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

Protocol Title	:	A Phase II, Open Label, Single-Center, Clinical Trial to Assess Safety and Efficacy of HB-adMSCs to Provide Immune Support Against Coronavirus Disease
Short Title	:	HB-adMSCs for Immune Support Against Coronavirus Disease
Study Number	:	HBCOVID-01
Phase	:	II
Product	:	HB-adMSCs Hope Biosciences Adipose Derived Mesenchymal Stem Cells
Indication	:	Coronavirus Disease
Sponsor name	:	Hope Biosciences
Effective date	:	20-APR-2020

Regulatory Agency Identifier Numbers(s)

Registry		ID
IND Number	:	19680
NCT Number	:	NCT04349631

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 HBCOVID-01. Details of the planned final analysis provided.

Additional detail 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), Estimand(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 Objective	**Secondary Endpoint**
• 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

Objectives	Endpoints
	• Clinically significant changes in laboratory values, vital signs, weight, and physical examination results. • Incidence of Adverse Events (AEs) and serious AEs (SAEs) related to the drug

2.2. Study Design

Overview of Study Design and Key Features	
This phase II, open label, single-center, safety and efficacy study is designed to evaluate HB-adMSCs to support immunity against Coronavirus Disease.	
Design Features	The trial includes, • There is a screening period of up to 14 days • A 14-week treatment period while on HB-adMSCs ▪ Infusion 1 (Week 0), Infusion 2 (Week 2), Infusion 3 (Week 6), Infusion 4 (Week 10) and Infusion 5 (Week 14) • A safety Follow-up periods and end of the study or early discontinuation visit. ▪ Follow up week of 18 and 22 and end of study at Week 26 • 55 Subjects
Study Intervention	• Intervention: HB-adMSCs (Hope Biosciences adipose derived mesenchymal stem cells) ▪ Dose: $2x10^8$ cells suspended in 20 ml sterile saline ▪ Route: Intravenous ▪ Regimen: Weeks 0, 2, 6, 10 and 14. ▪ 83 gts/min (250 mL/hr) • Study treatment details, ▪ Each syringe contains 20 ml of cells solution with 2x108 cells (+20%). The syringe content is to be diluted in 250 mL of 0.9% sodium chloride.
Study Intervention Assignment	• All participants receive HB-adMSCs
Interim Analysis	• No interim analysis will be performed in this study

3. STATISTICAL HYPOTHESES

No formal statistical hypothesis testing performed.

3.1. Multiplicity Adjustment

No multiplicity adjustments will be performed as this is early phase study and no formal statistical hypothesis testing performed.

4. ANALYSIS SETS

Population	Definition / Criteria	Analyses Evaluated
Safety analysis set	• All subjects that receive at least one HB-adMSC infusion will be included in safety analysis.	• Safety • Study Population
Efficacy analysis set	• All subjects that receive all 5 infusions of HB-adMSCs will be included in efficacy analysis.	• 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

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. Observed 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.

Study population analyses including analyses of subject disposition, demographic and baseline characteristics.

Disposition summary includes, subject screened, 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 Total MDS-UPDRS Part II 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 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-	Incidence of hospitalization for COVID-19. Incidence of symptoms associated with COVID-19

Objectives	Endpoints
19 associated symptoms ((fever 38C or higher, cough, shortness of breath/difficulty breathing).	

5.2.2. Main analytical approach

Endpoint/Variables
• Incidence of COVID-19 symptoms and Hospitalizations due to COVID-19 symptoms after Week 26 end of study
Model Specification/analysis method
• Incidence COVID-19 symptoms and Hospitalizations due to COVID-19 symptoms after Week 26 is summarized as counts and percentage

5.3. Secondary Endpoint(s) Analyses

5.3.1. Efficacy Endpoints / Variables

- 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

All the secondary efficacy endpoints will be summarized descriptively using N, Mean, Standard Error of mean (SE), Standard Deviation (SD), Median and Range (Minimum and Maximum).

- Absence of upper/lower respiratory infections (with hospitalization criteria) up to 3 months post infusions

Absence of upper/lower respiratory infections summarised as counts and percentages.

5.3.2. Safety Analyses

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

5.3.2.1. 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).

Individual adverse events will be listed.

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

5.3.2.2. Clinical Laboratory data

Laboratory evaluations including the analyses of Biochemistry laboratory tests, Hematology laboratory tests 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.

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

Sample size for this study is 55 patients.

7. SUPPORTING DOCUMENTATION

7.1. 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 safety analysis set.

Listings of demographic characteristics will also be produced.

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

7.1.3. 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

7.1.4. Criteria for Potential Clinical Importance

The potential clinical importance criteria are not defined for this trial.

7.1.5. 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

7.1.6. 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

7.1.7. 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.

7.1.8. 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.

8. REFERENCES

Hope Biosciences protocol number HBCOVID-01 A Phase II, Open Label, Single-Center, Clinical Trial to Assess Safety and Efficacy of HB-adMSCs to Provide Immune Support Against Coronavirus Disease