Oak Hill Bio

Protocol: SHP607-203

Long-Term Safety and Efficacy Outcomes Following Previously Administered Short-Term Treatment with SHP607 in Extremely Premature Infants

STATISTICAL ANALYSIS PLAN

Version 1.0

09SEP2022

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Client:	**Oak Hill Bio**
Protocol Number:	SHP607-203
Document Description:	Statistical Analysis Plan
SAP Title:	SHP607-203 SAP
SAP Version Number:	V1.0
Effective Date:	09 Sep 2022

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[illegible]

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87E9655C4E9A49FAB0F7E7CD3F8945BF

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ABBREVIATIONS

ADHD	Attention-Deficit/Hyperactivity Disorder
ADHD-RS	Attention-Deficit/Hyperactivity Disorder Rating Scale
AE	adverse event
ASD	Autism Spectrum Disorder
BSID	Bayley Scales of Infant and Toddler Development
CA	corrected age
CIQ	Caregiver Impact Questionnaire
CRM	chronic respiratory morbidity
eCRF	electronic case report form
EQ-5D-5L	EuroQol 5-dimensional 5-level descriptive system
GA	gestational age
GMFM-88	Gross Motor Function Measure-88
HCRU	health care resource use
HRQoL	health-related quality of life
HUI2/3	Health Utilities Index Mark 2 and Mark 3
IP	investigational product
KSPD	Kyoto Scale of Psychological Development
MedDRA	Medical Dictionary for Regulatory Activities
PedsQL	Pediatric Quality of Life Inventory
PT	preferred term
Q1	quartile 1
Q3	quartile 3
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SCQ	Social Communication Questionnaire
SOC	system organ class
VABS	Vineland Adaptive Behavior Scales
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

1. INTRODUCTION

This abbreviated statistical analysis plan (SAP) provides a detailed elaboration of the statistical analyses of designated safety data as described in the study protocol amendment 1, dated 08 April 2020. Specifications for tables, figures, and listings are contained in a separate document.

2. OBJECTIVES

2.1 Primary Objectives

The primary objectives of the study are:

- To evaluate long-term efficacy outcomes following previously administered short-term exposure to SHP607, as compared to a standard neonatal care group, as assessed by chronic respiratory morbidity (CRM) outcomes.
- To evaluate the long-term safety outcomes following previously administered short-term exposure to SHP607, as compared to a standard neonatal care group.

2.2 Secondary Objectives

The secondary objectives of the study are to evaluate long-term effects following previously administered short-term exposure to SHP607 on growth, cognitive and motor development, behavior, and resource utilization, as compared to a standard neonatal care group, by assessing:

- Growth parameters
- Physical development
- Cognitive development
- Gross motor function
- Child behavior
- Health-related quality of life (HRQoL)
- Health utility
- Health care resource use (HCRU)

2.3 Exploratory Objectives

The exploratory objectives of the study are:

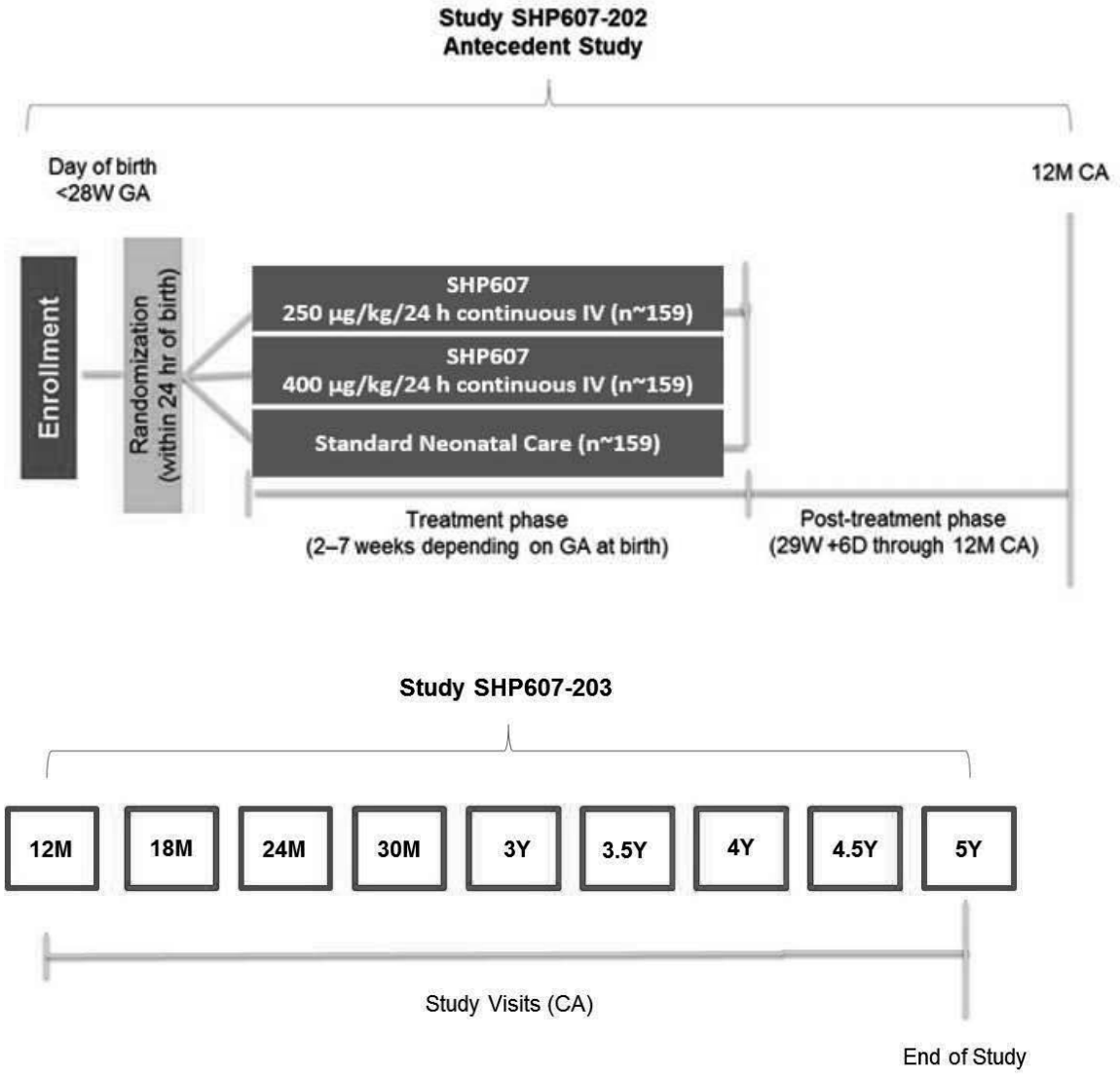
- To evaluate caregiver burden as assessed by the Caregiver Impact Questionnaire (CIQ).
- To evaluate caregiver health status using EuroQol 5-dimensional 5-level descriptive system (EQ-5D-5L).
- To evaluate cognitive impairment with an exploratory interactive electronic tablet application (BabyScreen) used by children at 24 months corrected age.
- To evaluate pulmonary function following previously administered short-term exposure to SHP607, as compared to a standard neonatal care group.
- To evaluate brain volume and cerebral neuroanatomic abnormalities following previously administered short-term exposure to SHP607, as compared to a standard neonatal care group.

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 2b, multicenter, long-term outcomes study of subjects who were randomized in Study OHB-607-202 (previously known as SHP607-202) to either treatment (received OHB-607 [previously known as SHP607]) or control (received standard neonatal care) groups. Subjects are followed from 12 months CA through 5 years CA. Subjects are not excluded from participating in other clinical studies. No investigational product is administered in this study. Approximately 477 subjects who previously received OHB-607 or standard neonatal care in Study OHB-607-202 were planned to be enrolled in Study SHP607-203. Although all subjects randomized into the primary Study OHB-607-202 (approximately 477) are eligible to enroll in Study SHP607 203, the actual number of subjects enrolled would more closely approximate the number of subjects who complete Study OHB-607-202 (a total of approximately 382 subjects). The study designs are presented in Figure 1.

Figure 1 Study Design Flow Diagram



CA=corrected age; D=days; GA=gestational age; IV=intravenous; M=months; W=weeks; Y=years. Visits conducted at the study site are indicated in blue. Visits conducted by telephone are indicated in red.

In the Protocol Amendment 2 of Study OHB-607-202, the study design was updated to include a follow-up period until 24 months CA. As a result the sponsor decided to terminate Study SHP607-203.. The number of subjects enrolled in this study is less than 10% of the planned number, and few subjects completed the study (i.e. completed 5-year CA assessments). Thus, only sponsor-designated safety data will be analyzed and reported in this early-terminated study.

3.2 Study Endpoints

3.2.1 Primary Efficacy Endpoints

The primary efficacy endpoint is the incidence of the following indicators of CRM:

1) Emergency room visit or hospitalization associated with a respiratory diagnosis.
2) Presence of coughing/wheezing.
3) Use of respiratory medications (eg, bronchodilators, steroids, leukotriene inhibitors, diuretics).
4) Home respiratory technology use (eg, home oxygen, continuous positive airway pressure [CPAP], tracheostomy).

3.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are defined as:

- Growth parameters including body weight, body length (or height), and head circumference.
- Physical development as assessed by standardized, age appropriate tools including physical exam, neurological examination for assessment of cerebral palsy, and vision assessment. Reports of past vision and hearing assessments will also be collected.
- Cognitive development as assessed by the following standardized, age-appropriate tools:
  - Bayley Scales of Infant and Toddler Development (BSID) (or Kyoto Scale of Psychological Development [KSPD])
  - Wechsler Preschool and Primary Scale of Intelligence (WPPSI)
- Gross motor function as assessed by Gross Motor Function Measure-88 (GMFM-88).
- Child behavior as assessed by the following:
  - Vineland Adaptive Behavior Scales (VABS)
  - Attention-Deficit/Hyperactivity Disorder Rating Scale-fifth edition (ADHD RS-V) for the assessment of symptoms of ADHD
  - Social Communication Questionnaire (SCQ) for screening of Autism Spectrum Disorder (ASD)
- HRQoL will be assessed by the Pediatric Quality of Life Inventory (PedsQL) Infant Scales appropriate for the child's age of development with the Total Scale Score and

5 domains within Physical Health (Physical Functioning and Physical Symptoms) and Psychosocial Health Scores (Emotional, Social, and Cognitive Functioning).

- Health status (eg, health utility) will be measured by the Health Utilities Index Mark 2 and Mark 3 (HUI2/3).
- Health care resource use associated with inpatient visits, outpatient visits, emergency room visits, and visits to specialists will be assessed.

3.2.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are defined as:

- CIQ: Descriptive statistics of the CIQ item responses at baseline, 24 months CA, and 5 years CA.
- EQ-5D-5L: Mean overall score on the EQ-5D-5L at 24 months CA, 3 years CA, 4 years CA, and change from 24 months CA.
- BabyScreen interactive electronic tablet application: Participation in the BabyScreen substudy is optional and has no impact on participation in the main study. The tool, used by children at 24 months CA to evaluate cognitive impairment, will be used for validation purposes only.
- Spirometry: Participation in the spirometry substudy is optional and has no impact on participation in the main study. Standard measures will be collected, including forced expiratory volume over 1 second (FEV1) and forced vital capacity (FVC).
- Cerebral Magnetic Resonance Imaging (MRI): Participation in the cerebral MRI substudy is optional and has no impact on participation in the main study. Brain volume and neuroanatomic abnormalities will be assessed utilizing cerebral MRI at specific sites with MRI capabilities.

3.2.4 Safety Endpoints

The safety endpoints of this study are:

- Adverse events (AEs) reported during the study period of SHP607-203.
- Targeted medical events occurring during the period of Study SHP607-203.
- Fatal serious adverse events (SAEs)

4. GENERAL STATISTICAL CONSIDERATIONS

4.1 Sample Size

No formal sample size calculation was performed because this is a follow-up study to Study OHB-607-202.

4.2 Randomization, Stratification, and Blinding

There is no randomization or stratification for this study.

Although the antecedent Study OHB-607-202 is open-label, to preserve the integrity of Study OHB-607-202, study personnel involved in Study SHP607-203 remain blinded to any efficacy-related aggregate by antecedent treatment group data review until the OHB-607-202 final database is locked.

4.3 Analysis Set

4.3.1 Enrolled Set

The Enrolled Set is defined as all subjects for whom written informed consent has been provided for this study.

4.3.2 Safety Set

The Safety Set is defined as all subjects in the Enrolled Set who have safety follow-up data (including absence of AEs) in this long-term outcome study.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

This section describes subject disposition for both the analysis sets and the study status.

The number of subjects included in each defined analysis set will be summarized by the antecedent treatment group as administered in Study OHB-607-202 (Standard Neonatal Care, SHP607 250 µg/kg/24 hours, and SHP607 400 µg/kg/24 hours) and overall. Percentages will be provided using the Enrolled Set as the denominator.

The number and percentage of subjects who completed through the study visits (12-month, 18-month, 24-month, 30-month, 3-year, 3.5-year, 4-year, and 4.5-year CA), who completed the study, and who prematurely discontinued from the study will be presented for each treatment group and overall for the Enrolled Set. Primary reasons for premature discontinuation as recorded on the Study Completion page of the electronic case report

form (eCRF) will be summarized (number and percentage) by treatment group and overall. All subjects who prematurely discontinued will be listed for the Enrolled Set.

A by-subject listing of study completion information, including the reason for premature study discontinuation, where applicable, will be presented.

5.2 Demographic and Other Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group and overall for the Enrolled Set. The following demographic and baseline characteristics will be summarized: CA (months) at enrollment, gestational age (GA) at birth (weeks), sex, ethnicity, and race. A listing will be presented to show all the demographic and baseline characteristics for each subject in the Enrolled Set.

5.3 Exposure to Investigational Product

Exposure to investigational product is not applicable as no investigational product is administered in this study.

6. EFFICACY ANALYSES

No efficacy data will be analyzed nor listed for this study due to early termination and lack of assessments.

7. SAFETY ANALYSIS

The safety analysis will be performed using the Safety Set. All safety analyses will be conducted according to the treatment the subject actually received in Study OHB-607-202.

7.1 Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or newer. For the purposes of this study only the following adverse events will be presented:

- Specified targeted medical events (Protocol Section 8.1.4)
- AEs related to investigational product (as administered in Study OHB-607-202)
- AEs leading to withdrawal from the study
- Serious AEs that occur during the study period or were previously present and worsen during the study period.

If it is determined that any of the following targeted medical events have been experienced by a subject, they will be recorded as AEs or SAEs, as appropriate, regardless of relationship to prior investigational product (as administered in Study OHB-607-202). The targeted medical events are considered as AEs of important potential risks and identified based on a list of pre-specified preferred terms (PTs):

- Intracranial hypertension: intracranial pressure increased, benign intracranial hypertension, fontanelle bulging, delayed fontanelle closure
- Any abnormality of glucose metabolism: hypoglycaemia, hypoglycaemia neonatal, blood glucose decreased
- Tonsillar hypertrophy (based on tonsil examination [part of the physical examination]): tonsillar hypertrophy, adenoidal hypertrophy, thymus enlargement, hypoacusis, snoring, ear tube insertion, tonsillectomy, adenoidectomy, sleep apnoea syndrome
- Increased cardiac size: cardiomegaly, cardiac hypertrophy, cardiac septal hypertrophy, ventricular hypertrophy, atrial hypertrophy, left ventricular hypertrophy, right ventricular hypertrophy, left atrial hypertrophy, right atrial hypertrophy, cardiomyopathy, cardiomyopathy neonatal, hypertrophic cardiomyopathy

An overall summary of the number of subjects as well as the number of events in each treatment group and overall will be presented, including the number and percentage of subjects with:

- Any AE (as specified in Protocol Section 8.1)
- Any SAE
- Any severe AE
- Any AE related to investigational product (IP) as administered in Study OHB-607-202

- Any SAE related to IP as administered in Study OHB-607-202
- Any severe AE related to IP as administered in Study OHB-607-202
- Any AE related to procedures performed in this study (SHP607-203)
- Any SAE related to procedures performed in this study (SHP607-203)
- Any severe AE related to procedures performed in this study (SHP607-203)
- Any AE leading to study discontinuation
- Any SAE leading to death

The number and percentage of subjects reporting AEs, as well as the number of events (except for tables by the maximum severity), in each treatment group and overall will be tabulated, respectively, in following ways:

- By system organ class (SOC) and PT for all AEs
- By the maximum severity, SOC and PT for all AEs
- By SOC and PT for all AEs considered related to IP as administered in Study OHB-607-202
- By SOC and PT for all AEs considered related to study procedures
- By SOC and PT for all AEs leading to death
- By SOC and PT for all AEs leading to study discontinuation
- By SOC and PT for all SAEs
- By risk term, seriousness, and relationship to antecedent IP for AEs of important potential risks
- Most frequent AEs by PT (sorted by frequency, occurring in ≥5% of subjects in any treatment arm)

In tables by severity or relationship, missing severity or missing relationship imputation will be applied, and handling of those missing cases are detailed in Section 9.2.2 and 9.2.3, respectively. If a subject had multiple occurrences of the same AEs, the subject will be counted only once per SOC and once per PT at the maximum severity. Handling of incomplete AE start/end dates is described in Section 9.2.1.

All AEs will be presented in a data listing. Separate data listings will be presented for AEs related to the antecedent IP, AEs related to study procedures, AEs leading to death, SAEs and AEs of important potential risks.

8. INTERIM ANALYSIS

After the last subject in the primary Study OHB-607-202 has completed the last study visit, an interim analysis for Study SHP607-203 was to be performed for all enrolled subjects who had either completed the 24 months CA visit assessments or prematurely withdrawn from Study SHP607-203, and after all associated data would have been entered into the database with queries and discrepancies resolved.

Since study SHP607-203 will be terminated early before the last subject in the primary Study OHB-607-202 has completed the last study visit, the planned interim analysis will not be conducted.

9. DATA HANDLING CONVENTIONS

9.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, quartile 1 (Q1), quartile 3 (Q3), minimum and maximum. Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category. The denominator for the proportion will be based on the total number of subjects for each treatment group and overall within the analysis set of interest.

Unless specified otherwise, median, mean, Q1 and Q3 will use 1 decimal place beyond the precision of data used for the measurement; standard deviation of the mean will use 2 decimal places beyond the precision; minimum and maximum values will use the same number of decimal places as the precision.

9.2 Handling of Missing, Unused, and Spurious Data

9.2.1 Missing Date Information for Adverse Events

To facilitate categorization of AEs as related to study procedure, imputation of start dates can be used. For AEs, the default is to only impute incomplete (i.e., partially missing) start dates. Incomplete stop dates may also be imputed when calculation of the duration of an AE is required. If imputation of an incomplete stop date is required, and both the start date and the stop date are incomplete for a subject, impute the start date first.

9.2.1.1 Incomplete Start Date

If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of informed consent, then the day and month of the date of informed consent will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the date informed consent, then December 31 will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of informed consent, then January 01 will be assigned to the missing fields.

Missing Month only

The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing Day only

- If the month and year of the incomplete start date are the same as the month and year of the date of informed consent, then the day of the date of informed consent will be assigned to the missing day.
- If either the year is before the year of the date of informed consent or if both years are the same but the month is before the month of the date of informed consent, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of informed consent or if both years are the same but the month is after the month of the date of informed consent, then the first day of the month will be assigned to the missing day.

9.2.1.2 Incomplete Stop Date

If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing Day and Month

- If the year of the incomplete stop date is the same as the year as of the end of study date, then the day and month of the end of study date will be assigned to the missing fields.
- If the year of the incomplete stop date is before the year of the end of study date, then 31 December will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the end of study date, then the stop date will be imputed as the end of study date.

Missing Month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing Day only

- If the month and year of the incomplete stop date are the same as the month and year of the end of study date, then the day of the end of study date will be assigned to the missing day
- If either the year is before the year of the end of study date or if both years are the same but the month is before the end of study date, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the end of study date or if both years are the same but the month is after the end of study date, then the stop date will be imputed as the end of study date.

9.2.2 Missing Severity Assessment for Adverse Events

If severity is missing for an AE, a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

9.2.3 Missing Relationship for Adverse Events

If the relationship to investigational product (as administered in Study OHB-607-202) is missing for an AE, a causality of "Related" will be assigned. If the relationship to study procedure performed in this study (SHP607-203) is missing for an AE starting on or after the date of informed consent, a causality of "Related" will be assigned. The imputed values for relationship will be used for incidence summaries, while the actual values will be presented in data listings.

9.3 ANALYSIS SOFTWARE

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® on a suitably qualified environment.

10. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

Protocol planned efficacy endpoints are not listed or analyzed in this abbreviated SAP due to early termination of the study.

11. REFERENCES

Not applicable.

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In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	11 November 2022 | 20:52
Certified Delivered	Security Checked	11 November 2022 | 21:08
Signing Complete	Security Checked	11 November 2022 | 21:12
Completed	Security Checked	14 November 2022 | 08:47

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

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