments vs Placebo are described in this table.

Primary endpoint will be analysed using the two sample Binomial proportion model for the comparison of HB-adMSCs 200MM vs. Placebo, HB-adMSCs 100MM vs. Placebo and HB-adMSCs 50MM vs. Placebo to test the the significance of the effects of the treatment.

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7.2. Secondary Efficacy Analyses

7.2.1. Endpoints / Variables

Change from baseline to the end of study period, Week 26 in,

- Leukocyte differential counts
- C-Reactive Protein
- TNF-alpha
- IL-6
- L-10
- SF-36 questionnaire score

7.2.2. Summary Measures

Least square mean (LSM) and LSM mean difference between treatments.

7.2.3. Population of Interest

The secondary efficacy analyses will be based on the Efficacy analysis set population, unless otherwise specified.

7.2.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 5: List of Data Displays.

7.2.4.1. Statistical Methodology Specification

Change from baseline to Week 26 of treatment:

The secondary endpoint analysis is the overall treatment comparison between HB-adMSCs treatments and placebo. A pair-wise comparison of HB-adMSCs 200MM vs Placebo, HB-adMSCs 100MM vs Placebo and HB-adMSCs 50MM vs Placebo are also described in this table.

Secondary endpoint will be analysed using the standard ANCOVA model followed by Tukey's multiple comparison test to test the the significance of the effects of the treatment. The model includes treatment as fixed factor and the baseline value as a covariate.

Change from baseline to Week 14 end of infusion treatment:

The secondary endpoint analysis is the overall treatment comparison between HB-adMSCs treatments and placebo after Week 14 of infusion. A pair-wise comparison of HB-adMSCs 200MM vs Placebo, HB-adMSCs 100MM vs Placebo and HB-adMSCs 50MM vs Placebo are also described in this table.

Secondary endpoint will be analysed using the standard ANCOVA model followed by Tukey's multiple comparison test to test the the significance of the effects of the

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treatment. The model includes treatment as fixed factor and the baseline value as a covariate.

Sensitivity/supportive analysis model

Change from baseline values of treatment will be analysed using the standard ANCOVA model based on efficacy analysis set followed by Tukey's multiple comparison test to test the the significance of the effects of the treatment. The model includes treatment as fixed factor and the baseline value as a covariate. A pair-wise comparison of HB-adMSCs 200MM vs Placebo, HB-adMSCs 100MM vs Placebo and HB-adMSCs 50MM vs Placebo are also described in this table for secondar endpoints.

A repeated measurements analysis (RMA) of value and change from baseline over Week 26 of treatment will be performed on the efficacy analysis sets, followed by Tukey's multiple comparison test to test the the significance of the effects of the treatment.

All observed measurements available post baseline and change from baseline, at scheduled measurement times, will also be analysed in a linear mixed model using an unstructured residual covariance matrix. The model will include treatment, visit as fixed factors and baseline as a covariate. Furthermore, the model will include interaction terms between treatment and visit, and between baseline and visit. Subject will be included as a random factor when fitting the model.

8. SAFETY ANALYSES

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

8.1. Adverse Events Analyses

Adverse events (AES) are summarised descriptively. AE 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 (%), the number of events (E) and the event rate per 100 years of exposure (R).

Summaries of AEs 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 reported terms are made for:

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

Individual adverse events will be listed.

The details of the planned displays are in Appendix 5: List of Data Displays.

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8.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Biochemistry laboratory tests, Hematology laboratory tests and Coagulation tests (PTT/PT/INR). The details of the planned displays are in Appendix 5: List of Data Displays.

All laboratory parameters, including numerical urine analysis parameters will be summarised descriptively. Also, p-value for treatment difference using Analysis of variance (ANOVA) is displayed for lab parameters. Categorical urine analysis results will be summarized using count and percentage based on subjects.

Change from baseline will be summarised descriptively. Also, p-value for treatment difference using one-way Analysis of variance (ANOVA) is displayed for change from baseline.

Individual laboratory evaluations will be listed.

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

8.3. Other Safety Analyses

The analyses of non-laboratory safety test results including physical examination and vital signs. The details of the planned displays are presented in Appendix 5: List of Data Displays.

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. Also, p-value for treatment difference using one-way Analysis of variance (ANOVA) is displayed for change from baseline.

Individual Vital signs, Physical Examination evaluations will be listed.

9. REFERENCES

1. ICHE9 guideline
2. ICHE3 Guidelines