PROTOCOL: SHP607-203

TITLE:	Long-Term Safety and Efficacy Outcomes Following Previously Administered Short-Term Treatment with SHP607 in Extremely Premature Infants
DRUG:	SHP607 (mecasermin rinfabate)
IND:	133,076
EUDRACT NO.:	TBD
SPONSOR:	Premacure AB, A Member of the Shire Group of Companies
SPONSOR CONTACT:	300 Shire Way, Lexington, MA 02421 USA +1-617-349-0200
PRINCIPAL/ COORDINATING INVESTIGATOR:	TBD
PROTOCOL HISTORY:	Original Protocol: 18 November 2019 Amendment 1: 08 Apr 2020

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PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: DocuSigned by: Linda Han 207BD4A5C3B84FA...	**Date:** 10-Apr-2020 | 04:20 JST
Linda Han, MD, MPH Global Clinical Lead	

Investigator's Acknowledgement

I have read this protocol for Study SHP607-203.

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

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the "Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol" within 24 hours to the Shire Global Drug Safety Department. The fax number and e-mail address are provided on the form (sent under separate cover). A copy of this form must also be sent to the contract research organization (CRO)/Shire medical monitor using the details below.

E-mail: drugsafety@shire.com
Fax: +1-866 557 4473 (North America)
+44(0) 1256 89 4715 (Global)

For protocol- or safety-related questions or concerns at any time, the investigator must contact the PPD medical monitor:

- **North America:** Anusha Streubel, MD, MPH, Medical Director, PPD, Pharmacovigilance
- **Europe:** Roxana Ruta, MD, Medical Director, PPD, Pharmacovigilance
- **Asia Pacific (APAC):** Amran Saifulanwar, MBBS, Medical Director, Medical Affairs and Pharmacovigilance

Hotline numbers (24 hours a day/7 days a week):
North America: +1-888-483-7729
Europe, Middle East, Africa (EMEA)/Asia-Pacific (APAC): +44-1223-374-240

Fax numbers:
North America: +1-888-529-3580 and +1-919-654-3836
EMEA/APAC: +44-1223-374-102

Email:
North America: rtpsafety@ppdi.com
EMEA/APAC: emeaasiasafetycentral.sm@ppdi.com

SUMMARY OF CHANGES FROM PREVIOUS VERSION

An overview of the updates incorporated into Amendment 1 is provided in the table below.

Summary of Change(s) Since Last Version of Approved Protocol	
Description of Change	**Section(s) Affected by Change**
Updated Signatory.	Protocol Signature Page
Updated Emergency Contact Information to match current template.	Emergency Contact Information
Updated Product Quality Complaints information to match current template.	Product Quality Complaints
Decreased the approximate number of subjects in Study SHP607-202, from 600 to 477; decreased the approximate number of subjects expected to complete Study SHP607-202 from 160 to 127 per arm; decreased the approximate number of subjects in Study SHP607-203 from 480 to 382.	Study Synopsis Section 1.3 Section 3.1 Figure 1 Section 9.5
Decreased the approximate number of sites in Study SHP607-203 from 70 to 60.	Study Synopsis Section 3.3
Added exploratory objective and endpoint of evaluation of cognitive impairment with an exploratory interactive electronic tablet application (BabyScreen)	Study Synopsis Table 1 Section 2.1.3 Section 7.1.2.2 Section 9.7.3
Clarified that concomitant medications, procedures, and therapies will be collected only in the context of SAEs. In addition, respiratory medications (and medications that may be associated with respiratory conditions) will be captured in the pulmonary morbidity assessment, along with respiratory therapies.	Section 5.2
Clarified that the pulmonary morbidity assessment consists of the respiratory conditions assessment and the respiratory risk factors assessment.	Section 7.2.5.1
Clarified that the EQ-5D-5L is a measure of the health of the subject's parent(s)	Section 7.2.5.6
Added section heading and description of the BabyScreen exploratory interactive electronic tablet application.	Section 7.2.5.7
Clarified that AEs will only be collected for specified targeted medical events, AEs related to investigational product, AEs leading to withdrawal from the study, and serious AEs that occur during the study period or were previously present and worsened during the study period.	Section 8.1

Summary of Change(s) Since Last Version of Approved Protocol	
Description of Change	**Section(s) Affected by Change**
Revised reporting procedures to provide actual contact information	Section 8.2.2
Added section heading and description of documentation and retention of electronic clinical outcome assessments records.	Section 10.2.3.2

AE=adverse event; EQ-5D-5L=EuroQol 5-dimensional 5-level descriptive system; IP=investigational product; SAE=serious adverse event.

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or non-medical complaints to Shire within 24 hours. If requested, defective product(s) will be returned to the sponsor for inspection and analysis.

A product quality complaint includes any instances where there is an allegation or report relating to Shire licensed or investigational products, received in writing, electronically, or orally, which indicates an impact to a product's strength, identity, safety, purity, or quality, or which suggests that the product did not meet the criteria defined in the regulatory applications, licenses, or marketing authorizations for the product. Examples of investigational product quality complaints include, but are not limited to, the following:

Unit issues	• Bottle/vial fill shortage or overage • Vial cracked/broken	• Missing components • Product discoloration
Labeling	• Label missing • Leaflet or Instructions For Use missing • Label illegible	• Incomplete, inaccurate, or misleading labeling • Lot number or serial number missing
Packaging	• Damaged packaging (eg, secondary, primary, bag/pouch) • Tampered seals • Inadequate or faulty closure	• Missing components within package
Foreign material	• Contaminated product • Particulate in bottle/vial	• Particulate in packaging

Please report the product quality complaint using the "Product Quality Complaint Data Collection Form" via the email address:

PQC@shire.com

Telephone numbers (provided for reference if needed):

Shire, Lexington, MA (USA)

+1-800-828-2088

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ABBREVIATIONS

ADHD	attention-deficit/hyperactivity disorder
ADHD-RS	Attention-Deficit/Hyperactivity Disorder Rating Scale
AE	adverse event
ALS	acid-labile subunit
APAC	Asia Pacific
ASD	Autism Spectrum Disorder
BPD	bronchopulmonary dysplasia
BSID	Bayley Scales of Infant and Toddler Development
CA	age (in months) after expected date of full-term delivery
CI	confidence interval
CIQ	Caregiver Impact Questionnaire
CPAP	continuous positive airway pressure
CRA	clinical research associate
CRF	case report form
CRM	chronic respiratory morbidity
CRO	contract research organization
D	days
DMC	data monitoring committee
EC	ethics committee
EMEA	Europe, Middle East, Africa
EQ-5D-5L	EuroQol 5-dimensional 5-level descriptive system
EU	European Union
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GA	gestational age (time elapsed between first day of last menstrual period and day of birth)
GCP	Good Clinical Practice
GH	growth hormone
GMFM	Gross Motor Function Measure
HCRU	health care resource use
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	health-related quality of life
HUI	Health Utilities Index
HUI2/3	Health Utilities Index Mark 2 and Mark 3
IB	investigator's brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee

IGF-1	insulin-like growth factor-1
IGFBP-3	insulin-like growth factor binding protein-3
IRB	institutional review board
IV	intravenous(ly)
IVH	intraventricular hemorrhage
KSPD	Kyoto Scale of Psychological Development
MRI	magnetic resonance imaging
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal Intensive Care Unit
PedsQL™	Pediatric Quality of Life Inventory
PK	pharmacokinetic
PMA	postmenstrual age
PROP	Prematurity and Respiratory Outcomes Program
ROP	retinopathy of prematurity
RTS	respiratory technology support
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SCQ	Social Communication Questionnaire
SEM	standard error of the mean
SOC	system organ class
$t_{1/2}$	terminal elimination half-life
US	United States
VABS	Vineland Adaptive Behavior Scales
W	weeks
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

STUDY SYNOPSIS

Protocol number: SHP607-203	**Drug:** SHP607 (mecasermin rinfabate)
Title of the study: Long-Term Safety and Efficacy Outcomes Following Previously Administered Short-Term Treatment with SHP607 in Extremely Premature Infants	
Number of subjects (total and for each treatment arm): Approximately 477 subjects who previously received SHP607 or standard neonatal care in Study SHP607-202 are planned to be enrolled in Study SHP607-203. Although all subjects randomized into the primary Study SHP607-202 (approximately 477) are eligible to enroll in Study SHP607-203, the actual number of subjects enrolled will more closely approximate the number of subjects who complete Study SHP607-202. A total of approximately 382 subjects (approximately 127 subjects randomized to SHP607 250 µg/kg/24 hours, approximately 127 subjects randomized to SHP607 400 µg/kg/24 hours, and approximately 127 subjects randomized to standard neonatal care) are expected to complete Study SHP607-202.	
Investigator(s): Multicenter	
Site(s) and Region(s): Approximately 60 sites including, but not limited to, countries in the following regions: North America, Europe, and Asia Pacific (APAC).	
Study period (planned): 2020-2026	**Clinical phase:** 2b

Objectives:

Primary:

- 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.

Secondary: 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

Exploratory:

- 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 (CA).
- 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.

Rationale:

Low levels of insulin-like growth factor-1 (IGF-1) in extremely preterm infants (gestational age [GA] of 23 weeks +0 days to 27 weeks +6 days) are a risk factor for CRM and other complications of extreme prematurity. Short-term administration of SHP607 may have long-lasting effects on safety and outcomes related to complications of prematurity. This non-interventional study will evaluate the long-term safety and efficacy outcomes of previously administered treatment with SHP607.

Investigational product, dose, and mode of administration:

No investigational product will be administered in this study.

Methodology:

This is a multicenter, long-term outcomes study of subjects who were randomized in Study SHP607-202 to either treatment (received SHP607) or control (received standard neonatal care) groups. Subjects will be followed from 12 months CA through 5 years CA. Subjects will not be excluded from participating in other clinical studies.

Inclusion and exclusion criteria:

Inclusion Criteria:

Subjects must meet all of the criteria below:

1. Subject was randomized into Study SHP607-202. Subjects who were randomized, but did not complete Study SHP607-202 must be at least 12 months CA.
2. Written informed consents (and assents, if applicable) must be signed and dated by the subject's parent(s)/legally authorized representative(s) prior to any study-related procedures. The informed consent and any assents for underage parents must be approved by the institutional review board (IRB)/independent ethics committee (IEC).

Exclusion Criterion: Subjects are excluded from the study if the subject or subject's parent(s)/legally authorized representative(s) is/are unable to comply with the protocol or is/are unlikely to be available for long-term follow-up as determined by the investigator.

Maximum duration of subject involvement in the study:

Duration for an individual subject's participation in this study is approximately 4 years.

Endpoints and statistical analysis:

Primary Efficacy Endpoints: Incidence of the following indicators of chronic respiratory morbidity through 5 years CA:

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).

Primary Safety Endpoint:

The primary safety analysis will be based on:

- AEs reported during the study period of SHP607-203

Secondary Endpoints:

- 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 the 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 attention-deficit/hyperactivity disorder (ADHD)
  - Social Communication Questionnaire (SCQ) for screening of Autism Spectrum Disorder (ASD)
- Health-related quality of life will be assessed by the Pediatric Quality of Life Inventory (PedsQL™) 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 (HUI2) and Mark 3 (HUI3).
- Health care resource use associated with inpatient visits, outpatient visits, emergency room visits, and visits to specialists will be assessed.

Secondary Safety Endpoints:

The secondary safety analysis will be based on:

- Targeted medical events occurring during the period of Study SHP607-203.
- Fatal SAEs.

Exploratory Endpoints:

- Caregiver Impact Questionnaire (CIQ): Descriptive statistics of the CIQ item responses at baseline, 24 months CA, and 5 years CA.
- EuroQol 5-dimensional 5-level descriptive system (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 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.

Statistical Analyses:

Continuous variables will be summarized using descriptive statistics including the number of subjects, mean, standard deviation (SD), median, minimum, and maximum values.

Categorical variables will be summarized using frequencies and percentages.

As referred to in descriptions of summary statistics, treatment groups refer to the antecedent SHP607 dose groups (SHP607 at 250 µg/kg/day and SHP607 at 400 µg/kg/day), combined SHP607 dose groups, and standard neonatal care group.

For analysis purposes, baseline is defined as the first assessment in this study (Study SHP607-203).

Interim Analysis:

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

STUDY SCHEDULE

Table 1 Schedule of Assessments

	Initial Study Visit	Months (CA)			Years (CA)				
	12 mo +2 wk[b]	18 mo ±6 wk	24 mo ±6 wk	30 mo ±6 wk	3 yr ±6 wk	3.5 yr ±6 wk	4 yr ±6 wk	4.5 yr ±6 wk	5 yr ±6 wk /ET
Procedures[a]	**Clinic**	**Phone**	**Clinic**	**Phone**	**Phone**	**Phone**	**Phone**	**Phone**	**Clinic**
Informed consent	•								
Eligibility criteria	•								
Demographics	•								
Medical history[c]	•								
Visual acuity[d]									•
Length	•		•						
Height									•
Body weight	•		•						•
Head circumference	•		•						
BSID (or KSPD)			•						
BabyScreen			•						
WPPSI									•
GMFM-88			•						•[e]
VABS			•						•
ADHD-RS									•
SCQ									•
CIQ	•		•						•
Physical examination[f]	•		•						•
Blood pressure, heart rate, respiratory rate	•		•						•
Vision and hearing assessment history[g]		•	•	•	•	•	•	•	•
Pulmonary morbidity assessment (in clinic or by phone interview)	•[h]	•	•	•	•	•	•	•	•
Cerebral MRI (optional)									•
Spirometry (optional)									•
EQ-5D-5L			•		•		•		
PedsQL™			•[i]		•		•		•[j]
HCRU	•[i]	•	•[i]	•	•	•	•	•	•[j]
HUI2/3									•
Assessment of participation in other clinical studies	•	•	•	•	•	•	•	•	•

Table 1 Schedule of Assessments

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Procedures[a]	**Clinic**	**Phone**	**Clinic**	**Phone**	**Phone**	**Phone**	**Phone**	**Phone**	**Clinic**
Medications, procedures, therapies	•	•	•	•	•	•	•	•	•
Adverse events[j]	•	•	•	•	•	•	•	•	•

ADHD-RS=Attention-Deficit/Hyperactivity Disorder Rating Scale; BSID=Bayley Scales of Infant and Toddler Development; CA=corrected age; CIQ=Caregiver Impact Questionnaire; EQ-5D-5L=EuroQol 5-dimensional 5-level descriptive system; GMFM=Gross Motor Function Measure; ET=early termination; HCRU=health care resource use; HUI2/HUI3=Health Utilities Index Mark 2 and Mark 3; KSPD=Kyoto Scale of Psychological Development; mo=months; MRI=magnetic resonance imaging; PedsQL™=Pediatric Quality of Life Inventory; SCQ=Social Communication Questionnaire; VABS=Vineland Adaptive Behavior Scales; wk=weeks; WPPSI=Wechsler Preschool and Primary Scale of Intelligence

[a] Visits at 12 months, 24 months, and 5 years CA will be conducted in clinic; all other visits can be conducted by telephone. Assessments at 24 months and 5 years CA may be completed over more than one visit, if needed.

[b] The initial visit in Study SHP607-203 should coincide with the final visit of the primary Study SHP607-202 at 12 months CA +2 weeks. If the initial visit in Study SHP607-203 does not occur at the 12-month CA visit, the subject may still be enrolled until 24 months CA +6 weeks. Subjects enrolling between the 12 months CA visit and the 24 months CA visit should complete all 12-month CA assessments, and vision and hearing assessment history. Subjects enrolling at the 24 months CA visit should complete informed consent, eligibility criteria, demographics, medical history, and all 24 months CA assessments. Subjects are no longer eligible to enroll in this study after 24 months CA +6 weeks. Completion of Study SHP607-202 is not required for enrollment into Study SHP607-203.

[c] Medical events or conditions should only be captured as medical history if they occur after the end of the subject's participation in the primary Study SHP607-202 and before informed consent in the current Study SHP607-203.

[d] Visual acuity will be assessed by eye chart only.

[e] GMFM-88 Sections D (Standing) and E (Walking, Running, and Jumping) only will be administered at 5 years CA.

[f] The physical examination should include tonsil assessment at all visits and should include cerebral palsy assessment at 24 months CA visit only.

[g] Results of previously completed vision and hearing assessments, if performed, may be recorded at any time during the study up to the 5-year CA visit.

[h] Only subjects who did not complete Study SHP607-202 should have pulmonary morbidity assessments performed at the 12-month visit.

[i] The PedsQL™, EQ-5D-5L, and HCRU assessments for the 12-month, 24-month and 5-year CA visits may be performed by telephone by clinical site staff if there are time constraints during the on-site visit. At the 3-year and 4-year CA visits, these assessments will be performed by clinical site staff and may be performed at any time within the visit window.

[j] Adverse event collection will include assessment of specified targeted medical events.

1. BACKGROUND INFORMATION

SHP607 (mecasermin rinfabate, rhIGF-1/rhIGFBP-3) is the recombinant human version of the naturally occurring protein complex of insulin-like growth factor-1 (IGF-1) and its most abundant binding protein, insulin-like growth factor binding protein-3 (IGFBP-3). rhIGF-1/rhIGFBP-3 was approved by the United States (US) Food and Drug Administration (FDA) in December 2005 for the treatment of growth failure in children with severe primary IGF-1 deficiency. This product, IPLEX™, has since been removed from the market following a patent dispute settlement, not safety concerns. SHP607 is currently being evaluated as a continuous intravenous (IV) infusion for prevention of chronic lung disease, including bronchopulmonary dysplasia (BPD), and other complications of premature birth.

Please refer to the current edition of the investigator's brochure (IB) for further information concerning the safety and clinical development of SHP607.

1.1 Indication and Current Treatment Options

Extremely premature infants are at very high risk for developing morbidities such as BPD, intraventricular hemorrhage (IVH), and retinopathy of prematurity (ROP), often resulting in delayed mortality or long-term disabilities. In fact, a simple count of the number of comorbidities in preterm infants with extremely low birth weight (BPD, IVH, and ROP) has been shown to strongly predict the risk of later death or neurocognitive impairment (Farooqi et al., 2011; Schmidt et al., 2003; Schmidt et al., 2015; Koo et al., 2010). In a retrospective analysis of 12,050 extremely preterm infants in the US, the frequent co-occurrence of these 3 morbidities is associated with an incremental increase in mortality, readmissions, length of hospital stay and costs (Mowitz et al., 2017). Although the survival rates have greatly improved in recent years for infants of borderline viability, these infants remain at risk of developing a wide array of neonatal and long-term complications (Saigal and Doyle, 2008).

When preterm infants are deprived of their natural intrauterine environment they lose important factors normally found in utero, such as proteins, growth factors, and cytokines. It has been demonstrated that IGF-1 is one such factor that is introduced through placental absorption or ingestion from amniotic fluid. Thus, agents such as IGF-1 that promote organ development and drive growth in extremely preterm infants have the potential to address multiple complications of prematurity (Hellstrom et al., 2016).

1.1.1 Bronchopulmonary Dysplasia and Long-Term Respiratory Complications

Bronchopulmonary dysplasia is a chronic lung disorder that is among the most common morbidities of preterm birth with an increased incidence with lower gestational age (GA) and birth weight, affecting at least one-quarter of infants born with weights <1500 g (Van Marter, 2009; Stoll et al., 2015). Although the definition of BPD has evolved over time, it is generally classified based on the requirement of oxygen, continuous positive airway pressure, and mechanical ventilation according to criteria established by the National Institute of Child Health and Human Development (NICHD) (Ehrenkranz et al., 2005; Walsh et al., 2003; Walsh et al., 2004; Pryhuber et al., 2015). Poor postnatal growth in preterm infants contributes to the multifactorial etiology of BPD (Lofqvist et al., 2012).

With advances in neonatal management, the current form of BPD is typically seen in neonates surviving at the threshold of viability and is characterized primarily by arrest of alveolar and vascular development (Iyengar and Davis, 2015).

Studies have been published demonstrating a critical role for IGF-1 in the regulation of prenatal lung development. Bronchopulmonary dysplasia in preterm infants, which is characterized by pulmonary immaturity, undifferentiated alveoli with the presence of hyaline membrane and atelectasis, dilated capillaries immersed in the mesenchyme, and a distorted deposition of the extracellular matrix is correspondingly modeled by the prenatal lung phenotype of IGF-1 knockout mice (IGF-1 -/-) (Pais et al., 2013). Treatment of IGF-1 -/- prenatal lung explants with recombinant IGF-1 induced alveolar morphogenesis, further supporting the idea that IGF-1 induces prenatal lung maturation. Furthermore, IGF-1 levels were found to be significantly lower in the first weeks after birth of preterm infants who develop BPD compared with infants without BPD (Lofqvist et al., 2012; Beardsall et al., 2014).

A number of therapies such as corticosteroids and diuretics are used in the management of BPD in clinical practice; however, there is insufficient evidence supporting the use of many of these agents and no single therapy has been shown to have a significant impact on the incidence or severity of BPD (Iyengar and Davis, 2015). The majority of the drugs studied in randomized, controlled studies failed to reduce the incidence of BPD. No pharmacologic therapies are currently indicated for the prevention or treatment of BPD. IGF-1 was recognized as one of the potential novel therapies for BPD during the recent NICHD Workshop on BPD (Higgins et al., 2018).

Chronic respiratory morbidity (CRM) after discharge from the Neonatal Intensive Care Unit (NICU) is a common adverse outcome of premature birth resulting in recurrent respiratory symptoms requiring treatment with pulmonary medications such as bronchodilators, need for supplementary home oxygen, frequent emergency room visits or hospital readmissions, especially during the first 2 years of life (Ali and Greenough, 2012). However, there is currently insufficient or conflicting evidence that the use of oxygen at term equivalence consistently predicts the later development of CLD in children born extremely premature. Extremely preterm infants diagnosed with BPD often continue to live with impaired lung or respiratory function after discharge from neonatal intensive care and put additional burden on health care systems with increased use of direct and indirect medical care that persists into infancy, school-age, adolescence, and possibly adulthood (Bhandari and McGrath-Morrow, 2013). The Prematurity and Respiratory Outcomes Program (PROP) study showed that 46-69% of extremely preterm infants had persistent respiratory morbidity, based on assessment of factors such as hospitalization, home support, and medications (Keller et al., 2017). Their lung function abnormalities may further increase their susceptibility for chronic obstructive pulmonary disease as they age (Filippone et al., 2009; Fakhoury et al., 2010; Fawke et al., 2010; Bhandari and McGrath-Morrow, 2013).

1.1.2 Intraventricular Hemorrhage

Intraventricular hemorrhage is estimated to occur in 20-25% of preterm infants with very low birth weight (<1500 g) in the US and is characterized initially by hemorrhage into the germinal matrix tissues of the developing brain (McCrea and Ment, 2008).

In the US between 1993 and 2012, 29,883 infants born at GA 22 through 28 weeks were diagnosed with severe intracranial hemorrhage, a mean of 1,494 infants per year (Stoll et al., 2015). Intraventricular hemorrhage has been attributed to fluctuations in cerebral blood flow to the immature germinal matrix microvasculature and secondary periventricular venous infarction. Approximately 80% of cases of IVH in preterm infants occur by 72 hours after birth with a considerable proportion occurring within a few hours of birth (Levene et al., 1982; Al-Abdi and Al-Aamri, 2014). The most common short-term outcomes associated with IVH are hydrocephalus and periventricular leukomalacia (McCrea and Ment, 2008). Intraventricular hemorrhage is associated with substantial mortality and morbidity and may result in long-term neurodevelopmental impairments (McCrea and Ment, 2008; Bolisetty et al., 2014; Klebermass-Schrehof et al., 2012; Horsch et al., 2005; Mukerji et al., 2015).

Studies have been published demonstrating a critical role for IGF-1 in prenatal neural development. IGF-1 is known to stimulate proliferation of progenitors that become neurons, oligodendrocytes, and astroglia (D'Ercole et al., 2002). In addition, IGF-1 augments neuron and oligodendrocyte survival and promotes differentiation, synaptogenesis, and myelination (Bondy and Cheng, 2004). Gene expression of IGF-1 in the prenatal rat brain displays distinct developmental patterns in different regions of the brain, supporting the idea that IGF-1 has a clear role in prenatal brain development (Bach et al., 1991). The phenotype of IGF-1 gene defect is characterized by low cranial circumference and the presence of microcephaly and developmental delay (Netchine et al., 2011). Increased levels of circulating IGF-1 in preterm infants are also correlated with increased brain volume and a decreased risk for subnormal developmental outcomes by 2 years of age (Hansen-Pupp et al., 2013). IGF-1 has important trophic effects and enhances barrier function by increasing expression of tight junction proteins in various organs, including the gut and lung, and may have a similar effect on the germinal matrix vascular bed (Dong et al., 2014; Drucker et al., 1997; Sabnis et al., 2015; Tian et al., 2010; Yan et al., 2016). Taken together, these observations demonstrate that the integrity of IGF-1 signaling is important for proper growth and development of the brain.

Ongoing preclinical studies utilize a rabbit pup model of IVH (Georgiadis et al., 2008; Gram et al., 2013) to assess the role of the IGF-1 system in the development of rabbit brain vasculature and whether exogenous IGF-1 can decrease the incidence of IVH.

Currently, the most effective option for prevention of IVH is antenatal glucocorticoids (Ballabh, 2014). Upon detection of IVH, treatment is generally focused on managing sequelae and other systemic factors that may influence further progression (McCrea and Ment, 2008; Ballabh, 2014). There is currently no approved treatment for IVH in extremely premature infants.Despite advances in neonatal care, the incidence of IVH among extremely preterm infants remains substantial, with limited treatment options once IVH is detected. Thus, there is a significant need for more effective preventive therapies.

1.1.3 Retinopathy of Prematurity

Retinopathy of prematurity is a major cause of blindness in children in the developed and developing world, despite current treatment of late-stage ROP (Silverman, 1980). As developing countries provide more neonatal and maternal intensive care, the incidence of ROP has increased.

Although ablation treatment, such as laser photocoagulation or cryotherapy of the retina reduces the incidence of blindness in those with late-stage disease, the visual outcomes after treatment are often poor (Good et al., 2010).

Retinal blood vessel development begins during the fourth month of gestation and is not completed until term (Foos and Kopelow, 1973; Roth, 1977). Therefore, infants born prematurely have incompletely vascularized retinas, with a peripheral avascular zone, the area of which depends on the GA. With maturation of the infant, the resulting nonvascularized retina becomes increasingly metabolically active and hypoxic. The hypoxia-induced retinal neovascularization phase of ROP is similar to other proliferative retinopathies, such as diabetic retinopathy.

IGF-1 is critical for the normal development of retinal vessels (Hellstrom et al., 2001). After preterm delivery, IGF-1 levels rapidly fall below in utero levels. IGF-1 is critical to normal retinal vascular development and lack of IGF-1 in the early neonatal period is associated with lack of vascular growth and with subsequent proliferative ROP. In IGF-1 -/- mice, normal retinal vascular development was examined to determine whether IGF-1 is critical to normal blood vessel growth. Retinal blood vessels grow more slowly in IGF-1 -/- mice than in normal mice, a pattern very similar to that seen in preterm infants with ROP. These observations were confirmed in patients with ROP (Hellstrom et al., 2001; Hellstrom et al., 2003).

In a prospective, longitudinal study measuring serum IGF-1 concentrations weekly in 84 premature infants, the mean serum IGF-1 ±standard error of the mean (SEM) level during postmenstrual age (PMA) 30 to 33 weeks was lowest in those with severe ROP (25 ±2.41 µg/L), higher in those with moderate ROP (29 ±1.76 µg/L), and highest in those with no ROP (33 ±1.72 µg/L). The duration of low IGF-1 also correlated strongly with the severity of ROP. The interval from birth until serum IGF-1 levels reached >33 µg/L was 52 ±7.5 days for severe ROP, 44 ±4.8 days for moderate ROP, and 23 ±2.6 days for no ROP. Each adjusted stepwise increase of 5 µg/L in mean IGF-1 during PMA 30 to 33 weeks decreased the risk of proliferative ROP by 45% (Hellstrom et al., 2003). These findings suggest the possibility that replacement therapy with rhIGF-1 to restore IGF-1 to intrauterine levels might prevent morbidity by allowing normal vascular and neural development (Hellstrom et al., 2016).

1.1.4 Other Complications of Prematurity

Extremely premature infants have recognized instability in glycemic control that includes both hypoglycemia (Lubchenco and Bard, 1971; Wybregt et al., 1964) and hyperglycemia (Dweck and Cassady, 1974) events throughout their clinical course.

In addition, extremely premature infants experience extrauterine growth restriction as assessed by body weight, body length, and head circumference (Laron et al., 1992). These infants are at higher risk of later growth failure in their early childhood and long-term consequences (Farooqi et al., 2011).

1.2 Product Background and Clinical Information

SHP607 is the recombinant protein complex of IGF-1 and its most abundant binding protein, IGFBP-3. In animal studies, SHP607 displays metabolic activities similar to those observed with rhIGF-1.

In healthy individuals, IGF-1 is constantly present in the bloodstream. In the circulation, IGF-1 is generally bound to one of several IGF binding proteins. The predominant circulating IGF binding protein is IGFBP-3. The binary complex of IGF-1/IGFBP-3 commonly forms a 150 kD ternary complex with a third circulating protein, acid-labile subunit (ALS). The vast majority of circulating IGF-1 exists in the form of this ternary complex. The estimated terminal elimination half-life ($t_{1/2}$) of the ternary complex is >12 hours compared with <15 minutes for free IGF-1. Because of its molecular size, the ternary complex is restricted to the circulation by the capillary endothelium and therefore serves as a circulating reservoir of IGF-1 with a long $t_{1/2}$. However, in preterm infants, ALS is not produced or is produced in very low quantities; thus, the ternary complex is not formed in preterm infants. As a result of this lack of ternary complex formation, a different pharmacokinetic (PK) profile of SHP607 has been shown in preterm infants than that seen in children and adults (Lofqvist et al., 2009); $t_{1/2}$ is markedly shortened to <1 hour.

IGF-1 elicits many of the physiological effects of insulin, which are mediated through specific cell surface receptors (Massague and Czech, 1982). IGF-1 is a small polypeptide with structural and functional homology to proinsulin. In addition to inducing insulin-like effects, IGF-1 also promotes cell division, growth and differentiation in most tissues.

Unlike many other growth factors, IGF-1 is relatively abundant in the bloodstream and exists in the serum largely in an inactive state, bound to specific carrier proteins, which serve to regulate its distribution and biological activity. Circulating levels of IGF-1 can be influenced by a number of factors, including growth hormone (GH), insulin, and nutritional status (Frystyk et al., 1999). Although the liver is considered the major site of synthesis of circulating IGF-1, virtually all tissues produce some IGF-1.

To date, 2 main classes of carrier proteins have been identified. Six variants of the IGF binding proteins (IGFBP-1-6) comprise the first class. ALS constitutes the second class. IGFBP-3 is the most abundant binding protein in the circulation and sequentially binds both IGF-1 and ALS to form a large ternary complex (Rosenfeld et al., 1990). All 3 components of the ternary complex are largely GH dependent. Unlike free IGF-1, which can readily cross the vascular endothelium, the molecular size of the ternary complex restricts IGF-1 to the circulation and increases IGF-1 $t_{1/2}$ from <15 minutes to >12 hours. IGFBP-3 influences the availability of IGF-1 by allowing IGF-1 to be slowly released for receptor interactions thus protecting receptors from down regulation by high IGF-1 exposure (Grimberg, 2000). The circulating reservoir of IGF-1 can facilitate endocrine actions and minimize the potential risk of acute, serious insulin-like effects that can be associated with supraphysiological exposure to free IGF-1 (Rosenfeld et al., 1990; Binoux and Hossenlopp, 1988; Martin and Baxter, 1992; Baxter and Martin, 1989; Zapf et al., 1995; Boisclair et al., 2001).

Many different effects have been observed upon administration of rhIGF-1 in animals and humans. These include promotion of linear growth (Laron et al., 1992), anabolic effects including enhanced wound healing (Froesch et al., 1985; Sommer et al., 1991), promotion of bone formation (Bagi et al., 1995), changes in body composition and muscle function (Vlachopapadopoulou et al., 1995), stimulation of lymphopoiesis (Clark et al., 1996), modified glucose metabolism and improved insulin sensitivity (Vlachopapadopoulou et al., 1995; Guler et al., 1987; Thrailkill et al., 1999), motor neuron survival and sprouting (Caroni and Grandes, 1990; Lewis et al., 1993), increased creatinine clearance (Guler et al., 1989), and recovery of renal function following ischemic injury (Ding et al., 1993).

In published clinical studies using rhIGF-1 administered without rhIGFBP-3, reported side effects have included hypoglycemia (Wilton, 1992); syncopal reactions in the absence of hypoglycemia, dizziness, seizure-like activity, bradycardia and asystole, and hypotension (Vlachopapadopoulou et al., 1995; Malozowski et al., 1994); intracranial hypertension and papilledema (Malozowski et al., 1993); cranial nerve palsy, and acute symptomatic hypophosphatemia (Usala et al., 1994); edema, parotid discomfort, jaw pain, arthralgia, myalgia, fatigue, tachycardia, flushing, orthostatic hypotension, headache, and dyspnea (Vlachopapadopoulou et al., 1995; Jabri et al., 1994; Bondy et al., 1994). In addition, injection site reactions, tonsillar and adenoid hypertrophy sometimes resulting in tonsillectomy/adenoidectomy, middle ear effusion, and hearing loss have occasionally been reported with administration of rhIGF-1 (Ranke et al., 1999; Ranke et al., 1995; Ehrnebo, 1998, Chernausek et al., 2004). Laboratory measurement abnormalities included hypoglycemia, anemia, hypokalemia, IGF-1 antibodies, and abnormal liver function tests (Ehrnebo, 1998; Guevara-Aguirre et al., 1995). Although most of the above adverse events (AEs) have not yet been observed in studies of SHP607, it is possible that these events might occur with SHP607 therapy.

1.2.1 Nonclinical Information

Appropriate PK, toxicokinetic, biodistribution, and toxicology studies have been performed in rats and monkeys, the 2 species used for nonclinical toxicology testing. In rats and monkeys, PK studies with SHP607, as compared to those with either rhIGF-1 or rhIGFBP-3 administered as single agents, demonstrated increased exposure to IGF-1 with the complex when compared to exposure obtained with either of the single proteins and were correspondingly associated with reduced clearance rate with the complex. These findings can be attributed to the ability of the SHP607 complex to bind to ALS in the circulation, as evidenced by size exclusion chromatography results (Baxter, 1990). SHP607 is well absorbed following subcutaneous (SC) administration as noted in both rats and monkeys. Though distribution studies with SHP607 have not been conducted, studies using radiolabeled rhIGF-1 in mice have shown wide distribution of radioactivity to highly vascularized tissues including lung and cerebrospinal fluid.

The potential acute toxic effects of single-dose IV administration of SHP607 have been characterized in rats and monkeys. In the rat, doses up to 200 mg/kg were well tolerated, except for the expected pharmacologic decrease in serum glucose (200 mg/kg), and produced no signs of systemic toxicity. In monkeys, except for hypoglycemia, doses of 100 mg/kg were well tolerated. No other clinically significant adverse effects were noted.

Fourteen consecutive days of IV dosing in rats (up to 100 mg/kg/day) and monkeys (up to 25 mg/kg/day) were well tolerated and produced no signs of toxicity. Daily SC administration of SHP607 for 3 months to rats (up to 30 mg/kg/day) and monkeys (up to 10 mg/kg/day) was well tolerated and produced no signs of systemic toxicity. Expected pharmacologic effects of IGF-1 were noted in both species. An increase in the T-cell component of the thymus, spleen, and possible lymph nodes was observed in the rats and trace to mild lymphoid hyperplasia was observed in the monkeys. In a local tolerance study of SHP607, daily SC dosing of SHP607 for 14 days to rats produced a mild to moderate inflammatory reaction in the SC tissue, which was reversed upon cessation of dosing.

1.2.2 Clinical Experience with SHP607

Two clinical studies, ROPP-2005-01 and ROPP-2008-01, have been conducted with SHP607 in premature infants. A third study, SHP607-201, is being conducted to assess the long-term efficacy and safety outcomes of SHP607 versus standard neonatal care (no investigational product is being administered) in subjects randomized in Study ROPP-2008-01, Section D. A fourth study, Study SHP607-202, is described in the section below. Subjects enrolled in this study are eligible for participation in Study SHP607-203.

In the Phase 1 Study ROPP-2005-01 in preterm infants, administration of SHP607 during a 3-hour infusion increased the serum concentrations of IGF-1 at the postnatal age of 3 days and no safety concerns were seen in the study. At postnatal age of 3 days (mean weight [range]: 973 g [760-1220 g]), 5 subjects were each administered an IV infusion of SHP607 in a dose of 6, 24, 33, 33, or 59 µg/kg/3 hours, containing 21% IGF-1 by weight. The doses were calculated based on the birth weight, but were administered on Day 3, the day the PK samples were drawn, and thus are expressed as the dose/kg based on the infant weight at Day 3. In this Phase 1 study, the calculated $t_{1/2}$ was 0.86 hours for a typical subject of 1 kg. The doses provided to these preterm infants were considerably lower than those studied in other SHP607 studies where the SHP607 was administered by the IV and SC routes to healthy human volunteers at doses up to 6 mg/kg/day without serious adverse events (SAEs). In these other Phase 1 studies, the maximum tolerated single IV dose administered intravenously was determined to be 3.0 mg/kg. SHP607 was well-tolerated at doses up to 2.0 mg/kg/day by SC injection.

The Phase 2 Study ROPP-2008-01 in preterm infants was designed in 4 sections (Sections A, B, C, and D). In Sections A, B and C, the dosing of SHP607 was highly individualized based upon an algorithm and required both a significant level of investigator oversight and frequent serum IGF-1 measures. Subjects in Study Section A received infusion of SHP607 for 7 days and subjects in Study Sections B and C were randomly assigned to treatment with SHP607 or to receive standard neonatal care. After a thorough review of the data from Study ROPP-2005-01, Study ROPP -2008-01 (Sections A, B and C), population PK modeling, and from the literature, a standardized dose was selected for use in Section D. Subjects in Study ROPP-2008-01 Section D received a continuous infusion of 250 µg/kg of SHP607 administered over 24 hours to keep the levels of IGF-1 within the normal intrauterine range for corresponding GA from Study Day 0 up to and including maximum PMA 29 weeks +6 days. Clinical activities for all 4 sections are complete and safety, dosing, and PK results have been reviewed (see the IB).

Study ROPP-2008-01 did not meet the primary endpoint in reducing severity of ROP; however, positive trends were observed in secondary endpoints related to BPD and IVH. For BPD, a nominally statistically significant shift was observed in the distribution of severity of BPD. This was most evident in the difference between the groups in the percentage of subjects with severe BPD: 10 subjects (21.28%) in the SHP607 group and 22 subjects (44.90%) in the Standard of Care group.

Although there were no statistically significant differences in IVH between the 2 groups, numerically the results favored the SHP607 group (13.1% in the treated vs 23.3% in the Standard of Care group with Grade 3 or 4). Upon review of data from the Safety Analysis Set of subjects treated with SHP607 in Sections A, B, and C (n=14) and in Section D (n=61), there were no newly identified risks and no important changes to the previous knowledge of safety for SHP607 that would impact the risk-benefit profile. Overall, the results of ROPP-2008-01 support the continued evaluation of SHP607 for the treatment of complications of premature birth at both the current dose and a higher dose, 400 µg/kg/24 hours. The high dose of 400 µg/kg/24 hours was chosen following modeling and simulation of IGF-1 levels in pre-term infants and is expected to result in concentrations within the upper bound of the 28-109 µg/L target range over the infusion duration.

SHP607-201 is a Phase 2, multicenter, long-term developmental outcome study enrolling subjects who were randomized in Section D of Study ROPP-2008-01 to receive either SHP607 (treated) or standard neonatal care (control). Enrolled subjects in this study will be followed through age 5 years corrected age (CA), with assessments that include measures of pulmonary morbidity and neurocognitive development.

Always refer to the latest version of the SHP607 IB for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, PK, efficacy, and safety of SHP607.

1.3 Study Rationale

Despite significant advances in care over the past 20 years, extremely premature infants remain at very high risk for developing morbidities that affect multiple organ systems and often result in delayed mortality or long-term disabilities. Additional therapeutic and preventive options are very much needed to continue progress in the care of extremely preterm infants. Therapeutic agents such as SHP607 that activate pathways with positive impact on organ development and drive growth in extremely preterm infants have the potential to address multiple complications of prematurity such as BPD, ultimately translating into healthier infants with fewer or less severe morbidities and improved outcomes.

Analysis of the Phase 2 Section D data showed that higher IGF-1 levels may have the potential to be associated with greater efficacy and scaled PK simulation models showed the exposure can be further improved by elevating the dose. Subjects with severe BPD were found to have significantly lower serum IGF-1 levels than subjects with no BPD. Similar trends were observed when comparing those with more severe stages of ROP to those without ROP. For IVH, there was an indication that the impact of IGF-1 may occur early in the course of the illness.

For safety reasons, the previously studied dose of 250 µg/kg/24 hours targeted the lower bound of the physiologic range. The PK model predicted that administration of this dose would result in a small proportion of subjects with serum IGF-1 that was below target level (<28 µg/L). This prediction was borne out in the observed study results. The updated PK model, which incorporated the Phase 2 Section D data, projects that at a dose of 400 µg/kg/24 hours, the resulting serum IGF-1 level should remain within the upper bound of the 28-109 µg/L target range, while the potential for under-dosing or overdosing will be minimal.

Study SHP607-202 is a Phase 2b, multicenter, randomized, open-label, controlled, 3-arm study that is being initiated to evaluate the clinical efficacy and safety of SHP607 in preventing chronic lung disease through 12 months CA compared to standard neonatal care in extremely premature infants. Approximately 477 subjects with GA of 23 weeks +0 days to 27 weeks +6 days will be randomized in a 1:1:1 ratio to receive either SHP607 at 250 µg/kg/24 hours, SHP607 at 400 µg/kg/24 hours, or standard neonatal care alone. Subjects randomly assigned to treatment will receive continuous IV infusion of study drug commencing within 24 hours of birth, once all baseline assessments have been completed. The infusion of study drug will continue to PMA 29 weeks +6 days. The primary objective of the study is to assess the effect of SHP607 on reducing the burden of CLD, as indicated by a reduction in time to final weaning off respiratory technology support (RTS) through 12 months CA, as compared to a standard neonatal care group.

Study SHP607-202 will evaluate the clinical efficacy and safety of SHP607 in preventing chronic lung disease through 12 months CA compared to standard neonatal care in extremely premature infants. Although treatment with SHP607 in Study SHP607-202 represents a short-term exposure (<2 months for each subject), SHP607 may have long-lasting effects on respiratory outcomes as well as other potential outcomes related to complications of prematurity such as neurodevelopment, vision, and growth impairments. In addition, it is critical to understand any long-term safety effects from short-term exposure to SHP607. The purpose of Study SHP607-203 is to evaluate the long-term safety and efficacy outcomes in subjects who received short-term treatment with SHP607 in Study SHP607-202.

The assessment tools used in this study will be different from those used in Study SHP607-202, given the changes in physical and cognitive development that will occur in the subjects as they age during their participation in this study.

1.4 Benefit/Risk Assessment

Always refer to the latest version of the SHP607 IB for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, pharmacokinetics, efficacy, and safety of SHP607.

1.5 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, 1996; E6 R2, 2017), Title 21 of the US Code of Federal Regulations (US CFR), the EU Directives (2001/20/EC; 2005/28/EC), and applicable national and local regulatory requirements.

The responsibilities of the study sponsor and investigator(s) are described fully in Section 10.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Study Objectives

2.1.1 Primary Objectives

The primary objectives of this 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 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.

2.1.2 Secondary Objectives

The secondary objectives of this 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

2.1.3 Exploratory Objectives

The exploratory objectives of this 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. STUDY DESIGN

3.1 Study Design and Flow Chart

This is a Phase 2b, multicenter, long-term outcomes study of subjects who were randomized in Study SHP607-202 to either treatment (received SHP607) or control (received standard neonatal care) groups. Subjects will be followed from 12 months CA through 5 years CA. Subjects will not be excluded from participating in other clinical studies. No investigational product will be administered in this study.

Approximately 477 subjects who previously received SHP607 or standard neonatal care in Study SHP607-202 are planned to be enrolled in Study SHP607-203. Although all subjects randomized into the primary Study SHP607-202 (approximately 477) are eligible to enroll in Study SHP607 203, the actual number of subjects enrolled will more closely approximate the number of subjects who complete Study SHP607-202. No investigational product will be administered in Study SHP607-203. A total of approximately 382 subjects (approximately 127 subjects randomized to SHP607 250 µg/kg/24 hours, approximately 127 subjects randomized to SHP607 400 µg/kg/24 hours, and approximately 127 subjects randomized to standard neonatal care) are expected to complete Study SHP607-202. At 12 months CA, subjects will be eligible to enroll into the long-term outcome Study SHP607-203.

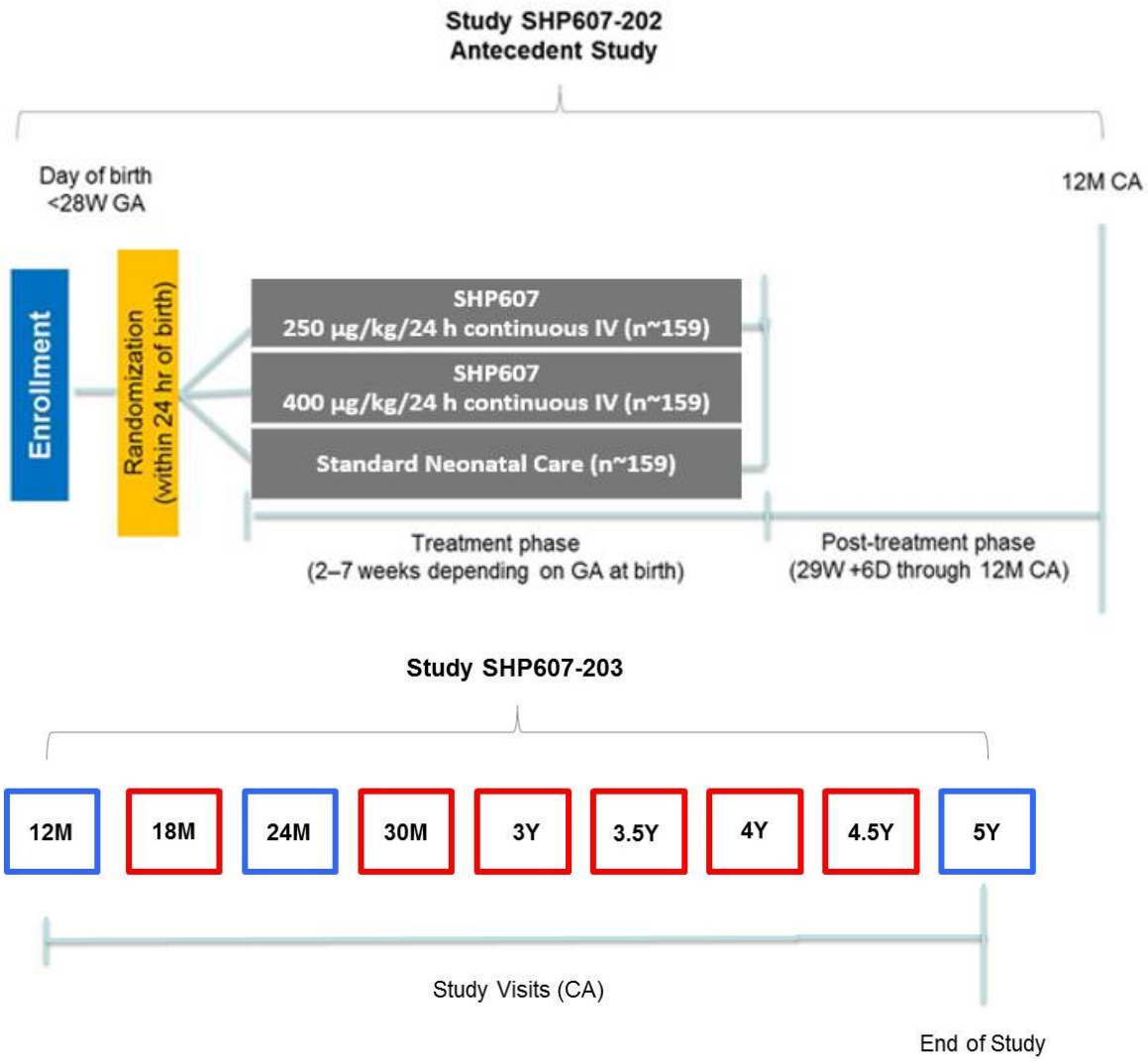
For subjects who complete the primary Study SHP607-202, the initial visit in Study SHP607-203 should coincide with the final visit of Study SHP607-202 at 12 months CA +2 weeks. If the initial visit in Study SHP607-203 does not occur at the 12-month CA visit, the subject may still be enrolled until 24 months CA +6 weeks. Subjects enrolling between the 12 months CA visit and the 24 months CA visit should complete all 12-month CA assessments, and vision and hearing assessment history. Subjects enrolling at the 24 months CA visit should complete informed consent, eligibility criteria, demographics, medical history, and all 24 months CA assessments. Subjects are no longer eligible to enroll in this study after 24 months CA +6 weeks. Completion of Study SHP607-202 is not required for enrollment into Study SHP607-203.

CRM will be assessed using pulmonary questionnaires, which will be administered to the parents or legally authorized representative(s) at regularly scheduled clinical site visits and telephone interviews through 5 years CA. Physical examinations (including tonsil examinations) will be performed at 12 months, 24 months, and 5 years CA. Additionally, AEs will be assessed to evaluate the long-term safety of SHP607.

Time points for assessments have been chosen to represent important developmental ages for premature infant follow-up. Both telephone and clinical site visits are included to minimize burden on families while maintaining contact with subjects throughout the 5-year duration of the study.

The study designs are presented in Figure 1 and the Schedule of Assessments is presented in Table 1.

Figure 1 Study Design Flow Diagram



CA=corrected age; D=days; GA=gestational age; IV=intravenous; M=months; PMA=postmenstrual age; W=weeks
Visits conducted at the study site are indicated in blue. Visits conducted by telephone are indicated in red. Visit windows are provided in the Schedule of Events (Table 1). After the last subject in the primary Study SHP607-202 has completed the last study visit, an interim analysis for Study SHP607-203 will be performed for all enrolled subjects who have either completed the 24 months CA visit assessments or prematurely withdrawn from Study SHP607-203, and after all associated data has been entered into the database with queries and discrepancies resolved

3.2 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 4 years. The study will be completed in approximately 8 years.

The Study Completion Date is defined as the date on which the last subject in the study completes the final protocol-defined assessment(s). This includes the follow-up visit or contact, whichever is later (refer to Section 7.1.2 for the defined follow-up period for this protocol).

3.3 Sites and Regions

The study will be conducted at approximately 60 sites including, but not limited to, countries in the following regions: North America, Europe, and Asia Pacific (APAC).

4. STUDY POPULATION

Subjects who previously received SHP607 or standard neonatal care in Study SHP607-202 are planned to be enrolled in Study SHP607-203. Subjects in Study SHP607-202 are premature infants (GA of 23 weeks +0 days to 27 weeks +6 days) who are randomized to receive either treatment with SHP607 at 250 ug/kg/day or 400 ug/kg/day, or standard neonatal care.

Each subject's parent(s) or legally authorized representative(s) must participate in the informed consent process and provide written informed consent and/or assent before any procedures specified in the protocol are performed.

4.1 Inclusion Criteria

Subjects must meet all of the criteria below.

1. Subject was randomized into Study SHP607-202. Subjects who were randomized, but did not complete Study SHP607-202 must be at least 12 months CA.
2. Written informed consents (and assents, if applicable) must be signed and dated by the subject's parent(s)/legally authorized representative(s) prior to any study-related procedures. The informed consent and any assents for underage parents must be approved by the institutional review board (IRB)/independent ethics committee (IEC).

4.2 Exclusion Criterion

Subjects are excluded from the study if the subject or subject’s parent(s)/legally authorized representative(s) is/are unable to comply with the protocol or is/are unlikely to be available for long-term follow-up as determined by the investigator.

4.3 Discontinuation of Subjects

A parent or legally authorized representative may withdraw the subject from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject with the medical monitor when possible.

4.3.1 Reasons for Discontinuation

The reason for withdrawal must be determined by the investigator and recorded in the subject’s medical record and on the case report form (CRF). If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the CRF.

Reasons for discontinuation include, but are not limited to:

- Adverse event
- Protocol deviation
- Lost to follow-up
- Withdrawal by parent/legally authorized representative
- Physician decision
- Other

Discontinuations due to AEs and protocol deviations should be reviewed in advance with the medical monitor, if possible.

Subjects withdrawn from the study for an SAE should be followed until the SAE has resolved. Appropriate supportive and/or definitive therapy should be administered as required.

4.3.2 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact the parent(s)/legally authorized representative(s) of any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations.

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Treatment

Not applicable as no investigational product will be administered in this study.

5.2 Concomitant Treatment and Medications

Medications, procedures, and therapies administered to study subjects from the time of informed consent through the 5 year CA visit (or until the subject is withdrawn or discontinued) will be collected, **only in the context of SAEs**. In addition, respiratory medications (and medications that may be associated with respiratory conditions) will be captured in the pulmonary morbidity assessment (Section 7.2.5.1), along with respiratory therapies. Any investigational products, procedures, and therapies received by subjects in other clinical studies will be recorded separately as part of an assessment of subjects' participation in other clinical studies (Section 7.2.9).

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

Not applicable as no investigational product will be administered in this study.

6.2 Administration of Investigational Product

Not applicable.

6.3 Labeling, Packaging, Storage, and Handling

Not applicable.

7. STUDY PROCEDURES

7.1 Study Schedule

See Table 1 for study procedures. The timing of all study visits is based on subjects' CA.

Although Study SHP607-202 is open-label, measures will be instituted in Study SHP607-203 to blind selected site personnel who are involved in efficacy assessments in order to minimize bias in study outcomes. Site personnel who administer the following study assessments will be blinded to the treatment status of each subject: BSID, KSPD, WPPSI, GMFM-88, spirometry, and MRI. Families will be instructed not to discuss treatment assignment with the assessors. The assessors will not be part of the study team or participate in study team meetings. The Sponsor will work with each site to clarify the process for blinding and each site will document the manner in which blinding will be maintained at the site.

7.1.1 Initial Study Visit (12 Months CA)

In general, the initial visit in Study SHP607-203 should coincide with the final visit of the primary Study SHP607-202 at 12 months CA +2 weeks.

At the initial visit, informed consent will be obtained followed by an assessment of study eligibility criteria and collection of demographic data. Additionally, the following assessments will be conducted:

- Medical history
- Body weight and length
- Head circumference
- Physical examination
- Blood pressure, heart rate, and respiratory rate
- Caregiver Impact Questionnaire (CIQ)
- Pulmonary morbidity assessment (only for subjects who did not complete Study SHP607-202)
- Health care resource use
- Assessment of participation in other clinical studies
- Medications, procedures, and therapies
- Adverse events, including targeted medical events (refer to Section 8.1).

Results of previously completed vision and hearing assessments, if performed, may be recorded at any time during the study up to the 5-year CA visit.

7.1.2 Study Visits

Study visits will take place at the following time points in CA:

- 18 months (±6 weeks); conducted by telephone
- 24 months (±6 weeks); clinical site visit
- 30 months (±6 weeks); conducted by telephone
- 3 years (±6 weeks); conducted by telephone
- 3.5 years (±6 weeks); conducted by telephone
- 4 years (±6 weeks); conducted by telephone
- 4.5 years (±6 weeks); conducted by telephone
- 5 years (±6 weeks); clinical site visit

The activities at the study visits are described in Section 7.1.2.1 and Section 7.1.2.2.

7.1.2.1 Assessments Conducted by Telephone

Visits at 18 months, 30 months, 3 years, 3.5 years, 4 years, and 4.5 years CA will be conducted by telephone. The following assessments will be conducted at each of these 6 visits, unless otherwise indicated:

- Pulmonary morbidity assessment
- Pediatric Quality of Life Inventory (PedsQL™) (3-year and 4-year visits)
- EQ-5D-5L (3-year and 4-year visits)
- Health care resource use
- Assessment of participation in other clinical studies
- Medications, procedures, and therapies
- Adverse events, including targeted medical events

Results of previously completed vision and hearing assessments, if performed, may be recorded at any time during the study up to the 5-year CA visit.

7.1.2.2 Assessments Conducted at Clinical Site Visits

Visits at 24 months and 5 years CA will be conducted at clinical site visits. The following assessments will occur at these visits:

- 24 months (±6 weeks)
  - Body weight and height/length
  - Head circumference

  - Bayley Scales of Infant and Toddler Development (BSID) (or Kyoto Scale of Psychological Development [KSPD])
  - Gross Motor Function Measure (GMFM-88)
  - Vineland Adaptive Behavior Scales (VABS)
  - Physical examination
  - Blood pressure, heart rate, and respiratory rate
  - Vision and hearing assessment history
  - Pulmonary morbidity assessment
  - PedsQL
  - Health care resource use
  - CIQ
  - EQ-5D-5L
  - Assessment of participation in other clinical studies
  - Medications, procedures, and therapies
  - Adverse events, including targeted medical events
  - BabyScreen (optional)

- 5 years (±6 weeks)
  - Visual acuity
  - Body weight and height
  - Wechsler Preschool and Primary Scale of Intelligence (WPPSI)
  - Gross Motor Function Measure (GMFM-88) Section D (Standing) and Section E (Walking, Running and Jumping)
  - Vineland Adaptive Behavior Scales (VABS)
  - Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS)
  - Social Communication Questionnaire (SCQ)
  - Physical examination
  - Blood pressure, heart rate, and respiratory rate
  - Vision and hearing assessment history
  - Pulmonary morbidity assessment
  - PedsQL
  - Health care resource use
  - Health Utilities Index Mark 2 and Mark 3 (HUI2/3)

- Caregiver Impact Questionnaire (CIQ)
- Assessment of participation in other clinical studies
- Medications, procedures, and therapies
- Adverse events, including targeted medical events
- Spirometry (optional)
- Cerebral magnetic resonance imaging (optional)

If a subject discontinues participation in the study or the subject is discontinued by the investigator, reasonable efforts will be made to perform any end of study examinations if deemed clinically relevant in the opinion of the investigator.

7.1.3 Additional Care of Subjects after the Study

No aftercare is planned for this study.

7.2 Study Evaluations and Procedures

7.2.1 Informed Consent

Prior to conducting any study-related procedures, written informed consent must be obtained from the subject's parent(s) or legally authorized representative(s). Since the subjects cannot provide any information and decide for themselves, the parents or legally authorized representatives of the subjects will take full responsibility of information and any decisions on behalf of subjects.

The nature, scope, and possible consequences, including risks and benefits, of the study will be explained to the subject, the subject's parent(s), or the subject's legally authorized representative by the investigator or designee in accordance with the guidelines described in Section 10.3.1. Documentation and filing of informed consent documents should be completed according to Section 10.3.1.

7.2.2 Study Entrance Criteria

At the initial visit, each subject will be reviewed for eligibility against the study entrance criteria. Subjects who do not meet the study entrance criteria will not be allowed to participate in the study. The reason(s) for the subject's ineligibility for the study will be documented. No exemptions will be allowed.

If the initial visit in Study SHP607-203 does not occur at the 12 month CA visit, the subject may still be enrolled until 24 months CA +6 weeks. Subjects are no longer eligible to participate in this study after 24 months CA +6 weeks.

7.2.3 Study Enrollment

At the initial visit, subjects meeting study entrance criteria will be enrolled.

7.2.4 Demographic and Other Baseline Characteristics

Subject demographic information including sex, date of birth, and ethnicity will be recorded at the initial visit.

7.2.5 Efficacy

7.2.5.1 Pulmonary Morbidity Assessment

Pulmonary morbidity will be assessed through an interviewer-administered questionnaire at the clinical site at 12 months (only for subjects who did not complete Study SHP607-202), 24 months and 5 years CA and by telephone visits at 18 months, 30 months, 3 years, 3.5 years, 4 years, and 4.5 years CA.

The questionnaire will be administered to the subject's parent(s) or legally authorized representative(s), and includes 2 components:

1) Respiratory Conditions Assessment: Data collected includes emergency room visits and hospitalizations for respiratory diagnoses, medications required for respiratory diagnoses, respiratory-related home technology use, and wheezing/coughing episodes. This is completed every 6 months through 5 years CA.

2) Respiratory Risk Factors Assessment: Data collected include second-hand smoke exposure, pets, and vaccinations/prophylaxis. This is completed annually through 5 years CA.

7.2.5.2 Growth Parameters

Body Length and Height

Body length (supine measurement) will be collected at the 12 months and 24 months CA visit. For the length measurement, the subject will be placed on his or her back so that the subject is lying straight and the shoulders and buttocks are flat against the measuring surface. The subject's eyes should be looking straight up and care should be taken that the head is in a neutral position (neither being flexed nor extended at the neck). Both legs should be fully extended and the toes should be pointing upward with feet perpendicular to the measuring surface.

Height (standing measure) will be collected at the 5 years CA visit. A stadiometer should be utilized for measurement of height. The subject should remove shoes.

For the measurement of standing height, the child is instructed to stand erect (stand up straight and look straight ahead) with the child’s head positioned in a horizontal plane. The moveable headpiece is brought onto the upper most (superior) point on the head with sufficient pressure to compress the hair.

For height and length, 2 measures should take place and both will be recorded. If the 2 measures are discrepant by >2 cm, the measures should be repeated. All measures should be recorded in metric units and measurement should be recorded to the nearest tenth centimeter (0.1 cm).

Body Weight

Body weight will be collected. Calibrated scales should be utilized for body weight measures. Care should be taken to remove any extraneous clothing prior to measures and shoes should be removed. Body weight should be recorded to the nearest 0.2 lb/0.1 kg.

Head Circumference

Head circumference will be measured for all subjects. An accurate head circumference measurement is obtained with a "lasso"-type, non-stretchable measuring tape such as the Lasso-o tape. Head circumference or occipital frontal circumference is measured over the occiput and just above the supraorbital ridge, which is the largest circumference of the head.

7.2.5.3 Visual Acuity

Visual acuity is a measure of how well a subject sees at different distances. Measurements will be recorded for the left (OS), right (OD), and both eyes (OU). Visual acuity will be attempted at 5 years CA by the LEA Symbols Chart.

7.2.5.4 Vision and Hearing Assessment History

Results of previously completed vision and hearing assessments, if performed, may be recorded at any time during the study up to the 5 year CA visit. Visual acuity will be measured at 5 years CA (see Section 7.2.5.3), but hearing tests are not being performed as part of this study.

7.2.5.5 Cognitive and Behavioral Assessments

Bayley Scales of Infant and Toddler Development (BSID)

The BSID will be used to assess cognitive, motor, and language skills at the 24 months CA visit.

The BSID is an assessment tool designed to measure a young child's skills in the 5 domains of development: cognitive, language, motor, social emotional and adaptive behavior. The 2 language subscales (expressive and receptive) combine to make a total language score and the 2 motor subtests (fine and gross motor) form a combined motor scale.

The tool is engaging, with colorful props and visual stimuli that capture the attention of the child. The individual test items are short, limiting the amount of attention required for each item. The test administration is flexible in that items can be administered out of order, provided the assessor adheres to the specific guidelines in the Study Operations Manual.

The BSID will be administered to the subject, with participation of the subject's parent(s) or legally authorized representative(s), by a trained professional. Scores to be recorded are detailed in the Study Operations Manual.

Kyoto Scale of Psychological Development (KSPD)

As an alternative to the BSID, the KSPD may be used to assess cognitive, motor, and language skills at the 24 months CA visit.

The KSPD is a validated neurodevelopmental outcome assessment that is standardized for Japanese children (Kono et al., 2016; Tatsuta et al., 2013), and has been evaluated in comparison to BSID in the assessment of developmental characteristics of very low birth weight Japanese infants.

The KSPD is designed to measure a young child's skills in three domains of development: Cognitive-Adaptive (non-verbal reasoning or visuospatial perception), Language-Social (interpersonal relationships, socialization, verbal abilities), and Postural-Motor (fine and gross motor functions). Scores are converted into a developmental quotient that measures attainment of developmental age for the corrected age of the child.

The KSPD will be administered to the subject, with participation of the subject's parent(s) or legally authorized representative(s), by a trained professional. Scores to be recorded are detailed in the Study Operations Manual.

Wechsler Preschool and Primary Scale of Intelligence (WPPSI)

The WPPSI is a measure of general cognitive development in children that has components of both verbal and nonverbal tasks. It is applicable to preschoolers and young children aged 2 years +6 months to 7 years +7 months.

It is composed of the following 5 scales:

- Verbal
- Performance
- Processing Speed
- Full Scale
- Language

It not only applies to healthy children, but in the course of the scale's standardization special group validity studies were performed, including, but not limited to, groups of children with developmental risk factors, autistic disorder, and intellectual disability. Scores may be interpreted in the context of provided norms, which reflect inclusion of the special groups.

The WPPSI will be administered to the subject by a trained professional at 5 years CA. Scores to be recorded are detailed in the Study Operations Manual.

Gross Motor Function Measure-88 (GMFM)

The GMFM-88 will be used to measure motor function while lying and rolling, sitting, crawling and kneeling, standing, and walking, running and jumping. The test is considered to be appropriate for children whose motor skills are at or below those of a 5-year-old child without any motor disability (Russell et al., 1989).

The GMFM-88 will be administered to the subject by a trained professional at 24 months CA. GMFM-88 Section D (Standing) and Section E (Walking, Running and Jumping) only will be administered at 5 years CA. Scores to be recorded are detailed in the Study Operations Manual.

Vineland Adaptive Behavior Scales (VABS)

The VABS Expanded Interview Form will be used to measure the personal and social skills. These scales are organized into domains, including Communication, Daily Living, Socialization, and Motor Skills.

The VABS Expanded Interview Form will be completed by the subject's parent(s) or legally authorized representative(s) at 24 months CA and at 5 years CA/end of study. Scores to be recorded are detailed in the Study Operations Manual.

Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS)

The ADHD-RS was developed to measure the behaviors of children with attention-deficit hyperactivity disorder (ADHD). The ADHD-RS consists of 18 items designed to reflect current symptomatology of ADHD based on DSM-V criteria. Each item is scored from a range of 0 (reflecting no symptoms) to 3 (reflecting severe symptoms) with total scores ranging from 0-54.

The 18 items are grouped into 2 subscales: hyperactivity impulsivity (even numbered items 2-18) and inattention ("inattentiveness") (odd numbered items 1-17).

The ADHD-RS (DuPaul et al., 1998) will be completed by the subject's parent(s) or legally authorized representative(s) at 5 years CA. The investigator or designee should review the assessment for completeness and to confirm all responses. Scores to be recorded are detailed in the Study Operations Manual.

Social Communication Questionnaire – Lifetime Form

The SCQ is a brief instrument that helps evaluate communication skills and social functioning in children (Rutter et al., 2003) that can be used for screening for autism or autism spectrum disorders in the general population (Chandler et al., 2007).

The SCQ will be completed by the subject's parent(s) or legally authorized representative(s) at 5 years CA. The investigator or designee should review the assessment for completeness and to confirm all responses. Scores to be recorded are detailed in the Study Operations Manual.

7.2.5.6 Health Economic Outcome Research Assessments

Health-related quality of life (HRQoL) is an important measure of health status or well-being and can be influenced by clinical interventions. It is an important concept used in determining the value of health care services and can serve as a screening tool for identifying physical and psychosocial health concerns from the perspectives of both the child and parent (Matza et al., 2004; Varni et al., 2005). HRQoL is a multidimensional construct; minimally it includes physical, psychological (including emotional and cognitive), and social health dimensions.

Pediatric Quality of Life Inventory (PedsQL) Infant Scales

In this study, HRQoL will be assessed via the validated Pediatric Quality of Life Inventory (PedsQL) Infant Scales appropriate for the child's age of development (Varni and Limbers, 2009; Varni et al., 2011; Varni et al., 2001).

The following scales will be used in this study:

- Infant Scale for ages 13-24 months (45 Items)
- Toddler Scale for 2-4 years of age (21 Items)s
- Young Child Scale for 5-7 years of age (23 Items)

The PedsQL will be administered to the subject's parent(s) or legally authorized representative(s) and may be conducted via telephone by clinical site staff at the time points specified in the Schedule of Assessments (Table 1). The scale(s) to be administered at each visit will be specified in the Study Operations Manual.

EQ-5D-5L

The EQ-5D-5L is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol, 1990; Orgeta et al., 2015; Nolan et al., 2016). The EQ-5D-5L provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of healthcare as well as in population health surveys. It consists of a 5-item descriptive system that measures 5 dimensions of the health of the subject's parent(s), including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is represented by a single item with 5 levels of responses.

The EQ-5D-5L will be administered to the subject's parent(s) or legally authorized representative(s) by site personnel at 24 months CA, 3 years CA, and 4 years CA. Details about the use and administration of the EQ-5D-5L instrument will be provided in the Study Operations Manual.

Health Care Resource Use (HCRU)

To understand the value of the investigational product administered in Study SHP607-202, inpatient and outpatient visits, including visits to specialists, will be recorded at the time points specified in the Schedule of Assessments (Table 1). Learning support needs and impairment of caregiver productivity will also be assessed.

This assessment may be conducted in person at clinic visits or via telephone by clinical site staff.

Health Utilities Index (HUI)

The Health Utilities Index (HUI) is a family of generic health profiles and preference-based systems used for measuring health status, reporting HRQoL, and producing utility scores.

The HUI2/3 each include a generic comprehensive health status classification system and a generic HRQoL utility scoring system (Horsman et al., 2003). The HUI2/3 will be administered to the subject's parent(s) or legally authorized representative(s) and may be conducted in person at clinic visits or via telephone by clinical site staff at 5 years CA as specified in the Schedule of Assessments (Table 1).

Caregiver Impact Questionnaire (CIQ)

Caregiver burden will be assessed by the CIQ. The CIQ includes 30 items in total and covers the key areas of impact for caregivers, including: 1) impact on relationships, family, social life, and leisure activities; 2) impact on personal time and daily activities; 3) psychological impacts; 4) impact on physical health; and 5) impact on finances and productivity. Data will be collected and summarized descriptively. Results may also contribute to the recommended scoring for studies. The CIQ will be administered to the subject's parent(s) or legally authorized representative(s) and may be conducted via telephone by clinical site staff at the time points specified in the Schedule of Assessments (Table 1).

7.2.5.7 BabyScreen Assessment (Optional)

BabyScreen is an interactive electronic tablet application to evaluate cognitive impairment, used by preterm children at approximately 24 months CA. The tool is engaging, with colorful screens and visual prompts that capture the attention of the child and promote engagement and interaction. Instructions for the site are minimal. The child is encouraged to play with the tablet; no or minimal prompting is needed. This exploratory, optional assessment will be used for validation purposes only, benchmarked against BSID for future use. Participation is limited to selected sites.

7.2.5.8 Spirometry (Optional)

Spirometry will be performed at the 5-year visit. Standard measures will be collected, including forced expiratory volume over 1 second (FEV1) and forced vital capacity (FVC). Participation is optional and has no impact on participating in the main study. Participation is limited to selected sites that have access to personnel with expertise in performing pediatric spirometry.

7.2.6 Cerebral Magnetic Resonance Imaging (Optional)

Participation in the MRI assessment is optional, limited to sites that participated in the MRI assessment in Study SHP607-202, and has no impact on participating in the main study. If consented to, MRI of the brain will be performed.

Volumetric analyses of the cortical gray matter, cortical white matter, corpus callosum, frontal lobes, cerebellum, and total volume will be analyzed for the purposes of this study.

The nature, scope, risks, benefits, and potential sedation associated with the procedure will be explained to the subject and subject's parent(s) or legally authorized representative(s) by the investigator or a designated trained study personnel. Subject's parent(s) or legally authorized representative(s) will be asked to separately opt in or decline participation in this part of the study in the informed consent document.

7.2.7 Safety

7.2.7.1 Medical History

Medical events or conditions should only be captured as medical history if they occur after the end of the subject's participation in the primary Study SHP607-202 and before informed consent in the current Study SHP607-203.

7.2.7.2 Physical Examination

Physical examinations will include a general examination (including assessment of tonsillar hypertrophy) and a neurological examination (Table 2). Examinations will be performed at the time points specified in the Schedule of Assessments (Table 1).

Table 2 Assessments for Physical Examinations

General appearance	Cardiovascular
Head and neck	Abdomen
Eyes	Genitourinary
Ears	Skin
Nose	Musculoskeletal
Throat	Neurological
Tonsils	Cerebral palsy (24 months CA only)
Chest and lungs	

7.2.7.3 Blood Pressure, Heart Rate, and Respiratory Rate

Blood pressure, heart rate, and respiratory rate will be measured at the 12-month, 24-month, and 5-year CA visits.

7.2.7.4 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). Please refer to Section 8, Adverse and Serious Adverse Events Assessment.

7.2.8 Medication Assessment

All medications received by study subjects will be collected from the time of enrollment through the 5-year CA visit (or upon discontinuation). Any investigational product received by subjects will be recorded separately as part of an assessment of subjects' participation in other clinical studies (Section 7.2.9).

7.2.9 Participation in Other Clinical Studies

Following enrollment, subjects in this study will not be restricted from enrolling in other clinical studies that involve the use of investigational product. The status of a subject's participation in such studies will be recorded (ie, yes/no). If a subject is enrolled in such a study, additional parameters will be recorded, including the masking status of the study, the identity of the investigational product or treatment being evaluated in the study, and the subject's treatment assignment in the study (if possible).

7.2.10 Appropriateness of Measurements

Overall, the primary and secondary efficacy and safety measures being employed in this study are considered appropriate for the follow-up of preterm infants. The validated tools being used to assess neurodevelopment, physical development, and health economic research outcomes in this pediatric population are widely used and recognized.

In some cases, tools were designed specifically for use in this study, namely, the pulmonary morbidity questionnaire. In this case, the assessment is based on published research in a similar pediatric population (Pryhuber et al., 2015).

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

According to the International Conference on Harmonization (ICH), an AE is "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product" (ICH Guidance E6 [R2] 2016).

In this long-term outcome study in follow-up to Study SHP607-202, no investigational product is being administered; it is therefore a non-interventional study. However, it seeks information on whether prior administration of IMP in Study SHP607-202 impacts long-term outcomes.

For the purposes of this study only the following AEs will be collected:

- Specified targeted medical events (Section 8.1.4)
- AEs related to investigational product
- 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.

All AEs described above are collected from the time the informed consent is signed until the defined follow-up period stated in Section 3.2. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs described above should be captured on the appropriate AE pages in the CRF and in source documents.

All AEs must be followed to closure (the subject’s health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event.

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to prior investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source.

The following additional guidance may be helpful:

Related	The temporal relationship between the event and the administration of the investigational product is compelling enough and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the CRF. Outcomes are as follows:

- Fatal
- Not recovered/Not Resolved
- Recovered/Resolved

- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Targeted Medical Events

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 (refer to Section 8.2.3), as appropriate, regardless of relationship to prior investigational product (SHP607 as administered in Study SHP607-202):

- Intracranial hypertension
- Any abnormality of glucose metabolism (eg, hypoglycemia, hyperglycemia, and diabetes)
- Tonsillar hypertrophy (based on tonsil examination [part of the physical examination])
- Increased cardiac size

8.1.5 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory or vital sign assessment can represent an AE if the change is clinically relevant. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If there are abnormal clinical laboratory values or vital signs which were not present at the start of the study, and which are relevant to AEs collected in this study, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory or vital sign is clinically significant and therefore represents an AE.

8.1.6 Abuse, Misuse, Overdose, and Medication Errors

Not applicable.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

Investigators should refer to the most current version of the SHP607 IB for reference safety information, which is found in IB Section 6, Summary of Data and Guidance for the Investigator.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to Shire Global Drug Safety within 24 hours of the first awareness of the event.

The investigator must complete, sign, and date the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or e-mail the SAE form to Shire Global Drug Safety (drugsafety@shire.com). A copy of this form must also be sent to the CRO/Shire medical monitor by fax or e-mail using the details provided below:

NA Safety Fax number: 1-888-529-3580

EMEA and APAC Safety Fax: +44 122 337 4102

E-mail: drugsafety@shire.com

8.2.3 Serious Adverse Event Definition

An SAE is any untoward clinical manifestation of signs, symptoms or outcomes (whether considered related to investigational product or not and at any dose:

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs.
- For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include:
- Bronchospasm associated with anaphylaxis requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization.
- Reviewed and confirmed seroconversion for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study drug) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.2 and must be reported to Shire Global Drug Safety within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product (SHP607 as administered in Study SHP607-202) and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Drug Safety within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the date the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was assessed as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For all fatal SAEs, all autopsy reports, pathology reports, death certificates, and other medical records should be provided to the sponsor.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor and clinical contract research organization (CRO) are responsible for notifying the relevant regulatory authorities and US central IRBs/European Union (EU) central ethics committees (ECs) of related, unexpected SAEs.

In addition, the clinical CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP607 program.

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the CRF. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO's data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics. The SAP will also include a description of how missing, unused and spurious data will be addressed.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock. All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC 27513).

9.4 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

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

9.5 Sample Size Calculation and Power Considerations

No formal sample size calculation was performed for this study because this is a follow-up study to Study SHP607-202. Any subjects enrolled in Study SHP607-202 are eligible to enroll in this study. Although all subjects randomized into the primary Study SHP607-202 (approximately 477) are eligible to enroll in Study SHP607-203 (completion of Study SHP607-202 is not required), the actual number of subjects enrolled will more closely approximate the number of subjects who complete Study SHP607-202. A total of approximately 382 subjects are expected to complete Study SHP607-202.

9.6 Study Population

The **Enrolled Population** will consist of all subjects for whom written informed consent has been provided for this study.

The **Safety Population** will consist of the subjects in the Enrolled Population who have safety follow-up data (including absence of AEs) in this long-term outcome study.

9.7 General Statistical Methodology

For variables following a continuous distribution, tabular summaries will consist of number of subjects, mean, standard deviation, minimum, maximum, and median. For categorical variables, tabular summaries will include the frequency and the percentage in each category by treatment group. For analysis purposes, baseline is defined as the first assessment in this study (Study SHP607-203). Treatment groups refer to the antecedent SHP607 dose groups (SHP607 at 250 µg/kg/day and SHP607 at 400 µg/kg/day), combined SHP607 dose groups, and standard neonatal care group.

All efficacy analyses will be performed using the Enrolled Population.

9.7.1 Primary Efficacy Endpoint

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).

The frequency and proportion of each component of CRM at 5 years CA for each treatment group (as administered in Study SHP607-202) will be summarized and their respective 95% confidence interval (CI) will be reported. The difference in the proportion between each of the SHP607 dose groups (individual dose and combined doses) and the standard neonatal care group and the corresponding 95% CI will also be summarized.

9.7.2 Secondary Endpoints

The secondary 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:
  - BSID (or KSPD)
  - WPPSI
- Gross motor function as assessed by GMFM-88.
- Child behavior as assessed by the following:
  - VABS
  - Attention-Deficit/Hyperactivity Disorder Rating Scale-fifth edition (ADHD RS-V) for the assessment of symptoms of ADHD
  - SCQ for screening of Autism Spectrum Disorder (ASD)
- HRQoL will be assessed by the 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 HUI2/3.
- Health care resource use associated with inpatient visits, outpatient visits, emergency room visits, and visits to specialists will be assessed.

Continuous endpoints will be summarized by number of subjects, minimum, maximum, median, mean, standard deviation, two sided 95% CI by treatment groups. Binary and categorical endpoints will be summarized by number of subjects, frequency, proportion and two-sided 95% CI by treatment groups.

9.7.3 Exploratory Endpoints

Caregiver Impact Questionnaire (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 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.

9.7.4 Health Economics and Outcomes Research Analyses

For PedsQL, CIQ, and EQ-5D-5L, descriptive statistics will be provided for summary scores by treatment group (as administered in Study SHP607-202) and at each time point.

The HUI 2/3 system contains a number of attributes/domains to classify the level of health status. Each attribute or domain (eg, mobility, cognition, emotion or pain) is rated on a 5-point ordinal scale to indicate the severity level, ranging from 1 to 5 (higher numbers indicating a more severe level). Summary statistics will be provided by treatment group.

For HCRU the utilization for each resource-item (eg, hospital days, physician visits) reported at each time point will be reported descriptively by treatment group.

9.8 Safety Analyses

Safety data will be analyzed for the Safety Population.

For safety analyses, baseline is defined as the first assessment in this study (Study SHP607-203). Treatment groups refer to the antecedent SHP607 dose groups (SHP607 at 250 µg/kg/day and SHP607 at 400 µg/kg/day), combined SHP607 dose groups, and standard neonatal care group.

The primary safety analysis will be based on:

- AEs reported during the study period of SHP607-203

The secondary safety analysis will be based on:

- Targeted medical events occurring during the period of Study SHP607-203.
- Fatal SAEs

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. The number of events, incidence, and percentage of AEs will be calculated overall, by system organ class (SOC), by preferred term, and by treatment group. Adverse events will be further summarized by severity and relationship to prior investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations including ICH E6, EU Directive 2001/20/EC, and all updates, as well as local ethical and legal requirements.

Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, current ICH GCP Guidelines, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the CRO as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance. The sponsor will provide the ECs with a copy of the same summary.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (R2) (2016), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the coordinating principal investigator, in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH GCP Guideline E6 (R2) (2016).

The coordinating principal investigator will be chosen by the sponsor.

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Case report forms are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly onto the CRF.

All data sent to the sponsor must be endorsed by the investigator.

The clinical research associate (CRA)/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Electronic Clinical Outcome Assessments

Assessment data collected electronically are maintained in a secure database with access controls in place to ensure only approved users have the ability to review the data. The data are maintained by a third-party vendor and may change during the course of the project and through an established data management process. Following database lock, the electronic clinical outcome assessments (eCOA) vendor will produce a study archive on electronic media to both sites and the sponsor. Site archive media will include information pertinent to their study patients, but the sponsor is provided with content for the entire study.

Archive media consists of the following: trial documentation, metadata directory, XML data director, final data transfer file, and electronic case report forms that are generated from the eCOA system.

10.2.3.3 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file and original clinical laboratory reports. All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/IEC or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/IEC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays etc.).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, UK Medicines and Healthcare Products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.4 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare Products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.5 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent (or assent) from all study subjects prior to any study-related procedures including screening assessments. All consent and assent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent and assent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form and assent form that was reviewed by the IRB/IEC and received their favorable opinion/approval. A copy of the IRB/IEC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/IEC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement. Investigational product supplies will not be released until the CRO has received written IRB/EC approval.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue. If required by local law, substantial amendments to the protocol must also be approved by the appropriate regulatory agency prior to implementation.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol at least annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. This can be the responsibility of the sponsor or investigator for sites within the EU; or for multicenter studies, the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs as required by IRB/EC procedures.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with Health Insurance Portability and Accountability Act (HIPAA) of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the CRO.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market SHP607; national or local regulatory authorities; and the IRBs/ECs which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies–containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth–will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

The term "Publication" shall mean any paper, article, manuscript, report, poster, internet posting, presentation slides, abstract, outline, video, instructional material, presentation (in the form of a written summary), or other public disclosure of the study results, in printed, electronic, oral, or other form. The parties understand and agree that participation in the study may involve a commitment to publish the data from all sites participating in the study in a cooperative publication with other investigators prior to publication or oral presentations of the study results on an individual basis.

The site agrees not to publish or present the site's study results until such time as either the aggregate multi-site study results are published in a cooperative publication or for a period of one (1) year after termination or completion of the study at all participating sites, whichever shall first occur. After that time, the site may publish the site's study results in scientific journals or present the study results at symposia or other professional meetings in accordance with the following provisions:

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single site data being presented.

At least sixty (60) days prior to submitting an abstract, manuscript, or other document for publication, a copy of the proposed publication will be provided to the sponsor by the site for review. Upon the sponsor's request, the site agrees to remove any and all confidential information (expressly excluding study results) identified in the publication and to delay such submission or presentation for an additional sixty (60) day period in order to allow the sponsor time to file any patent application(s). All publications of the study results shall appropriately reference the multi-site study publication, if any, or the fact that the study results are a subset of data resulting from a larger multi-site study.

Shire is committed to transparent dissemination of all scientific, technical and medical manuscripts generated from Shire-supported research. Therefore, after January 1, 2018, Shire will require the submission of all Shire-supported research manuscripts to journals that offer public availability via Open Access (including publisher platforms/repositories and self-archiving). Open Access refers to the free at point of entry, online availability of published research output with, where available, rights of re-use according to an End User License.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) Recommendation for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical journals. Participation as an investigator does not confer any rights to authorship of publications.

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Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	18 Nov 2019	Global
Protocol Amendment 1	08 April 2020	Global