CLINICAL STUDY PROTOCOL

NCT Number: NCT02386839

Study Title: Long-term Outcome of Children Enrolled in Study ROPP-2008-01 Previously Treated with rhIGF-1/rhIGFBP-3 for the Prevention of Retinopathy of Prematurity (ROP) or Who Received Standard Neonatal Care

Study Number: SHP607-201

Protocol Version and Date:

Original Protocol: 27 Aug 2014

Amendment 1: 19 Feb 2016

Amendment 2: 21 Feb 2017

Amendment 3: 11 May 2017

Amendment 4: 09 Apr 2018

Clinical Trial Protocol: SHP-607-201

Study Title:	Long-term Outcome of Children Enrolled in Study ROPP-2008-01 Previously Treated with rhIGF-1/rhIGFBP-3 for the Prevention of Retinopathy of Prematurity (ROP) or Who Received Standard Neonatal Care
Study Number:	SHP-607-201
Study Phase:	II
Product Name:	Mecasermin rinfabate (rhIGF-1/rhIGFBP-3)
IND Number:	121698
EUDRACT Number	2014-003556-31
Indication:	Retinopathy of Prematurity
Investigators:	Multicenter
Sponsor:	Premacure AB, A Member of the Shire Group of Companies
Sponsor Contact:	300 Shire Way Lexington, MA 02421 USA
Medical Monitor:	[redacted], MD, MBA Rare Diseases Business Unit Shire

	Date
Original Protocol:	27 August 2014

Confidentiality Statement

SYNOPSIS

Sponsor:

Premacure AB, A Member of the Shire Group of Companies

Name of Finished Product:

Mecasermin rinfabate (rhIGF-1/rhIGFBP-3)

Study Title:

Long-term Outcome of Children Enrolled in Study ROPP-2008-01 Previously Treated with rhIGF-1/rhIGFBP-3 for the Prevention of Retinopathy of Prematurity (ROP) or Who Received Standard Neonatal Care

Study Number:

SHP-607-201

Study Phase: II

Investigational Product, Dose, and Mode of Administration:
Not applicable.

Primary Objectives

The primary objectives of this study are:

- To evaluate the long-term efficacy outcomes following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D) as assessed by ROP associated visual outcomes
- To evaluate the long-term safety outcomes following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D)

Secondary Objectives

The secondary objectives of this study are to evaluate the effect following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D) on:

- Growth parameters
- Cognitive development
- Physical development
- Child behavior
- Pulmonary morbidity
- Survival
- Health-related quality of life (HRQoL)
- Health utility
- Health care resource use (HCRU)

Exploratory Objective

[redacted]

Study Endpoints

The primary efficacy endpoints of this study are:

- Visual acuity as assessed by an age appropriate method
- Ocular alignment and ocular motor examination in primary gaze and in as many of 9 positions of gaze as possible as assessed by corneal light reflex and by the cover test
- Assessment of nystagmus by observation
- Refraction as assessed by retinoscopy with cycloplegia
- Stereoacuity as assessed with the Lang Stereotest

The secondary efficacy endpoints of this study are:

- Growth parameters including body weight, body length (or height), and head circumference
- Cognitive development as assessed by the following standardized, age-appropriate tools:
    - Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)
    - Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV)
- Physical development as assessed by standardized, age appropriate tools including physical exam, neurological examination for assessment of cerebral palsy, and hearing assessment
- Child behavior as assessed by the following:
    - Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
    - Child Behavior Checklist (CBCL; 1 ½ to 5)
    - Attention Deficit/Hyperactivity Disorder Rating Scale-fourth edition (ADHD RS-IV) for the assessment of symptoms of attention deficit/hyperactivity disorder (ADHD)
    - Social Communication Questionnaire (SCQ) for screening of Autism Spectrum Disorder (ASD)
- Pulmonary morbidity data (eg, hospitalizations, emergency room [ER] visits, pulmonary medications)
- Survival as assessed by death during the study due to any cause

The health economic outcome research endpoints of this study are:

- Health-related quality of life (HRQoL) 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, respectively)
- Health status (eg, health utility) will be measured by the Health Status Classification System-Preschool (HSCS-PS)
- Resource use associated with inpatient visits, outpatient visits, medical utilization and pharmacy utilization will be assessed

The safety endpoints of this study are:

- Physical examination including tonsil examination

- Adverse events (AEs), as follows:
  - those considered related to rhIGF-1/rhIGFBP-3 (as administered in Study ROPP-2008-01, Section D)
  - those considered related to procedures performed in this study (Study SHP-607-201)
  - specified targeted medical events regardless of causality
  - fatal SAEs regardless of causality
- Cardiac size as assessed by echocardiogram
- Kidney and spleen size and any other gross abnormalities as assessed by abdominal ultrasound

Exploratory Endpoints:

[redacted]

Study Population:

Subjects randomized in Study ROPP-2008-01, Section D are eligible to enroll in this study; completion of Study ROPP-2008-01 Section D is not required. Subjects in Study ROPP-2008-01 are premature infants (gestational age of 23 weeks + 0 days to 27 weeks + 6 days) who are randomized to receive either treatment with rhIGF-1/rhIGFBP-3 or standard neonatal care. Up to 120 subjects are planned to be randomized in Study ROPP-2008-01 Section D.

Study Design:

This is a Phase II, multicenter, long-term developmental outcome study enrolling subjects who were randomized in Section D of Study ROPP-2008-01. Enrolled subjects in this study will be followed through age 5 years corrected age (CA). This study will enroll both subjects who were in the treated (received rhIGF-1/rhIGFBP-3) and control (received standard neonatal care) groups of Study ROPP-2008-01 (Section D) to enable assessment of rhIGF-1/rhIGFBP-3 long-term efficacy and safety outcomes versus standard neonatal care. No investigational product will be administered in this study.

Study Duration:

Duration for an individual subject's participation in the study will vary depending upon age at enrollment, but subjects will not be followed beyond age 5.5 years corrected age (CA).

Study Inclusion and Exclusion Criteria:

Subjects randomized in Study ROPP-2008-01, Section D are eligible to enroll in this study. Subjects will not be excluded from participating in other clinical studies.

Efficacy Assessments:

Efficacy will be assessed by visual outcomes, growth parameters, cognitive development, physical development, child behavior, pulmonary morbidity, and survival.

Safety Assessments:

Safety will be assessed by physical examination (including tonsil examination), AEs (as specified), echocardiogram, and abdominal ultrasound.

Statistical Methods

Details regarding the statistical methods and definitions will be provided in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to database lock. All statistical analyses will be performed by the sponsor or CRO after the database is locked. Statistical analyses will be performed using Version 9.1 or higher of SAS® (SAS Institute, Cary, NC 27513).

Continuous variables will be summarized using descriptive statistics including the number of observations, 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 2 possible treatment assignments in the antecedent study, ROPP-2008-01, Section D (rhIGF-1/rhIGFBP-3 or standard neonatal care).

For analysis purposes, baseline is defined as the first assessment either in the antecedent study (ROPP-2008-01) or in this study (SHP-607-201). As necessary, relevant data from Study ROPP-2008-01 may be summarized with the data from this study (SHP-607-201).

Date of Original Protocol: 27 August 2014

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AAO	American Academy of Ophthalmology
ADHD	attention-deficit hyperactivity disorder
ADHD-RS-IV	Attention-Deficit/Hyperactivity Disorder Rating Scale-fourth edition
AE	adverse event
ASD	Autism Spectrum Disorder
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
CBCL	Child Behavior Checklist (1 ½ to 5)
CFR	Code of Federal Regulations
CA	corrected age
CI	confidence interval
CRF	case report form (electronic)
CRO	contract research organization
DMC	data monitoring committee
eCRF	electronic case report form
EOS	end of study
ETDRS	Early Treatment of Diabetic Retinopathy Study
ER	emergency room
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GH	growth hormone
HRQoL	health-related quality of life
HSCS-PS	Health Status Classification System-Preschool
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IGF	insulin-like growth factor
IGFBP-3	insulin-like growth factor binding protein-3
IND	Investigational New Drug application
IRB	institutional review board
LV	left ventricle
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
OD	right eye
OS	left eye

Abbreviation	Definition
OU	both eyes
PedsQL	Pediatric Quality of Life Inventory
REB	research ethics board
ROP	retinopathy of prematurity
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System©
SCQ	Social Communication Questionnaire
SD	standard deviation
SOE	schedule of events
SUSAR	suspected unexpected serious adverse reaction
UK	United Kingdom
US	United States
VABS-II	Vineland Adaptive Behavior Scales, Second Edition
VLBW	very low birth weight
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
WPPSI-IV	Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition

1 INTRODUCTION

Retinopathy of prematurity (ROP) is a rare disorder of the developing retinal blood vessels and retinal neurons of the preterm infant and is one of the leading causes of preventable blindness in children.[1]

Visual acuity is decreased in infants with a history of ROP.[2] In addition to acuity, other aspects of eye health are also significantly impacted by ROP. Strabismus and myopia are clearly increased in patients with a history of ROP.[3-6] Additionally, more than half of patients at 6 to 10 years of age with a history of Stage 1 and Stage 2 ROP were reported to have ongoing visual issues.[7]

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. During fetal life, IGF-1 is available through placental absorption and ingestion from amniotic fluid.[8] Deprivation of such factors is likely to cause inhibition or improper stimulation of important pathways, which in the eye may cause abnormal retinal vascular development, the hallmark of ROP.

The finding in both a mouse model of ROP and preterm infants that development of ROP is associated with low levels of IGF-1 after premature birth, indicates a possible role for replacement of IGF-1 to levels found in utero as a strategy to potentially decrease abnormal retinal vascularization and abnormal retinal neural development, and ultimately, ROP.

Mecasermin rinfabate (rhIGF-1/rhIGFBP-3) is the human recombinant form of the naturally occurring protein complex of IGF-1 and insulin-like growth factor binding protein-3 (IGFBP-3). rhIGF-1/rhIGFBP-3 was developed to enhance the systemic exposure of administered rhIGF-1 and to improve the safety profile of rhIGF-1 therapy. rhIGF-1/rhIGFBP-3 was approved by the Food and Drug Administration (FDA) in 2005 for the treatment of growth failure in children with severe primary IGF-1 deficiency or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.

The pharmacokinetics and safety of rhIGF-1/rhIGFBP-3 have been evaluated in a Phase I study (ROPP-2005-01) and pharmacokinetics, safety, and efficacy are being evaluated in the ongoing phase II study (ROPP-2008-01). Sections A-C of the ROPP-2008-01 study are complete. Section D of the ROPP-2008-01 study is currently being conducted to assess pharmacokinetics, safety and efficacy of rhIGF-1/rhIGFBP-3 for the prevention of ROP in premature infants (up to a corrected age [CA] of 40 weeks [± 4 days]). Subjects in Study ROPP-2008-01are randomly assigned to receive rhIGF-1/rhIGFBP-3 or standard neonatal care. The target dose of rhIGF-1/rhIGFBP-3 for Study Section D is 250 µg/kg/24 hours to be administered via continuous infusion starting on Study Day 0 (day of birth) and continuing through postmenstrual age (gestational age + time elapsed from birth) 29 weeks + 6 days.

Although the rhIGF-1/rhIGFBP-3 therapy in Section D of the Phase II study (Study ROPP-2008-01) represents a short-term exposure (< 2 months for each subject), rhIGF-1/rhIGFBP-3 may have long-lasting effects on visual outcomes as well as other potential outcomes related to complications of prematurity such as neurodevelopment, pulmonary

function, and growth. In addition, it is critical to understand any long term safety effects from short term exposure to rhIGF-1/rhIGFBP-3.

The long-term outcomes assessed in this study will require utilization of different assessment tools than are utilized in the Phase II study, ROPP-2008-01 Section D, given the changes in physical and cognitive development that will occur in the subjects as they age during their participation in this study.

Please refer to the current edition of the Investigator's Brochure for further information concerning the safety and clinical development of rhIGF-1/rhIGFBP-3.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are:

- To evaluate the long-term efficacy outcomes following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D) as assessed by ROP-associated visual outcomes
- To evaluate the long-term safety outcomes following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D)

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate the effect following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D) on:

- Growth parameters
- Cognitive development
- Physical development
- Child behavior
- Pulmonary morbidity
- Survival
- Health-related quality of life (HRQoL)
- Health utility
- Health care resource use (HCRU)

2.3 Exploratory Objective

[redacted]

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

3.1.1 Primary Efficacy Endpoints

- Visual acuity as assessed by an age-appropriate method
- Ocular alignment and ocular motor examination in primary gaze and in as many of 9 positions of gaze as possible as assessed by corneal light reflex and by the cover test
- Assessment of nystagmus by observation
- Refraction as assessed by retinoscopy with cycloplegia
- Stereoacuity as assessed with the Lang Stereotest

3.1.2 Secondary Efficacy Endpoints

- Growth parameters including body weight, body length (or height), and head circumference
- Cognitive development as assessed by the following standardized, age-appropriate tools:
    - Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)
    - Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV)
- Physical development as assessed by standardized, age appropriate tools including physical examination, neurological examination for assessment of cerebral palsy, and hearing assessment
- Child behavior as assessed by the following:
    - Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
    - Child Behavior Checklist (CBCL; 1 ½ to 5)
    - Attention-Deficit/Hyperactivity Disorder Rating Scale-fourth edition (ADHD-RS-IV) for the assessment of symptoms of attention-deficit/hyperactivity disorder (ADHD)
    - Social Communication Questionnaire (SCQ) for screening of Autism Spectrum Disorder (ASD)
- Pulmonary morbidity data (eg, hospitalizations, emergency room [ER] visits, pulmonary medications)
- Survival as assessed by death during the study due to any cause

3.2 Health Economic Outcome Research Endpoints

- Health Related Quality of Life (HRQoL) 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, respectively)
- Health status (eg, health utility) will be measured by the Health Status Classification System-Preschool (HSCS-PS)
- Resource use associated with inpatient visits, outpatient visits, medical utilization and pharmacy utilization will be assessed

3.3 Safety Endpoints

- Physical examination including tonsil examination
- Adverse events (AEs), as follows:
  - those considered related to rhIGF-1/rhIGFBP-3 (as administered in Study ROPP-2008-01, Section D)
  - those considered related to procedures performed in this study (SHP-607-201)
  - specified targeted medical events regardless of causality
  - fatal serious adverse events (SAEs) regardless of causality
- Cardiac size as assessed by echocardiogram
- Kidney and spleen size and any other gross abnormalities as assessed by abdominal ultrasound

3.4 Exploratory Endpoints

[redacted]

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase II, multicenter, long-term developmental outcome study enrolling subjects who were randomized in Section D of Study ROPP-2008-01 to receive either rhIGF-1/rhIGFBP-3 (treated) or standard neonatal care (control). Enrolled subjects in this study will be followed through age 5 years CA. This study will enroll both subjects who were in the treated (received rhIGF-1/rhIGFBP-3) and control (received standard neonatal care) groups of Study ROPP-2008-01 (Section D) to enable assessment of rhIGF-1/rhIGFBP-3 long-term efficacy and safety outcomes versus standard neonatal care. No investigational product will be administered in this study.

In this study, the Initial Visit will occur at 40 weeks CA (ie, term equivalent) or upon discontinuation from Study ROPP-2008-01 or may occur any time up to the visit at 3 months CA. Subjects in Study ROPP-2008-01 are premature infants enrolling at gestational age of 23 weeks + 0 days to 27 weeks + 6 days.

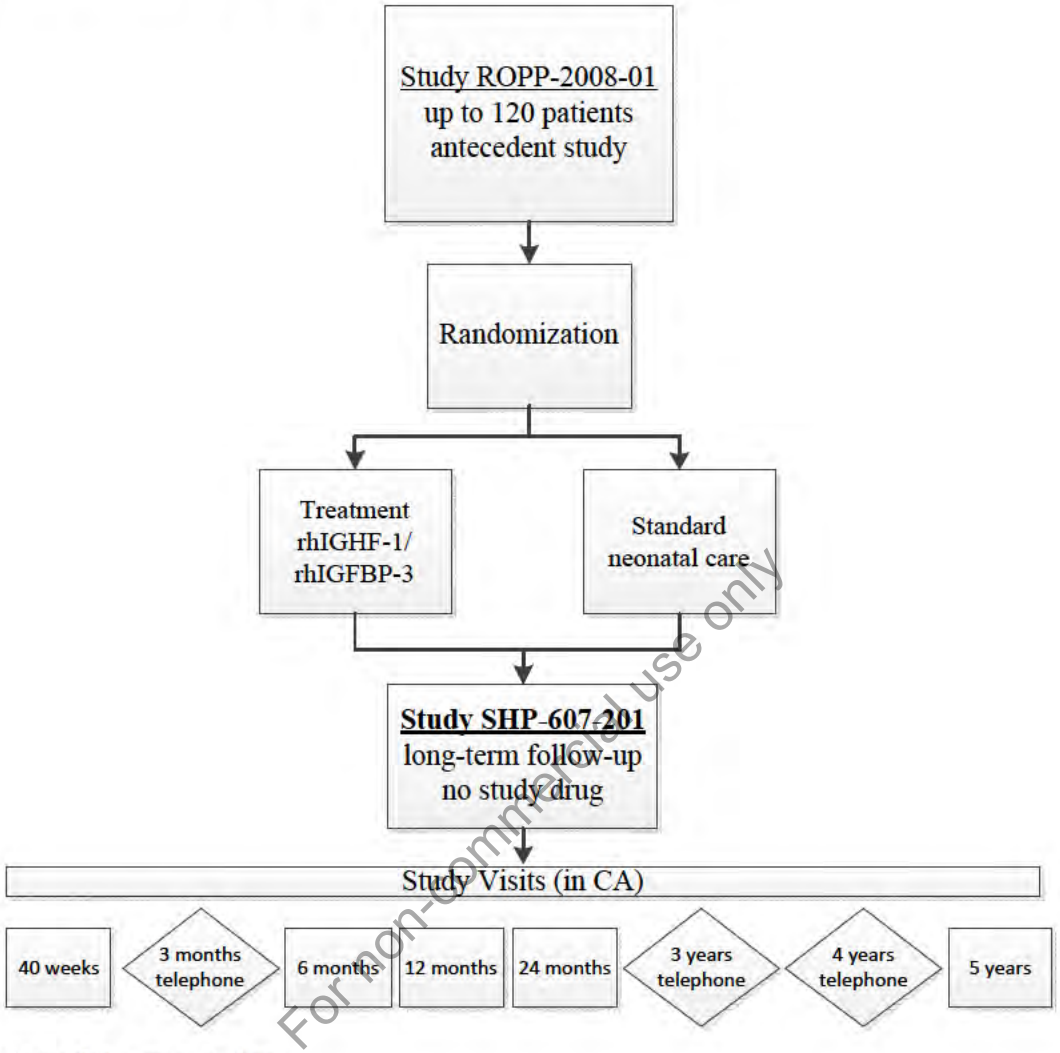
Time points for assessments have been chosen based on standard premature infant follow-up periods and represent important developmental ages for premature infant follow-up. Both telephone and clinical site visits are included to help maintain contact with subjects throughout the 5-year duration of the study.

Subjects will be evaluated at appropriate follow-up site locations with expertise in the assessment of the developmental outcomes of premature infants. Pediatric ophthalmology expertise will also be required.

See Appendix 1 for the Study Schedule of Events table.

The overall study design is outlined in Figure 4-1.

Figure 4-1 Overview of Study Design, Study SHP-607-201



Abbreviations: CA = corrected age

Note: Visits conducted by telephone are indicated with a diamond shape. Visits conducted at the study site are indicated with rectangles. Visit windows are provided in the Schedule of Events (Appendix 1).

4.2 Rationale for Study Design

The only approved therapies for ROP are ablative (cryotherapy or laser therapy). To date, there are no commercially available preventative treatments for ROP.

Although treatment with rhIGF-1/rhIGFBP-3 in ROPP-2008-01 (Section D) after premature birth is limited to less than 2 months of therapy, it remains important to assess the long-term outcomes of treatment on both efficacy and safety. Thus, this long-term follow-up study to Study ROPP-2008 01 (Section D) has been designed to assess long-term efficacy and safety outcomes following short-term exposure to rhIGF-1/rhIGFBP-3.

Insulin-like growth factor-1 (IGF-1) mediates its primary actions by binding to its specific receptor, the insulin-like growth factor 1 receptor (IGF-1R), which is present on many cell types in many tissues. Binding to its receptor initiates intracellular signaling including via the AKT signaling pathway. This pathway is involved in stimulation of cell division, growth and differentiation and inhibits programmed cell death. Specifically regarding premature infants, IGF-1 is an important mediator of fetal growth and has been shown to play a role in early postnatal growth following pre-term delivery.[9, 10]

Insulin-like growth factor-1 (IGF-1) has also been shown to play a role in pulmonary development[11] and neural development.[12, 13] Given the potential role for IGF-1 in the development of multiple systems, this study has been designed to evaluate the long-term effects of rhIGF-1/rhIGFBP-3, both from a safety and efficacy perspective, on the development of the premature infant.

4.3 Study Duration

Duration for an individual subject's participation in the study will vary depending upon age at enrollment, but subjects will not be followed beyond age 5.5 years CA.

5 STUDY POPULATION SELECTION

5.1 Study Population

Subjects randomized in Study ROPP-2008-01, Section D are eligible to enroll in this study; completion of Study ROPP-2008-01 Section D is not required. Subjects in Study ROPP-2008-01 are premature infants (gestational age of 23 weeks + 0 days to 27 weeks + 6 days) who are randomized to receive either treatment with rhIGF-1/rhIGFBP-3 or standard neonatal care. Up to 120 subjects are planned to be randomized in Study ROPP-2008-01 Section D.

5.2 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study.

1. Subject was randomized in Study ROPP-2008-01, Section D
2. Subject's parent or legally authorized representative(s) must provide written informed consent prior to performing any study-related activities. Study-related activities are any procedures that would not have been performed during normal management of the subject.

5.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study.

1. Any other condition or therapy that, in the Investigator's opinion, may pose a risk to the subject or interfere with the subject's ability to be compliant with this protocol or interfere with the interpretation of results
2. The subject or subject's parent or legally authorized representative(s) is unable to comply with the protocol as determined by the Investigator

6 STUDY TREATMENT

6.1 Description of Treatment

No investigational product will be administered in this study.

6.2 Treatments Administered

Not applicable.

6.3 Selection and Timing of Dose for Each Subject

Not applicable.

6.4 Method of Assigning Subjects to Treatment Groups

Not applicable.

6.5 Masking

Not applicable.

6.6 Medications

Any medications administered to the subjects will be collected from the time of informed consent through the 5-year CA visit (or until the subject withdraws or is discontinued). Any investigational product received by subjects will be recorded separately as part of an assessment of subjects' participation in other clinical studies (Section 7.11.1).

6.7 Restrictions

6.7.1 Prior Therapy

There are no restrictions related to prior therapy.

6.7.2 Other Restrictions

There are no restrictions related to fluid or food intake, or subject activity.

6.7.3 Treatment Compliance

Not applicable.

6.7.4 Packaging and Labeling

Not applicable.

6.8 Storage and Accountability

Not applicable

7 STUDY PROCEDURES

Detailed descriptions of subject procedures and evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of the study (see Schedule of Events in Appendix 1).

All data collected are to be recorded on the subject's appropriate eCRF.

Details for study procedures are described in the Operations Manual for this study.

7.1 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).

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 11.4. Documentation and filing of informed consent documents should be completed according to Section 11.4.

7.2 Study Entrance Criteria and Eligibility

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.

7.3 Study Enrollment

Subjects will be considered enrolled in the study once written informed consent has been obtained from the subject's parent(s) or legally authorized representative(s).

7.4 Demographics

Subject demographic information including gender, date of birth, and race will be recorded.

7.5 Growth Parameters: Length (and Height), Weight, and Head Circumference

7.5.1 Length and Height

Body length (supine measurement) will be collected when subjects are 24-months CA or younger. 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 when subjects are older than 24-months CA. 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).

7.5.2 Body Weight

Body weight will be collected. Calibrated scales should be utilized for body weight measures (type of scale will depend upon subject's age). Care should be taken to remove any extraneous clothing prior to measures and shoes should be removed.

The measure should be recorded to the nearest 0.1 kg.

7.5.3 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.

7.6 Efficacy Assessments

7.6.1 Visual Assessments

After corrective lens determination has occurred (Section 7.6.1.2), all visual assessments should be conducted with best-corrected vision, ie, with corrective lenses in place (if required); this applies to 24-month and 5-year visits.

7.6.1.1 Visual Acuity

Visual acuity is a measure of how well a subject sees at different distances. It will be assessed by the methods summarized in Table 7-1; the method employed will be selected based on the subject's age (CA) at the time of the study visit. Visual acuity measurements will be measured and recorded for the left (OS), right (OD) eye, and both eyes (OU).

At ages 6 months and 12 months CA, visual acuity will be assessed with Teller acuity cards. At ages 24 months and 5 years CA an attempt should be made to assess visual acuity by the LEA Symbols Test and LEA Symbols Chart, respectively. If during this attempt, the examiner determines that it will not be possible to perform an accurate assessment with the relevant LEA tool, visual acuity should be assessed with the Teller acuity cards.

The visual acuity assessments should be performed by an optometrist or ophthalmologist trained in pediatrics.

Table 7-1 Summary of Visual Acuity Assessments

Visual Acuity Assessment Tool	Description	Unit of Measure	Applicable Age/Study Visit (CA)
Teller acuity cards	Resolution acuity – discrimination of a grating optotype from a background with the same mean luminance	cycles per degree	6 months 12 months
LEA Symbols Test	Recognition acuity - tests recognition of 4 optotypes	Snellen fraction (eg, 20/20)	24 months[a]
LEA Symbols (ETDRS-style) chart	Distance visual acuity test	Snellen fraction (eg, 20/20)	5 years[a]

Abbreviations: CA = corrected age; ETDRS = Early Treatment of Diabetic Retinopathy Study

[a] At ages 24 months and 5 years CA an attempt should be made to assess visual acuity by the LEA Symbols Test and LEA Symbols Chart, respectively. If during this attempt, the examiner determines that it will not be possible to perform an accurate assessment with the relevant LEA tool, visual acuity should be assessed with the Teller acuity cards.

7.6.1.2 Corrective Lens Determination

An assessment to determine if the subject requires vision correction with corrective lenses will be performed. This is being performed to ensure the accuracy of subjects' subsequent visual acuity assessments (at the 24-month and 5-year visits). The corrective lens determination will be performed according to the guidelines published by the American Academy of Ophthalmology (AAO).[14]

This assessment should be performed by an optometrist or ophthalmologist trained in pediatrics.

7.6.1.3 Ocular Alignment and Oculomotor Examination (Motility)

Ocular alignment will be assessed in primary gaze by comparing the position of the corneal light reflection in OS and OD (corneal light reflection assessment). Presence or absence of strabismus will be recorded in primary gaze and in as many of the 9 positions of gaze as feasible with the cover test assessment of refixation movement. Extraocular muscle over-action or deficiency will be recorded. The assessment will be performed according to the AAO guidelines.[14]

Presence or absence of nystagmus as observed during the ocular alignment assessments will also be recorded.

The assessment will be performed by a pediatric ophthalmologist or an ophthalmologist trained in the care of pediatric subjects with a history of premature birth. Degree of adherence to the AAO guidelines will be at the discretion of the examining physician in consideration of the need for patient cooperation.

Ocular motility refers to eye movements, which are governed by the 6 extraocular muscles in each eye. It will be assessed by examiner observation of the subject's ability to abduct, adduct, supra, and inferoduct each eye (to assess for strabismus). Any of the observed misalignment (strabismus classifications) will be recorded:

- esotropia
- exotropia
- hypertropia
- hypotropia

The frequency (constant or intermittent) with which any misalignment occurs and whether the turning eye is always the same eye or if it alternates between OS and OD, will be recorded. Extraocular muscle over-action or deficiency will be recorded.

This assessment should be performed by an optometrist or ophthalmologist trained in pediatrics.

7.6.1.4 Refraction with Cycloplegia

Refraction is a measure of the lens power required for a focused image on the retina. Refraction with cycloplegia will be measured and recorded in diopters for each eye individually (OS and OD).

Cycloplegia may be induced according to site standard practice.

This assessment should be performed by an optometrist or ophthalmologist trained in pediatrics.

7.6.1.5 Stereoacuity

Stereoacuity is a measure of depth perception and will be assessed using the Lang Stereotest and performed by certified personnel. The presence or absence of stereopsis will be recorded.

7.6.1.6 [redacted]

[redacted]

7.6.2 Hearing Assessment History

Results of previously completed hearing assessments will be recorded; hearing tests are not being performed as part of this study.

7.6.3 Behavioral Assessments

7.6.3.1 Bayley Scales of Infant and Toddler Development, Third Edition

The BSID-III will be used to assess cognitive, motor, and language skills, and is applicable to children aged 1 to 42 months.

The BSID-III is an assessment tool designed to measure a young child's skills in the 3 core areas of development: cognitive, language, and motor. There are 5 subscales, the cognitive subscale stands alone while 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 examiner's manual.

The BSID-III 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.

7.6.3.2 Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV)

The WPPSI-IV is a measure of general cognitive development in children that has components of both verbal and nonverbal tasks.[19] It is applicable to preschoolers and young children aged 2 years + 6 months to 7 years + 7 months, and is a direct assessment of a child's cognitive skills.

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[20] 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-IV will be administered to the subject by a trained professional. Scores to be recorded are detailed in the Study Operations Manual.

7.6.3.3 Child Behavior Checklist (CBCL)

The CBCL (1 ½ to 5) is a parent-reported outcome measure used to assess behavioral, emotional, and social functioning of toddlers and preschool children aged 18 to 60 months.[21] It is composed of 99 items that are rated on a Likert scale and includes the following 7 syndrome scales arranged under 2 domains (ie, Internalizing and Externalizing Problems):[22]

- Internalizing Problems
- Emotionally Reactive
- Anxious/Depressed
- Somatic Complaints
- Withdrawn
- Sleep Problems
- Attention Problems
- Aggressive Behavior

The questionnaire is widely used and has been employed to assess long-term behavioral outcomes in children born prematurely, aged similarly to the subjects expected in this study population.[22 - 24] It is associated with well-established normative data;[25] norms may be selected to aid in interpretation of the scale scores.

The CBCL (1 ½ to 5) is a questionnaire that will be administered to 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.

7.6.3.4 Vineland Adaptive Behavior Scales, Second Edition

The VABS-II Expanded Interview Form will be used to measure the personal and social skills of subjects serially over time; these scales are organized within a 3-domain structure: Communication, Daily Living, and Socialization. In addition, the VABS-II offers a Motor Skills Domain and an optional Maladaptive Behavior Index. The VABS-II Expanded Interview Form assesses what a subject actually does, rather than what he or she is able to do.

The VABS-II Expanded Interview Form will be administered to 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.

7.6.3.5 Attention-Deficit/Hyperactivity Disorder Rating Scale-Fourth Edition

The ADHD-RS-IV was developed to measure the behaviors of children with ADHD. The ADHD-RS-IV consists of 18 items designed to reflect current symptomatology of ADHD based

on DSM-IV 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-IV, [26] will be completed by the subject's parent(s) or legally authorized representative(s). Scores to be recorded are detailed in the Study Operations Manual.

7.6.3.6 Social Communication Questionnaire – Lifetime Form

The SCQ is a brief instrument that helps evaluate communication skills and social functioning in children[27] that can be used for screening for autism or autism spectrum disorders in the general population.[28]

The SCQ will be completed by the subject's parent(s) or legally authorized representative(s). 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.

7.6.4 Cerebral Palsy Assessment

Comprehensive neurological examination for the diagnosis of cerebral palsy (CP) will be conducted. The Amiel-Tison neurological examination framework[29] will be utilized for this assessment and conducted by trained medical professionals.

7.6.5 Pulmonary Morbidity Assessment

Pulmonary morbidity will be assessed with questions related to family history and smoking status as well as diagnosis of select pulmonary symptoms, conditions and related hospitalizations. The questionnaire will be administered to the subject's parent(s) or legally authorized representative(s).

7.6.6 Survival Assessment

Survival status will be assessed and recorded.

7.6.7 Health Economic Outcome Research Assessments

7.6.7.1 Health Related Quality of Life

Health-related quality of life (HRQoL) is an important outcome towards improving the health care of pediatric patients as it is that part of a person's overall quality of life that is determined primarily by their health status and which can be influenced by clinical interventions. It is an important concept, which is also used in determining the value of health care services in this population.[30, 31] It is a multidimensional construct whose content is guided by the World Health Organization[32]; minimally it includes physical, psychological (including emotional and cognitive), and social health dimensions.

In this study, HRQoL will be assessed via the validated Pediatric Quality of Life Inventory (PedsQL™) Scales appropriate for the child's age of development.[33 - 35] The development of the PedsQL was based on the delineations of the World Health Organization (WHO) and is a modular approach to assessing HRQoL in the pediatric population. Initially, the PedsQL Generic Scales were developed and continue to be used in children aged 2 to 18 years. More recently Infant Scales have been developed that apply to ages 1 to 24 months.[34]

The following scales will be used in this study:

- Infant Scale for ages 1-12 months (36 Items)
- Infant Scale for ages 13–24 months (45 Items)
- Toddler Scale for 2-4 years of age (21 Items)
- Young Child Scale for 5-7 years of age (23 Items)

The PedsQL will be administered to the subject's parent and may be conducted via telephone through a call center. The scale(s) to be administered at each visit will be specified in the Study Operations Manual.

7.6.8 Health Care Resource Use

To understand the value of the investigational product administered in Study ROPP-2008-01 (Section D), the resource use associated with inpatient visits, outpatient visits, and medical and pharmacy utilization in this study will be recorded.

This assessment may be conducted via telephone through a call center.

7.6.8.1 Health Status Classification System-Preschool

Health status (eg, health utility) will be measured by the Health Status Classification System-Preschool (HSCS-PS), which is a validated instrument adapted for use via parent proxy within the pediatric population age 2.5 to 5 (adapted from the validated Health Utilities Index Mark 2 and 3 [HUI 2/3]).[36] Validity of the HSCS-PS concepts has not been established for ages younger than 2.5 years.

The HSCS-PS was developed to provide a consistent measure of health status in preschool-aged children who had been born prematurely.[36] The system is applicable to children with special needs as may be included in this study; validation cohorts for the system included children with very low birth weight (VLBW), which is congruent with this study population.

The instrument is composed of 12 dimensions (Vision, Hearing, Speech, Mobility, Dexterity, Self-care, Emotion, Learn/remember, Think/problem solve, Pain, General Health, and Behavior) intended to provide a comprehensive assessment of a child's health status as it pertains to health-related quality of life. The individual domains of the instrument will be scored as a mean score, representing the overall state for each concept individually. The global score will be recorded as well as the scores for each of the dimensions.

The HSCS-PS is a questionnaire that will be administered to the subject's parent(s) or legally authorized representative(s) and may be conducted via telephone through a call center.

7.7 Safety Assessments

7.7.1 Abdominal ultrasound

An abdominal ultrasound will be performed to assess the size of the spleen and kidneys. The spleen will be measured in the coronal longitudinal plane and the longest longitudinal length will be measured for each kidney (left and right).[37] Ultrasound results will be assessed by a central reader.

Organ size will be interpreted in the context of reference values established for children.[37, 38]

7.7.2 Echocardiogram

Echocardiographic examination (conventional M-mode recording of the left ventricle [LV] parasternal long axis view) will be performed for the evaluation of cardiac size, assessed by measuring the following:

- interventricular septal thickness (during end diastole)
- LV posterior wall thickness
- LV intracavity volume (both in end diastole and end systole)

Echocardiogram results will be assessed by a central reader.

7.7.3 Physical Examination

Physical examinations will include a review of the subject's general appearance, neurological examination, as well as a tonsillar examination (Table 7-2). Any abnormal change in findings will be recorded as an AE.

Table 7-2 Assessments for Physical Examinations

Assessment	Assessment
General appearance	Endocrine
Head and neck	Cardiovascular
Eyes	Abdomen
Ears	Genitourinary
Nose	Skin
Throat	Musculoskeletal
Chest and lungs	Neurological
Tonsils	

7.8 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 7.11.1).

7.9 Adverse Events Assessments

7.9.1 Definitions of Adverse Events, Serious Adverse Events, and Suspected Unexpected Serious Adverse Reactions

7.9.1.1 Adverse Event

An AE is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered investigational product-related. This includes an exacerbation of a pre-existing condition.

In this long-term outcome study in follow-up to Study ROPP-2008-01 (Section D), no investigational product is being administered. However, the relationship to the investigational product (rhIGF-1/rhIGFBP-3) as administered in Study ROPP-2008-01 (Section D) will be assessed.

Adverse events collected in this study will be the following:

- those considered related to investigational product (rhIGF-1/rhIGFBP-3 as administered in Study ROPP -2008-01, Section D)
- those considered related to procedures performed in this study (Study SHP-607-201)
- specified targeted medical events (Section 7.9.1.3) regardless of causality
- fatal SAEs regardless of causality

Adverse events include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study
- Intercurrent illnesses
- Drug interactions
- Events related to or possibly related to concomitant medications
- Abnormal laboratory values (this includes significant shifts from baseline within the range of normal that the Investigator considers to be clinically important)
- Clinically significant abnormalities in physical examination, vital signs, and weight

Throughout the study, the Investigator must record AEs on the AE electronic case report form (eCRF), regardless of the severity. The Investigator should treat subjects with AEs appropriately and observe them at suitable intervals until the events stabilize or resolve. Adverse events may be discovered through observation or examination of the subject, questioning of the subject, complaint by the subject, or by abnormal clinical laboratory values.

In addition, AEs may also include laboratory values that become significantly out of range. In the event of an out-of-range value, the laboratory test should be repeated until it returns to normal or can be explained and the subject's safety is not at risk.

Additional illnesses present at the time when informed consent is given are regarded as AEs and will be documented on the appropriate pages of the eCRF. Illnesses first occurring or detected during the study, and worsening of a concomitant illness during the study, are to be regarded as AEs and must be documented as such in the eCRF.

7.9.1.2 Serious Adverse Event

An SAE is any AE that results in any of the following outcomes:

- Death
- Is life-threatening
- Requires hospitalization
- Requires prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect

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 one of the outcomes listed in this definition. A life-threatening AE is defined as an AE that placed the subject, in the view of the initial reporter, at immediate risk of death from the AE as it occurred

(ie, it does not include an AE that, had it occurred in a more severe form, might have caused death).

7.9.1.3 Suspected Unexpected Serious Adverse Reaction

Suspected unexpected serious adverse reactions (SUSAR) are suspected adverse reactions related to an investigational product (investigational products and comparators [if applicable]), which occur in the concerned study, and that are both serious and unexpected according to the current Investigator's Brochure.

7.9.1.4 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, as appropriate, regardless of relationship to investigational product (rhIGF-1/rhIGFBP-3 as administered in Study ROPP-2008-01, Section D):

- intracranial hypertension
- any abnormality of glucose metabolism (eg, hypoglycemia, hyperglycemia, and diabetes)
- tonsillar hypertrophy (based on tonsil exam [part of the physical exam])
- increased kidney size
- increased cardiac size
- increased spleen size

7.9.2 Classification of Adverse Events and Serious Adverse Events

The severity of AEs will be assessed by the Investigator based on the definition indicated in Table 7-3. The severity of all AEs/SAEs should be recorded on the appropriate eCRF page to a severity of mild, moderate, or severe.

Table 7-3 Adverse Event Severity

Severity	Definition
Mild	No limitation of usual activities.
Moderate	Some limitation of usual activities.
Severe	Inability to carry out usual activities.

7.9.3 Clarification between Serious and Severe

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on the outcome or action criteria usually associated with events that pose a threat to life or

functioning. Seriousness (not severity) and causality serve as a guide for defining regulatory reporting obligations.

7.9.4 Relatedness of Adverse Events and Serious Adverse Events

Relationship of an AE or SAE to investigational product (rhIGF-1/rhIGFBP-3 as administered in Study ROPP-2008-01, Section D) is to be determined by the Investigator based on the following definitions (See Table 7-4).

Table 7-4 Adverse Event Relatedness

Relationship to Product	Definition
Not Related	Unrelated to investigational product
Possibly Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, but which could also be explained by concurrent disease or other drugs or chemicals.
Probably Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on de-challenge. The association of the clinical event or laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds.
Definitely related	The event follows a reasonable temporal sequence from administration of the investigational product, follows a known or suspected response pattern to the investigational product, is confirmed by improvement upon stopping the investigational product (de-challenge), and reappears upon repeated exposure (re-challenge). Note that this is not to be construed as requiring re-exposure of the subject to investigational product; however, the determination of definitely related can only be used when recurrence of event is observed.

7.9.5 Procedures for Recording and Reporting Adverse Events

7.9.5.1 Adverse Event Monitoring and Period of Observation

Adverse events will be monitored throughout the study.

For the purposes of this study, the period of observation extends from the time at which the subject's parent(s) or legally authorized representative(s) gives informed consent until the subject's final evaluation of the study. For safety purposes, the final evaluation will be defined as the last study visit when the subject is 5 years-old in CA.

If the Investigator considers it necessary to report an AE in a study subject after the end of the safety observation period, he or she should contact the Sponsor to determine how the AE should be documented and reported.

7.9.5.2 Reporting Serious Adverse Events

Any SAE meeting the reporting criteria for this study should be recorded by the clinical site on an SAE form. The SAE must be completely described on the subject's eCRF, including the judgment of the Investigator as to the relationship of the SAE to the investigational product. The Investigator will promptly supply all information identified and requested by the Sponsor (or contract research organization [CRO]) regarding the SAE.

The Investigator must report the SAE to the Shire Pharmacovigilance and Risk Management Department AND to the Shire Medical Monitor on an SAE form. This form must be completed and FAXED or EMAILED within 24 hours of the Investigator's learning of the event to:

Shire Pharmacovigilance and Risk Management Department:

International FAX: [redacted] **(UK) OR United States FAX:** [redacted]

Email: [redacted]

AND

Shire Medical Monitor: [redacted]**, MD, MBA**

Email: [redacted]

FAX: [redacted] **(USA)**

Any follow-up information must also be completed on an SAE form and faxed or emailed to the same numbers or emails listed above.

In the event of a severe and unexpected, fatal, or life-threatening SAE, the clinical site must contact the Shire Medical Monitor by telephone as soon as possible and within 24 hours of awareness; this is in addition to completing and transmitting the SAE form as stated above. The following provides contact information for the Shire Medical Monitor.

If an SAE is assessed as severe and unexpected, or life-threatening, contact:
[redacted]**, MD, MBA** [redacted] **Shire, Inc.** **300 Shire Way** **Lexington, MA 02421 USA** **Telephone:** [redacted] **Mobile:** [redacted] **(24-hr access)**

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

The Sponsor and the CRO are responsible for notifying the relevant regulatory authorities/US central IRBs/European Union (EU) central ECs of related, unexpected SAEs.

For some European regulatory authorities, these reports are submitted directly to Eudravigilance. In case of deaths or life-threatening SUSARs, these must be reported to the relevant regulatory authorities before 7 days have elapsed from that the initial SAE report has reached the Sponsor or its representatives. A full report has to be submitted within another 8 days. For other SUSARs the timelines for reporting are 15 days.

In addition, the CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the rhIGF-1/rhIGFBP-3 program at Shire.

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.

7.10 Removal of Subjects from the Trial

A subject's participation in the study may be discontinued at any time at the discretion of the Investigator. The following may be justifiable reasons for the Investigator to remove a subject from the study:

- Non-compliance, including failure to appear at one or more study visits
- The subject was erroneously included in the study
- The subject develops an exclusion criterion
- The study is terminated by the Sponsor

The subject, the subject's parent(s), or the subject's legally authorized representative acting on behalf of the subject is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment.

If a subject or the subject's parent(s) or the subject's legally authorized representative(s) acting on behalf of the subject, discontinues participation in the study, or the subject is discontinued by the Investigator, reasonable efforts will be made to follow the subject through the end of study assessments. The reason for refusal will be documented on the eCRF. Any AEs experienced up to the point of discontinuation must be documented on the AE eCRF. If AEs are present when the subject withdraws from the study, the subject will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal will be followed until resolution.

7.11 Other Study Procedures

7.11.1 Participation in Other Clinical Studies

Following enrollment, subjects in this study will not be restricted from enrolling in another clinical study that involves 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 being evaluated in the study, and the subject's treatment assignment in the study (if possible).

7.12 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. These are the pulmonary morbidity assessment and the cerebral palsy assessment. In these cases, the tools are either based on validated tools or the current state of knowledge in the literature. For example, the cerebral palsy assessment is based on the Amiel-Tison neurological examination framework[29] and the pulmonary assessment is based on published research in a similar pediatric population.[39, 40]

8 STUDY ACTIVITIES

The timing of the visits in this study is based on subjects' corrected age (CA).

8.1 Initial Study Visit (40 weeks CA [term equivalent])

The Initial Visit will occur at 40 weeks CA (ie, term equivalent) or upon discontinuation from Study ROPP-2008-01, Section D or any time up to the visit at 3 months CA.

At the Initial Visit, informed consent will be obtained followed by an assessment of study eligibility criteria and collection of demographic data.

The following AE data, collected as part of Study ROPP-2008-01 (Section D) will also be recorded:

- Ongoing targeted medical events regardless of causality
- Ongoing study drug-related AEs, including SAEs

8.2 Study Visits

Study visits for follow-up outcome assessments will take place at the following time points in CA:

- 3 months (±2 weeks) – conducted by telephone
- 6 months (±1 month) – clinical site visit
- 12 months (±3 months) – clinical site visit
- 24 months (±3 months) – clinical site visit
- 3 years (±3 months) – conducted by telephone
- 4 years (±3 month) – conducted by telephone
- 5 years (+6 months) – clinical site visit

In addition, there will be 2 visits that must occur at least 1 month prior to the 24-month and 5-year CA study visits to assess the need for corrective lenses. The timing of these 2 visits (20 months [-1 month] and 4.75 years [-1 month]) was set to ensure that any prescribed corrective lenses would be worn for at least 1 month prior to the visual assessments at the 24-month and 5-year study visits CA.

The activities at the study visits are described in Sections 8.2.1 and 8.2.2.

8.2.1 Outcome Assessment Visits Conducted by Telephone

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

- HRQoL
- HCRU
- HSCS-PS (3-year and 4-year visits only)
- Medications
- Survival assessment
- Assessment of participation in other clinical studies
- Adverse events (including targeted medical events)

8.2.2 Clinical Site Visits

8.2.2.1 Outcome Assessment Site Visits

The following clinical site visits (in CA) to capture follow-up outcome data will occur at the clinical site:

- 6 months (±1 month)
- 12 months (±3 months)
- 24 months (±3 months)
- 5 years (+6 months)

The following assessments will be performed at the 6-month visit:

- Visual acuity
- Refraction with cycloplegia
- Length
- Weight
- Head circumference
- VABS-II
- Physical examination (including tonsil examination)
- Hearing Assessment History (Historical hearing test data may be recorded at any time prior to the 6-month visit)
- Pulmonary morbidity assessment
- Survival assessment
- HRQoL (may be performed by telephone if there are time constraints during this clinical site visit)

- HCRU (may be performed by telephone if there are time constraints during this clinical site visit)
- Abdominal ultrasound
- Echocardiogram
- Assessment of participation in other clinical studies
- Medications
- Adverse events (including targeted medical events)

The following assessments will be performed at the 12-month visit:

- Visual acuity
- Corrective lens determination
- Ocular alignment and motility
- Refraction with cycloplegia
- Length
- Weight
- Head circumference
- BSID-III
- VABS-II
- Physical examination (including tonsil examination)
- Pulmonary morbidity assessment
- Survival assessment
- HRQoL (may be performed by telephone if there are time constraints during this clinical site visit)
- HCRU (may be performed by telephone if there are time constraints during this clinical site visit)
- Assessment of participation in other clinical studies
- Medications
- Adverse events (including targeted medical events)

The following assessments will be performed at the 24-month visit:

- Visual acuity
- Ocular alignment and motility

- Refraction with cycloplegia
- Length
- Weight
- Head circumference
- BSID-III
- CBCL
- VABS-II
- Physical examination (including tonsil examination)
- Cerebral Palsy assessment
- Pulmonary morbidity assessment
- Survival assessment
- HRQoL (may be performed by telephone if there are time constraints during this clinical site visit)
- HCRU (may be performed by telephone if there are time constraints during this clinical site visit)
- HSCS-PS (may be performed by telephone if there are time constraints during this clinical site visit)
- Assessment of participation in other clinical studies
- Medications
- Adverse events (including targeted medical events)

The following assessments will be performed at the 5-year visit:

- Visual acuity
- Ocular alignment and motility
- Refraction with cycloplegia
- Stereoacuity
- Height
- Weight
- WPPSI-IV
- CBCL
- VABS-II
- ADHD-RS-IV

- SCQ
- Physical examination (including tonsil examination)
- Pulmonary morbidity assessment
- Survival assessment
- [redacted]
- HRQoL (may be performed by telephone if there are time constraints during this clinical site visit)
- HCRU (may be performed by telephone if there are time constraints during this clinical site visit)
- HSCS-PS (may be performed by telephone if there are time constraints during this clinical site visit)
- Assessment of participation in other clinical studies
- Medications
- Adverse events (including targeted medical events)

8.2.2.2 Visits Dedicated to Corrective Lens Determination

The following clinical site visits are dedicated solely to corrective lens determination in preparation for the outcome assessment visits at 24-months and 5-years CA:

- 20 months (-1 month)
- 4.75 years (-1 month)

At these visits, the following will be performed:

- Visual acuity
- Refraction with cycloplegia
- Corrective lens determination

The 20-month visit and the 4.75-year (4 years, 9 months) visit must occur at least 1 month prior to the 24-month and 5-year visits, respectively. Any prescribed corrective lenses must be worn for at least 1 month prior to the 24 month and 5 year assessments.

8.3 Assessments upon Discontinuation

If a subject discontinues prior to the 5-year CA visit, every attempt will be made to complete the assessments scheduled for the subject's next visit.

9 QUALITY CONTROL AND ASSURANCE

Training will occur at an Investigator meeting or at the site initiation visit or both, and instruction manuals will be provided to aid consistency in data collection and reporting across sites.

Clinical sites will be monitored by the Sponsor or its designee to ensure the accuracy of data against source documents. The required data will be captured in a validated clinical data management system that is compliant with the FDA 21 Code of Federal Regulations (CFR) Part 11 Guidance. The clinical trial database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be trained and given restricted access, based on their role(s) in the study, through a password-protected environment.

Data entered in the system will be reviewed manually for validity and completeness against the source documents by a clinical monitor from the Sponsor or its designee. If necessary, the study site will be contacted for corrections or clarifications; all missing data will be accounted for.

Serious adverse event information captured in the clinical trial database will be reconciled with the information captured in the Pharmacovigilance and Risk Management database.

10 STATISTICAL ANALYSES

10.1 General Methodology

Details regarding the statistical methods and definitions will be provided in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to database lock. All statistical analyses will be performed by the Biometrics department at Shire. Statistical analyses will be performed using Version 9.1 or higher of SAS® (SAS Institute, Cary, NC 27513).

Continuous variables will be summarized using descriptive statistics including the number of observations, 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 2 possible treatment assignments in the antecedent study, ROPP-2008-01, Section D (rhIGF-1/rhIGFBP-3 or standard neonatal care).

For analysis purposes, baseline is defined as the first assessment either in the antecedent study (ROPP-2008-01) or in this study (SHP-607-201). As necessary, relevant data from Study ROPP-2008-01 may be summarized with the data from this study (SHP-607-201).

10.2 Determination of Sample Size

No formal sample size calculation was performed for this study because this is a follow-up study to Section D of Study ROPP-2008-01. Any subjects enrolled in Study ROPP-2008-01 are eligible to enroll in this study. There are up to 120 subjects who will be eligible to enroll in this long-term developmental outcome study.

10.3 Method of Assigning Study Subjects to Treatment Groups

Not applicable.

10.4 Population Description

10.4.1 Analysis Populations

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

- Safety Population- the Safety Population will consist of the subjects in the Enrolled Population who have safety follow-up data in this long-term outcome study.

10.4.2 Subject Disposition

Subjects who complete the study and subjects who prematurely discontinue from the study will be summarized by treatment group using descriptive statistics. In addition, for subjects who

prematurely discontinue from the study, the reasons for discontinuation will be summarized by treatment group.

10.4.3 Protocol Violations and Deviations

Protocol violations and deviations will be listed. Details of the criteria for deviations and violations will be provided in the SAP.

10.4.4 Demographics and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group for the Enrolled Population.

Demographics and baseline characteristics will be examined to assess the comparability of the treatment groups. Continuous variables such as age (including corrected age), weight, and length/height will be summarized using number of observations, mean, standard deviation, median, minimum and maximum values. Categorical variables, like gender and race, will be summarized using number of observations and percentages.

Medical history, including maternal and perinatal history, (as obtained from the antecedent study, ROPP-2008-01) will be summarized by treatment group using the number of observations and percentages of subjects reporting each category.

10.5 Efficacy Analysis

All efficacy analyses will be performed using the Enrolled Population.

10.5.1 Primary Efficacy Analysis

The primary efficacy endpoints consist of the following:

- Visual Acuity: Visual acuity will be categorized as the following:
    - normal (measurable acuity ≥20/40),
    - below normal (20/200≤ measurable acuity <20/40),
    - poor (measurable acuity ≤20/200)
    - blind/low vision (only the ability to detect the 2.2 cm wide stripes on the low-vision Teller acuity card and at any location in the visual field).

  The number and proportion of patients within each category listed above will be summarized by treatment group and visit. In addition, acuity results in the normal and below normal categories will be classified as favorable outcomes, and acuity results in the poor and blind/low-vision categories will be classified as unfavorable outcomes. Tabular summaries by treatment group and visit will include the frequency and the percentage for each visual acuity category. In addition, shift tables of favorable outcomes from baseline (first assessment during this study) to each of the subsequent assessments, including the last assessment, will be presented by treatment group.

- Ocular Alignment and Oculomotor Exam (Motility): Findings from the ocular motility assessment will be either presence or absence of strabismus (esotropia, exotropia, hypertropia, or hypotropia). Tabular summaries by treatment group and visit will include the frequency and the percentage in each category. In addition, shift tables from baseline (first assessment during this study) to the last assessment will be provided by treatment group.
- Nystagmus: Presence or absence of nystagmus will be summarized by treatment group and visit
- Refraction with Cycloplegia: Findings from the refraction with cycloplegia will be summarized by treatment group and visit
- Stereoacuity: Presence or absence of stereopsis will be summarized by treatment group and visit

10.5.2 Secondary Efficacy Analysis

- Growth Parameters (body weight, body length [and height], and head circumference): A standard Z-score, utilizing WHO child growth standards, will be calculated for each assessment by adjusting age- and sex- matched means and standard deviations (norm). The descriptive statistics of the Z-score for each of these parameters will be summarized at each assessment and the corresponding change from baseline. When appropriate, a 95% CI for the corresponding mean change within each group and the difference in the mean change between the 2 treatment groups and the corresponding 95% CI will be presented as appropriate. If the parametric assumption for the distribution of the above endpoints cannot be justified, a non-parametric approach will be utilized to estimate the treatment difference (ie, median difference or Hodges-Lehmann estimator and the corresponding confidence intervals)
- BSID-III and WPPSI-IV: The raw score for each domain within each questionnaire will be summarized by treatment group and visit using descriptive statistics.
- ADHD-RS-IV: ADHD-RS-IV total score and subscales (Hyperactivity/Impulsivity and Inattentiveness) will be summarized by treatment group and visit using descriptive statistics.
- SCQ: The SCQ subscales (communication and social) will be summarized by treatment group and visit using descriptive statistics
- VABS-II: The raw score for each domain of the scale will be summarized by treatment group and visit using descriptive statistics.
- CBCL: The raw score and change from baseline for each domain of the scale will be summarized by treatment group and visit using descriptive statistics.
- Pulmonary morbidity questionnaire: The binary response of each question will be by treatment group and visit using descriptive statistics.
- Survival: For subjects who have an event (ie, death), the event time will be calculated as the length of time from the subject's date of birth to death during the study due to any cause. Subjects who do not have an event (ie, death) during the study will be

censored at the end of the study. The survival endpoint will be analyzed by treatment group using Kaplan-Meier methods.

10.5.3 Subset Analyses

Subgroup analyses may be explored based on factors that may have influence on the efficacy or safety endpoints. Subgroup analyses will be specified in the SAP.

10.5.4 Exploratory Analyses

[redacted]

10.6 Health Economics and Outcomes Research Analyses

For PedsQL, descriptive statistics will be provided for summary scores by treatment group 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 and at each time point.

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.

10.7 Analysis of Safety

Safety summaries will be based on all assessments post-baseline. The safety data will be assessed by AE monitoring, change in cardiac size, and kidney and spleen size over time.

Adverse events will be summarized by system organ class and preferred term for each treatment group and overall, the number and percentage of subjects having any AE, having an AE in each body system and having each individual AE. In addition, those events which resulted in death, or were otherwise classified as serious will be presented in a separate listing. In addition, the summary of AEs will be presented by severity and relationship to trial medication.

The change in cardiac size, and size of kidney and spleen will be assessed at the 6-month CA visit via echocardiogram and abdominal ultrasound, respectively. These data will be analyzed as a binary response (ie, normal/abnormal) and summarized using frequency count. The number and proportion of patients with each category (ie, normal/abnormal) for each of these safety endpoints will be summarized by treatment group. In addition, the 2-sided 95% CI for the proportion of patients with a normal status for each of the endpoints will be estimated by treatment group.

Physical examinations findings will be summarized descriptively.

10.8 Statistical/Analytical Issues

10.8.1 Adjustment for Covariates

If any baseline data are imbalanced and are considered to be clinically relevant, between-group comparisons for efficacy outcomes will be adjusted for covariates and detailed in the SAP.

10.8.2 Handling of Dropouts or Missing Data

Handling of missing data rules will be described in the SAP.

10.8.3 Interim Analyses and Data Monitoring

An interim analysis will be performed after all data from all enrolled subjects in this study have either completed 2-year follow-up (24-month visit) assessments or have prematurely withdrawn from the study (before completing 2 years of follow-up) has been entered into the database, queried and discrepancies resolved. A full 2-year study report based on these data, including efficacy and safety endpoint analyses, will be completed.

Additionally, descriptive analyses of the data at other time points before study completion may be performed for safety monitoring, regulatory reporting or general planning purposes.

10.8.4 Multiple Comparisons/Multiplicity

Not applicable.

10.8.5 Sensitivity Analyses

Sensitivity analyses for the efficacy outcomes will be detailed in the SAP, as necessary.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

Before initiation of the study, the Investigators must provide the Sponsor with a completed Form FDA 1572 and Investigator Agreement. Curriculum vitae must be provided for the Investigators and sub-investigators listed on Form FDA 1572 or Investigator Agreement.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, and their study related duties and functions. The Investigator must maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study related duties.

11.2 Institutional Review Board or Independent Ethics Committee Approval

Before initiation of the study, the Investigator must provide the Sponsor with a copy of the written IRB/IEC/REB approval of the protocol and the informed consent form. This approval must refer to the informed consent form and to the study title, study number, and version and date of issue of the study protocol, as given by the Sponsor on the cover page of the protocol.

Status reports must be submitted to the IRB/IEC/REB at least once per year. The IRB/IEC/REB must be notified of completion of the study. Within 3 months of study completion or termination, a final report must be provided to the IRB/IECREB. A copy of these reports will be sent to the study clinical monitor. The Investigators must maintain an accurate and complete record of all submissions made to the IRB/IEC, including a list of all reports and documents submitted. AEs which are reported to the US (FDA or other Regulatory agencies (Safety Reports) must be submitted promptly to the IRB/IEC/REB.

11.3 Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigators abide by good clinical practice (GCP) as described in the 21 CFR Parts 50, 56, and 312 and the International Conference on Harmonization (ICH) GCP Guidelines Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

11.4 Subject Information and Consent

Before enrolling in the clinical study, the subject or the subject's parent(s) or legally authorized representative(s) must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her.

An informed consent form (assent form if applicable) that includes information about the study will be prepared and given to the subject or the subject's parent(s) or legally authorized representative(s). This document will contain all FDA and ICH-required elements. The informed consent (or assent) form must be in a language understandable to the subject or the subject's

parent(s) or legally authorized representative(s) and must specify who informed the subject, the subject's parent(s), or the subject's legally authorized representative(s).

After reading the informed consent document, the subject or the subject's parent(s) or legally authorized representative(s) must give consent in writing. Consent must be confirmed at the time of consent by the personally dated signature of the subject, the subject's parent(s) or the subject's legally authorized representative(s) and by the personally dated signature of the person conducting the informed consent discussions.

If the subject or the subject's parent(s) or legally authorized representative(s) is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the subject or by a local legally recognized alternative (eg, the subject's thumbprint or mark) or by the personally dated signature of the subject's parent(s) or the subject's legally authorized representative. The witness and the person conducting the informed consent discussions must also sign and personally date the informed consent document. It should also be recorded and dated in the source document that consent was given.

A copy of the signed and dated consent document(s) must be given to the subject or the subject's parent(s) or legal representative(s). The original signed and dated consent document will be retained by the Investigator.

The Investigator will not undertake any measures specifically required solely for the clinical study until valid consent has been obtained.

A model of the informed consent form to be used in this study will be provided to the sites separately from this protocol.

11.5 Subject Confidentiality

Subject names will not be supplied to the Sponsor. Only the subject number and subject initials will be recorded in the eCRF, and if the subject name appears on any other document, it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be told that representatives of the Sponsor, a designated CRO, the IRB/IEC/REB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. The Investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

11.6 Study Monitoring

Monitoring procedures that comply with current Good Clinical Practice (GCP) guidelines will be followed. Review of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by the Sponsor or its designee. Monitoring will be performed by a representative of the Sponsor (Clinical Study Monitor) who will review the eCRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and communications (letter, telephone, and facsimile).

11.7 Case Report Forms and Study Records

11.7.1 Case Report Forms

Electronic case report forms (eCRFs) are provided for each subject. All forms must be filled out by authorized study personnel. All corrections to the original eCRF entry must indicate the reason for change. The Investigator is required to sign the eCRF after all data have been captured for each subject. If corrections are made after review and signature by the Investigator, he or she must be made aware of the changes, and his or her awareness documented by resigning the eCRF.

11.7.2 Critical Documents

Before the Sponsor initiates the trial (ie, obtains informed consent from the first subject), it is the responsibility of the Investigator to ensure that the following documents are available to Sponsor or their designee:

- Completed FDA Form 1572 (Statement of Investigator), signed, dated, and accurate
- Curricula vitae of Investigator and sub-investigator(s) (current, dated and signed within 12 months of study initiation)
- Copy of Investigator and sub-investigator(s) current medical license (indicating license number and expiration date)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/IEC/REB clearly identifying the documents reviewed by name, number and date of approval or re approval: protocol, any amendments, Subject Information/Informed Consent Form, and any other written information to be provided regarding subject recruitment procedures
- Copy of IRB/IEC/REB approved Subject Information/Informed Consent Form/any other written information/advertisement (with IRB approval stamp and date of approval)
- Current list of IRB/IEC/REB Committee members/constitution (dated within 12 months prior to study initiation)
- Financial Disclosure Form signed by Investigator and sub-investigator(s)
- Current laboratory reference ranges (if applicable)
- Certification/QA scheme/other documentation (if applicable)

Regulatory approval and notification as required must also be available; these are the responsibility of Shire.

11.8 Data Monitoring Committee

Given that any long-term safety signal observed in this study could impact the safety profile of rhIGF-1/rhIGFBP-3 as administered in premature neonates being enrolled in the antecedent study (ROPP-2008-01, Section D), the Data Monitoring Committee (DMC) for Study ROPP-2008-01 will review safety data from this long-term outcome study.

11.9 Protocol Violations/Deviations

The Investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the IRB/IEC/REB and the appropriate regulatory authorities, where applicable, have given approval/favorable opinion. Modifications to the protocol will not be made without agreement of the Sponsor. Changes to the protocol will require written IRB/IEC/REB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB/IEC/REB may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC/REB. The Sponsor will submit all protocol modifications to the regulatory authorities, where applicable, in accordance with the governing regulations.

A record of subjects screened, but not entered into the study, is also to be maintained. No protocol exemption will be granted for this study.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Sponsor or its designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will need to be reviewed by the medical monitor and may also be required to be submitted to the IRB/IEC/REB.

Protocol modifications will only be initiated by the Sponsor and must be approved by the IRB/IEC/REB and submitted to the FDA or other applicable international regulatory authority before initiation, if applicable.

11.10 Premature Closure of the Study

If the Sponsor, Investigator, or regulatory authorities discover conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable subject risk, the study may be terminated after appropriate consultation between the Sponsor and the Investigator(s). In addition, a decision on the part of the Sponsor to suspend or discontinue development of the investigational product may be made at any time. Conditions that may warrant termination of the study or site include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study

- Failure of the Investigator to comply with pertinent global regulations
- Submission of knowingly false information from the study site to the Sponsor or other pertinent regulatory authorities
- Insufficient adherence by the Investigator to protocol requirements

11.11 Access to Source Documentation

Regulatory authorities, the IRB/IEC/REB, or the Sponsor may request access to all source documents, eCRFs, and other study documentation for onsite audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Monitoring and auditing procedures that comply with current GCP guidelines will be followed. On-site review of the eCRFs for completeness and clarity, crosschecking with source documents, and clarification of administrative matters may be performed.

11.12 Data Generation and Analysis

The clinical database will be developed and maintained by a contract research organization or an electronic data capture technology provider as designated by the Sponsor. The Sponsor or its designee will be responsible for performing study data management activities.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medication will be coded using WHO-Drug Dictionary (WHO-DD). Central reads will be employed as described in the study manual to aid in consistent measurement of abdominal ultrasound and echocardiogram parameters.

11.13 Retention of Data

Essential documents should be retained until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The Sponsor will notify the Investigator if these documents must be retained for a longer period of time. It is the responsibility of the Sponsor to inform the Investigator or institution as to when these documents no longer need to be retained.

11.14 Financial Disclosure

The Investigator should disclose any financial interests in the Sponsor as described in 21 CFR Part 54 prior to beginning this study. The appropriate form will be provided to the Investigator by the Sponsor, which will be signed and dated by the Investigator, prior to the start of the study.

11.15 Publication and Disclosure Policy

All information concerning the study material, such as patent applications, manufacturing processes, basic scientific data, and formulation information supplied by the Sponsor and not previously published are considered confidential and will remain the sole property of the

Sponsor. The Investigator agrees to use this information only in accomplishing this study and will not use it for other purposes.

It is understood by the Investigator that the information developed in the clinical study may be disclosed as required to the authorized regulatory authorities and governmental agencies. In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the Sponsor with complete test results and all data developed in the study in a timely manner.

The Investigator and any other clinical personnel associated with this study will not publish the results of the study, in whole or in part, at any time, unless they have consulted with the Sponsor, provided the Sponsor a copy of the draft document intended for publication, and obtained the Sponsor's written consent for such publication. All information obtained during the conduct of this study will be regarded as confidential.

12 LIST OF REFERENCES

1. Maida JM, Mathers K, Alley CL. Pediatric ophthalmology in the developing world. Current opinion in ophthalmology 2008;19:403-8.
2. O'Connor AR, Stephenson TJ, Johnson A, et al. Visual function in low birthweight children. The British journal of ophthalmology 2004;88:1149-53.
3. Keith CG, Kitchen WH. Ocular morbidity in infants of very low birth weight. The British journal of ophthalmology 1983;67:302-5.
4. Laws D, Shaw DE, Robinson J, Jones HS, Ng YK, Fielder AR. Retinopathy of prematurity: a prospective study. Review at six months. Eye 1992;6:477-83.
5. O'Connor AR, Stephenson T, Johnson A, et al. Long-term ophthalmic outcome of low birth weight children with and without retinopathy of prematurity. Pediatr 2002;109:12-8.
6. Schaffer DB, Quinn GE, Johnson L. Sequelae of arrested mild retinopathy of prematurity. Archives of ophthalmology 1984;102:373-6.
7. Cats BP, Tan KE. Prematures with and without regressed retinopathy of prematurity: comparison of long-term (6-10 years) ophthalmological morbidity. Journal of pediatric ophthalmology and strabismus 1989;26:271-5.
8. Chard T. Insulin-like growth factors and their binding proteins in normal and abnormal human fetal growth. Growth Regul 1994;4:91-100.
9. Hansen-Pupp I, Lofqvist C, Polberger S, et al. Influence of insulin-like growth factor I and nutrition during phases of postnatal growth in very preterm infants. Pediatr Res 2011;69:448-53.
10. Ohkawa N, Shoji H, Kitamura T, et al. IGF-I, leptin and active ghrelin levels in very low birth weight infants during the first 8 weeks of life. Acta Paediatr 2010;99:37-41.
11. Lofqvist C, Hellgren G, Niklasson A, Engstrom E, Ley D, Hansen-Pupp I. Low postnatal serum IGF-I levels are associated with bronchopulmonary dysplasia (BPD). Acta Paediatr 2012;101:1211-6.
12. Ishii DN, Glazner GW, Whalen LR. Regulation of peripheral nerve regeneration by insulin-like growth factors. Annals of the New York Academy of Sciences 1993;692:172-82.
13. Lewis ME, Neff NT, Contreras PC, et al. Insulin-like growth factor-I: potential for treatment of motor neuronal disorders. Experimental neurology 1993;124:73-88.
14. Pediatric Ophthalmology/Strabismus Preferred Practice Pattern Development Process and Participants. Pediatric Eye Evaluations: American Academy of OphthalmologyPediatric Ophthalmology/Strabismus Preferred Practice Pattern Panel; 2012.

[redacted]

[redacted]

19. Wechsler D. Wechsler preschool and primary scale of intelligence 4th ed. Bloomington, MN: Pearson; 2012.
20. Wechsler D. Technical and Interpretive Manual Supplement: Special Group Validity Studies With Other Measures2012.
21. Achenbach T, Rescorla L. Manual for the ASEBA preschool forms and profiles. Burlington, VT: University of Vermont; 2000.
22. Vinall J, Miller SP, Synnes AR, Grunau RE. Parent behaviors moderate the relationship between neonatal pain and internalizing behaviors at 18 months corrected age in children born very prematurely. Pain 2013;154:1831-9.
23. Scott MN, Taylor HG, Fristad MA, et al. Behavior disorders in extremely preterm/extremely low birth weight children in kindergarten. J Dev Behav Pediatr 2012;33:202-13.
24. Wu YC, Leng CH, Hsieh WS, et al. A randomized controlled trial of clinic-based and home-based interventions in comparison with usual care for preterm infants: Effects and mediators. Res Dev Disabil 2014;35:2384-93.
25. Ebesutani C, Bernstein A, Nakamura BJ, Chorpita BF, Higa-McMillan CK, Weisz JR. Concurrent Validity of the Child Behavior Checklist DSM-Oriented Scales: Correspondence with DSM Diagnoses and Comparison to Syndrome Scales. Journal of psychopathology and behavioral assessment 2010;32:373-84.
26. DuPaul G, Power T, Anastopoulos A, Reed R. The ADHD rating scale IV: checklists, norms and clinical interpretation. New York: Guilford Press; 1998.
27. Rutter M, Bailey A, Lord C. Manual for the Social Communication Questionnaire2003.
28. Chandler S, Charman T, Baird G, et al. Validation of the social communication questionnaire in a population cohort of children with autism spectrum disorders. Journal of the American Academy of Child and Adolescent Psychiatry 2007;46:1324-32.
29. Gosselin J, Amiel-Tison C. Neurological Assessment from Birth to 6 Years. 2nd ed. Montreal: CHU Sainte-Justine; 2011.
30. Matza LS, Swensen AR, Flood EM, Secnik K, Leidy NK. Assessment of health-related quality of life in children: a review of conceptual, methodological, and regulatory issues. Value Health 2004;7:79-92.
31. Varni JW, Burwinkle TM, Lane MM. Health-related quality of life measurement in pediatric clinical practice: an appraisal and precept for future research and application. Health Qual Life Outcomes 2005;3:34.
32. Constitution of the World Health Organization: basic document. Geneva, Switzerland: World Health Organization; 1948.

33. Varni JW, Limbers CA. The pediatric quality of life inventory: measuring pediatric health-related quality of life from the perspective of children and their parents. Pediatr Clin North Am 2009;56:843-63.

34. Varni JW, Limbers CA, Neighbors K, et al. The PedsQL Infant Scales: feasibility, internal consistency reliability, and validity in healthy and ill infants. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2011;20:45-55.

35. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Medical care 2001;39:800-12.

36. Saigal S, Rosenbaum P, Stoskopf B, et al. Development, reliability and validity of a new measure of overall health for pre-school children. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2005;14:243-57.

37. Rosenbaum DM, Korngold E, Teele RL. Sonographic assessment of renal length in normal children. Am J Roentgenol 1984;142:467-9.

38. Rosenberg HK, Markowitz RI, Kolberg H, Park C, Hubbard A, Bellah RD. Normal splenic size in infants and children: sonographic measurements. Am J Roentgenol 1991;157:119-21.

39. Stevens TP, Finer NN, Carlo WA, et al. Respiratory Outcomes of the Surfactant Positive Pressure and Oximetry Randomized Trial (SUPPORT). J Pediatr 2014;165:240-9.e4.

40. Zivanovic S, Peacock J, Alcazar-Paris M, et al. Late outcomes of a randomized trial of high-frequency oscillation in neonates. N Engl J Med 2014;370:1121-30.

Appendix 1 Study Schedule of Events

Procedures	Initial Study Visit[e]	Months (CA)					Years (CA)			
	40 weeks (CA)/term equivalent	3[f] ± 2 wks	6 ± 1 mth	12 ± 3 mths	20 -1 mth[g]	24 ± 3 mth	3[f] ± 3 mths	4[f] ± 3 mths	4.75 -1 mth[g]	5 + 6 mths
Informed Consent	•									
Eligibility Criteria	•									
Demographics	•									
Visual acuity[a]			•	•	•	•			•	•
Corrective lens determination				•	•[g]				•[g]	
Ocular alignment and motility				•		•				•
Refraction with cycloplegia			•	•	•	•			•	•
Stereoacuity										•
Length			•	•		•				
Height										•
Weight			•	•		•				•
Head Circumference			•	•		•				
BSID-III				•		•				
WPPSI-IV										•
CBCL						•				•
VABS-II			•	•		•				•
ADHD-RS-IV										•
SCQ										•
Physical Examination including tonsil examination			•	•		•				•
Cerebral Palsy Assessment						•				
Hearing Assessment History[b]			•							
Pulmonary Morbidity Assessment			•	•		•				•
Survival assessment		•	•	•		•	•	•		•
[redacted]		[redacted]								
HRQoL[c]		•	•[h]	•[h]		•[h]	•	•		•[h]
HCRU		•	•[h]	•[h]		•[h]	•	•		•[h]
HSCS-PS						•[h]	•	•		•[h]
Abdominal Ultrasound			•							
Echocardiogram			•							
Assessment of Participation in Other Clinical Studies		•	•	•		•	•	•		•

Procedures	Initial Study Visit[e]	Months (CA)					Years (CA)			
	40 weeks (CA)/term equivalent	3[f] ± 2 wks	6 ± 1 mth	12 ± 3 mths	20 -1 mth[g]	24 ± 3 mth	3[f] ± 3 mths	4[f] ± 3 mths	4.75 -1 mth[g]	5 + 6 mths
Medications		•	•	•		•	•	•		•
Adverse events[d]	•[i]	•	•	•		•	•	•		•

Abbreviations: ADHD-RS-IV = Attention-Deficit/Hyperactivity Disorder Rating Scale-fourth edition; BSID-III = Bayley Scales of Infant and Toddler Development-Third Edition, CBCL = Child Behavior Checklist; CA = corrected age; HCRU = health care resource use; HRQoL = health-related quality of life; HSCS-PS = Health Status Classification System; mth(s) = months; [redacted]; PedsQL = Pediatric Quality of Life Inventory; SCQ = Social Communication Questionnaire; VABS-II = Vineland Adaptive Behavior Scales, Second Edition; wks = weeks; WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition

[a] The tools used to assess visual acuity will change as the subject ages during their participation in the study. The tools that will be used in this study and are summarized by applicable study visit in Table 12-1.

[b] Historical hearing test data may be recorded at any time during the study prior to the 6-month visit.

[c] HRQoL will be assessed via the validated PedsQL™ scales appropriate for the child's age of development as specified in the Study Operations Manual

[d] Adverse event collection will include an assessment of the specified targeted medical events

[e] The Initial Visit may be performed prior to 40 weeks CA for any subject who discontinued from Study ROPP-2008-01 and, for all subjects, any time after 40 weeks CA, up to the study visit to occur at 3 months CA.

[f] Visits at 3 months, 3 years, and 4 years CA will be conducted by telephone.

[g] The 20-month visit and the 4.75-year (4 years, 9 months) visit must occur at least 1 month prior to the 24-month and 5-year visits, respectively. Any prescribed corrective lenses must be worn for at least 1 month prior to the 24-month and 5-year assessments.

[h] The HRQoL, HCRU, and HSCS-PS assessments for the 6-month, 12-month, 24-month and 5-year visits may be performed through a call center if there are time constraints during the on-site visit. At the 3-month, 3-year, and 4-year visits, these assessments will be performed through a call center and may be performed at any time within the visit window.

[i] The following, collected as part of the ROPP-2008-01 study, will be used as part of this study (SHP-607-201): any ongoing targeted medical events regardless of causality and any ongoing study drug-related AEs, including SAEs.

Table 12-1 Summary of Visual Acuity Assessments

Visual Acuity Assessment Tool	Description	Unit of Measure	Applicable Age/Study Visit (CA)
Teller acuity cards	Resolution acuity – discrimination of a grating optotype from a background with the same mean luminance	cycles per degree	6 months 12 months
LEA Symbols Test	Recognition acuity - tests recognition of 4 optotypes	Snellen fraction (eg, 20/20)	24 months[a]
LEA Symbols (ETDRS-style) chart	Distance visual acuity test	Snellen fraction (eg, 20/20)	5 years[a]

Abbreviations: CA = corrected age; ETDRS = Early Treatment of Diabetic Retinopathy Study

[a] At ages 24 months and 5 years CA an attempt should be made to assess visual acuity by the LEA Symbols Test and LEA Symbols Chart, respectively. If during this attempt, the examiner determines that it will not be possible to perform an accurate assessment with the relevant LEA tool, visual acuity should be assessed with the Teller acuity cards.

Appendix 2 Protocol Signature Page

Study Title: Long-term Outcome of Children Enrolled in Study ROPP-2008-01 Previously Treated with rhIGF-1/rhIGFBP-3 for the Prevention of Retinopathy of Prematurity (ROP) or Who Received Standard Neonatal Care

Study Number: SHP-607-201

Final Date: 27 August 2014

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signatory:

Investigator

_____
Signature **Date**

_____
Printed Name

I have read and approve the protocol described above.

Signatory:

Shire Medical Monitor [redacted] _____ [redacted]

[redacted], MD, MBA
Printed Name

Clinical Trial Protocol: SHP-607-201

Study Title:	Long-term Outcome of Children Enrolled in Study ROPP-2008-01 Previously Treated with rhIGF-1/rhIGFBP-3 for the Prevention of Retinopathy of Prematurity (ROP) or Who Received Standard Neonatal Care
Study Number:	SHP-607-201
Study Phase:	II
Product Name:	Mecasermin rinfabate (rhIGF-1/rhIGFBP-3)
IND Number:	121698
EUDRACT Number	2014-003556-31
Indication:	Retinopathy of Prematurity
Investigators:	Multicenter
Sponsor:	Premacure AB, A Member of the Shire Group of Companies
Sponsor Contact:	300 Shire Way Lexington, MA 02421 USA [redacted]
Medical Monitor:	North America [redacted], MD, MPH Europe [redacted] MD, PhD

	Date
Original Protocol:	27 August 2014
Amendment 1	19 February 2016

Confidentiality Statement

SYNOPSIS

Sponsor:

Premacure AB, A Member of the Shire Group of Companies

Name of Finished Product:

Mecasermin rinfabate (rhIGF-1/rhIGFBP-3)

Study Title:

Long-term Outcome of Children Enrolled in Study ROPP-2008-01 Previously Treated with rhIGF-1/rhIGFBP-3 for the Prevention of Retinopathy of Prematurity (ROP) or Who Received Standard Neonatal Care

Study Number:

SHP-607-201

Study Phase: II

Investigational Product, Dose, and Mode of Administration:

Not applicable.

Primary Objectives

The primary objectives of this study are:

- To evaluate the long-term efficacy outcomes following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D) as assessed by ROP associated visual outcomes
- To evaluate the long-term safety outcomes following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D)

Secondary Objectives

The secondary objectives of this study are to evaluate the effect following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D) on:

- Growth parameters
- Cognitive development
- Physical development
- Child behavior
- Pulmonary morbidity
- Survival
- Health-related quality of life (HRQoL)
- Health utility
- Health care resource use (HCRU)

Exploratory Objective

[redacted]

Study Endpoints

The primary efficacy endpoints of this study are:

- Visual acuity as assessed by an age appropriate method
- Ocular alignment and ocular motor examination in primary gaze and in as many of 9 positions of gaze as possible as assessed by corneal light reflex and by the cover test
- Assessment of nystagmus by observation
- Refraction as assessed by retinoscopy with cycloplegia
- Stereoacuity as assessed with the Lang Stereotest

The secondary efficacy endpoints of this study are:

- Growth parameters including body weight, body length (or height), and head circumference
- Cognitive development as assessed by the following standardized, age-appropriate tools:
    - Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)
    - Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV)
- Physical development as assessed by standardized, age appropriate tools including physical exam, neurological examination for assessment of cerebral palsy, and hearing assessment
- Child behavior as assessed by the following:
    - Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
    - Child Behavior Checklist (CBCL; 1 ½ to 5)
    - Attention Deficit/Hyperactivity Disorder Rating Scale-fourth edition (ADHD RS-IV) for the assessment of symptoms of attention deficit/hyperactivity disorder (ADHD)
    - Social Communication Questionnaire (SCQ) for screening of Autism Spectrum Disorder (ASD)
- Pulmonary morbidity data (eg, hospitalizations, emergency room [ER] visits, pulmonary medications)
- Survival as assessed by death during the study due to any cause

The health economic outcome research endpoints of this study are:

- Health-related quality of life (HRQoL) 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, respectively)

- Health status (eg, health utility) will be measured by the Health Status Classification System-Preschool (HSCS-PS)
- Resource use associated with inpatient visits, outpatient visits, medical utilization and pharmacy utilization will be assessed

The safety endpoints of this study are:

- Physical examination including tonsil examination
- Adverse events (AEs), as follows:
  - those considered related to rhIGF-1/rhIGFBP-3 (as administered in Study ROPP-2008-01, Section D)
  - those considered related to procedures performed in this study (Study SHP-607-201)
  - specified targeted medical events regardless of causality
  - fatal SAEs regardless of causality
- Cardiac size as assessed by echocardiogram
- Kidney and spleen size and any other gross abnormalities as assessed by abdominal ultrasound

Exploratory Endpoints:

[redacted]

Study Population:

Subjects randomized in Study ROPP-2008-01, Section D are eligible to enroll in this study; completion of Study ROPP-2008-01 Section D is not required. Subjects in Study ROPP-2008-01 are premature infants (gestational age of 23 weeks + 0 days to 27 weeks + 6 days) who are randomized to receive either treatment with rhIGF-1/rhIGFBP-3 or standard neonatal care. Up to 120 subjects are planned to be randomized into Study ROPP-2008-01 Section D.

Study Design:

This is a Phase II, multicenter, long-term developmental outcome study enrolling subjects who were randomized in Section D of Study ROPP-2008-01. Enrolled subjects in this study will be followed through age 5 years corrected age (CA). This study will enroll both subjects who were in the treated (received rhIGF-1/rhIGFBP-3) and control (received standard neonatal care) groups of Study ROPP-2008-01 (Section D) to enable assessment of rhIGF-1/rhIGFBP-3 long-term efficacy and safety outcomes versus standard neonatal care. No investigational product will be administered in this study.

Study Duration:

Duration for an individual subject's participation in the study will vary depending upon age at enrollment, but subjects will not be followed beyond age 5.5 years corrected age (CA).

Study Inclusion and Exclusion Criteria:

Subjects randomized in Study ROPP-2008-01, Section D are eligible to enroll in this study. Subjects will not be excluded from participating in other clinical studies.

Efficacy Assessments:

Efficacy will be assessed by visual outcomes, growth parameters, cognitive development, physical development, child behavior, pulmonary morbidity, and survival.

Safety Assessments:

Safety will be assessed by physical examination (including tonsil examination), AEs (as specified), echocardiogram, and abdominal ultrasound.

Statistical Methods

Details regarding the statistical methods and definitions will be provided in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to database lock. All statistical analyses will be performed by the sponsor or CRO after the database is locked. Statistical analyses will be performed using Version 9.1 or higher of SAS® (SAS Institute, Cary, NC 27513).

Continuous variables will be summarized using descriptive statistics including the number of observations, 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 2 possible treatment assignments in the antecedent study, ROPP-2008-01, Section D (rhIGF-1/rhIGFBP-3 or standard neonatal care).

For analysis purposes, baseline is defined as the first assessment either in the antecedent study (ROPP-2008-01) or in this study (SHP-607-201). As necessary, relevant data from Study ROPP-2008-01 may be summarized with the data from this study (SHP-607-201).

Date of Original Protocol: 27 August 2014

Date of Amendment 1: 19 February 2016

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AAO	American Academy of Ophthalmology
ADHD	attention-deficit hyperactivity disorder
ADHD-RS-IV	Attention-Deficit/Hyperactivity Disorder Rating Scale-fourth edition
AE	adverse event
ASD	Autism Spectrum Disorder
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
CBCL	Child Behavior Checklist (1 ½ to 5)
CFR	Code of Federal Regulations
CA	corrected age
CI	confidence interval
CRF	case report form (electronic)
CRO	contract research organization
DMC	data monitoring committee
eCRF	electronic case report form
EOS	end of study
ETDRS	Early Treatment of Diabetic Retinopathy Study
ER	emergency room
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GH	growth hormone
HRQoL	health-related quality of life
HSCS-PS	Health Status Classification System-Preschool
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IGF	insulin-like growth factor
IGFBP-3	insulin-like growth factor binding protein-3
IND	Investigational New Drug application
IRB	institutional review board
LV	left ventricle
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
OD	right eye

Abbreviation	Definition
OS	left eye
OU	both eyes
PedsQL	Pediatric Quality of Life Inventory
REB	research ethics board
ROP	retinopathy of prematurity
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System©
SCQ	Social Communication Questionnaire
SD	standard deviation
SOE	schedule of events
SUSAR	suspected unexpected serious adverse reaction
UK	United Kingdom
US	United States
VABS-II	Vineland Adaptive Behavior Scales, Second Edition
VLBW	very low birth weight
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
WPPSI-IV	Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition

1 INTRODUCTION

Retinopathy of prematurity (ROP) is a rare disorder of the developing retinal blood vessels and retinal neurons of the preterm infant and is one of the leading causes of preventable blindness in children.[1]

Visual acuity is decreased in infants with a history of ROP.[2] In addition to acuity, other aspects of eye health are also significantly impacted by ROP. Strabismus and myopia are clearly increased in patients with a history of ROP.[3-6] Additionally, more than half of patients at 6 to 10 years of age with a history of Stage 1 and Stage 2 ROP were reported to have ongoing visual issues.[7]

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. During fetal life, IGF-1 is available through placental absorption and ingestion from amniotic fluid.[8] Deprivation of such factors is likely to cause inhibition or improper stimulation of important pathways, which in the eye may cause abnormal retinal vascular development, the hallmark of ROP.

The finding in both a mouse model of ROP and preterm infants that development of ROP is associated with low levels of IGF-1 after premature birth, indicates a possible role for replacement of IGF-1 to levels found in utero as a strategy to potentially decrease abnormal retinal vascularization and abnormal retinal neural development, and ultimately, ROP.

Mecasermin rinfabate (rhIGF-1/rhIGFBP-3) is the human recombinant form of the naturally occurring protein complex of IGF-1 and insulin-like growth factor binding protein-3 (IGFBP-3). rhIGF-1/rhIGFBP-3 was developed to enhance the systemic exposure of administered rhIGF-1 and to improve the safety profile of rhIGF-1 therapy. rhIGF-1/rhIGFBP-3 was approved by the Food and Drug Administration (FDA) in 2005 for the treatment of growth failure in children with severe primary IGF-1 deficiency or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.

The pharmacokinetics and safety of rhIGF-1/rhIGFBP-3 have been evaluated in a Phase I study (ROPP-2005-01) and pharmacokinetics, safety, and efficacy are being evaluated in the ongoing phase II study (ROPP-2008-01). Sections A-C of the ROPP-2008-01 study are complete. Section D of the ROPP-2008-01 study is currently being conducted to assess pharmacokinetics, safety and efficacy of rhIGF-1/rhIGFBP-3 for the prevention of ROP in premature infants (up to a corrected age [CA] of 40 weeks [± 4 days]). Subjects in Study ROPP-2008-01are randomly assigned to receive rhIGF-1/rhIGFBP-3 or standard neonatal care. The target dose of rhIGF-1/rhIGFBP-3 for Study Section D is 250 µg/kg/24 hours to be administered via continuous infusion starting on Study Day 0 (day of birth) and continuing through postmenstrual age (gestational age + time elapsed from birth) 29 weeks + 6 days.

Although the rhIGF-1/rhIGFBP-3 therapy in Section D of the Phase II study (Study ROPP-2008-01) represents a short-term exposure (< 2 months for each subject), rhIGF-1/rhIGFBP-3 may have long-lasting effects on visual outcomes as well as other potential

outcomes related to complications of prematurity such as neurodevelopment, pulmonary function, and growth. In addition, it is critical to understand any long term safety effects from short term exposure to rhIGF-1/rhIGFBP-3.

The long-term outcomes assessed in this study will require utilization of different assessment tools than are utilized in the Phase II study, ROPP-2008-01 Section D, given the changes in physical and cognitive development that will occur in the subjects as they age during their participation in this study.

Please refer to the current edition of the Investigator's Brochure for further information concerning the safety and clinical development of rhIGF-1/rhIGFBP-3.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are:

- To evaluate the long-term efficacy outcomes following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D) as assessed by ROP-associated visual outcomes
- To evaluate the long-term safety outcomes following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D)

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate the effect following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D) on:

- Growth parameters
- Cognitive development
- Physical development
- Child behavior
- Pulmonary morbidity
- Survival
- Health-related quality of life (HRQoL)
- Health utility
- Health care resource use (HCRU)

2.3 Exploratory Objective

[redacted]

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

3.1.1 Primary Efficacy Endpoints

- Visual acuity as assessed by an age-appropriate method
- Ocular alignment and ocular motor examination in primary gaze and in as many of 9 positions of gaze as possible as assessed by corneal light reflex and by the cover test
- Assessment of nystagmus by observation
- Refraction as assessed by retinoscopy with cycloplegia
- Stereoacuity as assessed with the Lang Stereotest

3.1.2 Secondary Efficacy Endpoints

- Growth parameters including body weight, body length (or height), and head circumference
- Cognitive development as assessed by the following standardized, age-appropriate tools:
    - Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)
    - Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV)
- Physical development as assessed by standardized, age appropriate tools including physical examination, neurological examination for assessment of cerebral palsy, and hearing assessment
- Child behavior as assessed by the following:
    - Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
    - Child Behavior Checklist (CBCL; 1 ½ to 5)
    - Attention-Deficit/Hyperactivity Disorder Rating Scale-fourth edition (ADHD-RS-IV) for the assessment of symptoms of attention-deficit/hyperactivity disorder (ADHD)
    - Social Communication Questionnaire (SCQ) for screening of Autism Spectrum Disorder (ASD)
- Pulmonary morbidity data (eg, hospitalizations, emergency room [ER] visits, pulmonary medications)
- Survival as assessed by death during the study due to any cause

3.2 Health Economic Outcome Research Endpoints

- Health Related Quality of Life (HRQoL) 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, respectively)
- Health status (eg, health utility) will be measured by the Health Status Classification System-Preschool (HSCS-PS)
- Resource use associated with inpatient visits, outpatient visits, medical utilization and pharmacy utilization will be assessed

3.3 Safety Endpoints

- Physical examination including tonsil examination
- Adverse events (AEs), as follows:
    - those considered related to rhIGF-1/rhIGFBP-3 (as administered in Study ROPP-2008-01, Section D)
    - those considered related to procedures performed in this study (SHP-607-201)
    - specified targeted medical events regardless of causality
    - fatal serious adverse events (SAEs) regardless of causality
- Cardiac size as assessed by echocardiogram
- Kidney and spleen size and any other gross abnormalities as assessed by abdominal ultrasound

3.4 Exploratory Endpoints

[redacted]

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase II, multicenter, long-term developmental outcome study enrolling subjects who were randomized in Section D of Study ROPP-2008-01 to receive either rhIGF-1/rhIGFBP-3 (treated) or standard neonatal care (control). Enrolled subjects in this study will be followed through age 5 years CA. This study will enroll both subjects who were in the treated (received rhIGF-1/rhIGFBP-3) and control (received standard neonatal care) groups of Study ROPP-2008-01 (Section D) to enable assessment of rhIGF-1/rhIGFBP-3 long-term efficacy and safety outcomes versus standard neonatal care. No investigational product will be administered in this study.

In this study, the Initial Visit will occur at 40 weeks CA (ie, term equivalent) or upon discontinuation from Study ROPP-2008-01 or may occur any time up to the visit at 3 months CA. Subjects in Study ROPP-2008-01 are premature infants enrolling at gestational age of 23 weeks + 0 days to 27 weeks + 6 days.

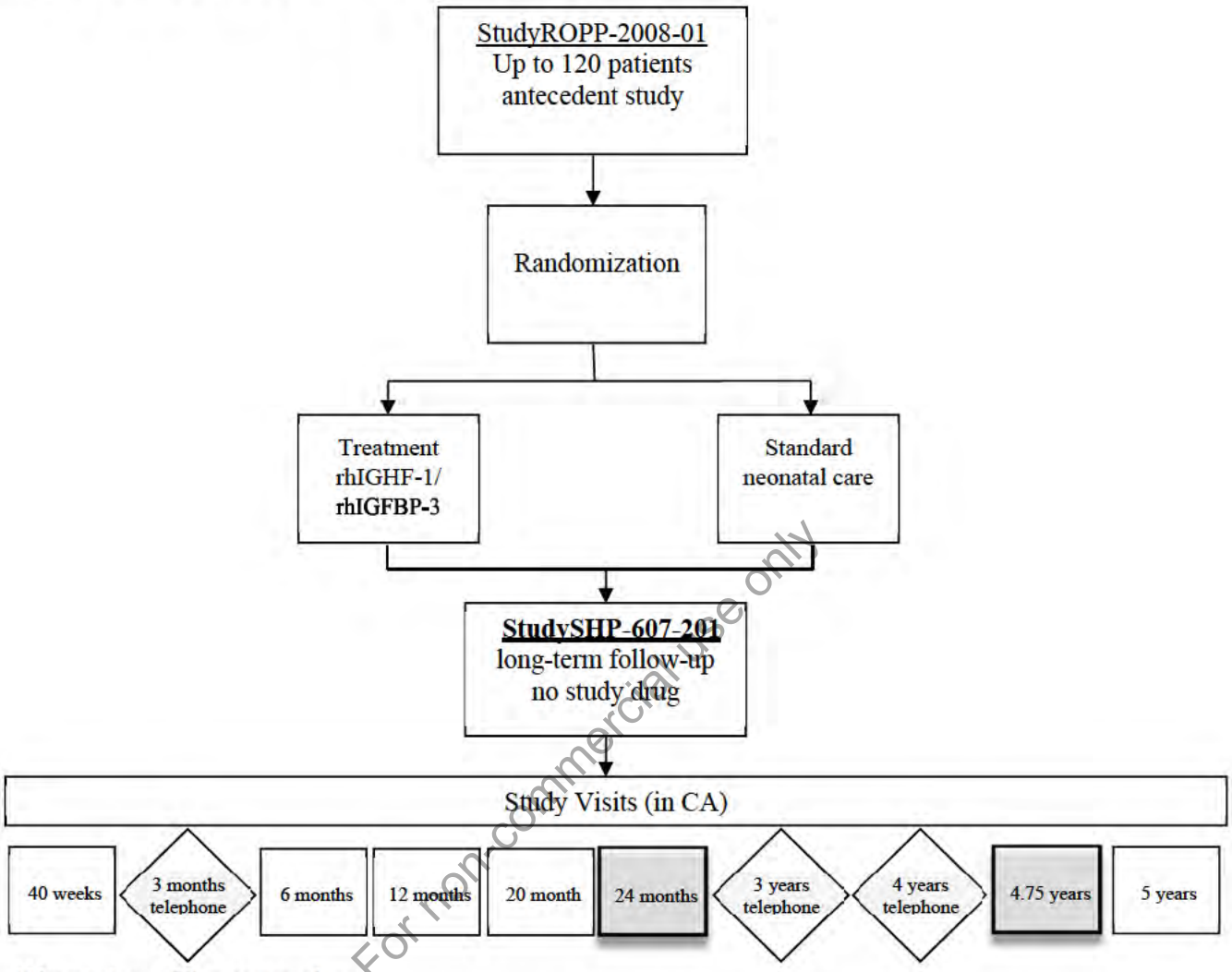
Time points for assessments have been chosen based on standard premature infant follow-up periods and represent important developmental ages for premature infant follow-up. Both telephone and clinical site visits are included to help maintain contact with subjects throughout the 5-year duration of the study.

Subjects will be evaluated at appropriate follow-up site locations with expertise in the assessment of the developmental outcomes of premature infants. Pediatric ophthalmology expertise will also be required.

See Appendix 1 for the Study Schedule of Events table.

The overall study design is outlined in Figure 4-1.

Figure 4-1 Overview of Study Design, Study SHP-607-201



Abbreviations: CA = corrected age

Note: Visits conducted by telephone are indicated with a diamond shape. Visits conducted at the study site are indicated with rectangles. Visit windows are provided in the Schedule of Events (Appendix 1).

4.2 Rationale for Study Design

The only approved therapies for ROP are ablative (cryotherapy or laser therapy). To date, there are no commercially available preventative treatments for ROP.

Although treatment with rhIGF-1/rhIGFBP-3 in ROPP-2008-01 (Section D) after premature birth is limited to less than 2 months of therapy, it remains important to assess the long-term outcomes of treatment on both efficacy and safety. Thus, this long-term follow-up study to Study ROPP-2008 01 (Section D) has been designed to assess long-term efficacy and safety outcomes following short-term exposure to rhIGF-1/rhIGFBP-3.

Insulin-like growth factor-1 (IGF-1) mediates its primary actions by binding to its specific receptor, the insulin-like growth factor 1 receptor (IGF-1R), which is present on many cell types in many tissues. Binding to its receptor initiates intracellular signaling including via the AKT signaling pathway. This pathway is involved in stimulation of cell division, growth and differentiation and inhibits programmed cell death. Specifically regarding premature infants, IGF-1 is an important mediator of fetal growth and has been shown to play a role in early postnatal growth following pre-term delivery.[9,10]

Insulin-like growth factor-1 (IGF-1) has also been shown to play a role in pulmonary development[11] and neural development.[12,13] Given the potential role for IGF-1 in the development of multiple systems, this study has been designed to evaluate the long-term effects of rhIGF-1/rhIGFBP-3, both from a safety and efficacy perspective, on the development of the premature infant.

4.3 Study Duration

Duration for an individual subject's participation in the study will vary depending upon age at enrollment, but subjects will not be followed beyond age 5.5 years CA.

5 STUDY POPULATION SELECTION

5.1 Study Population

Subjects randomized in Study ROPP-2008-01, Section D are eligible to enroll in this study; completion of Study ROPP-2008-01 Section D is not required. Subjects in Study ROPP-2008-01 are premature infants (gestational age of 23 weeks + 0 days to 27 weeks + 6 days) who are randomized to receive either treatment with rhIGF-1/rhIGFBP-3 or standard neonatal care. Up to 120 subjects are planned to be randomized in Study ROPP-2008-01 Section D.

5.2 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study.

1. Subject was randomized in Study ROPP-2008-01, Section D
2. Subject's parent or legally authorized representative(s) must provide written informed consent prior to performing any study-related activities. Study-related activities are any procedures that would not have been performed during normal management of the subject.

5.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study.

1. Any other condition or therapy that, in the Investigator's opinion, may pose a risk to the subject or interfere with the subject's ability to be compliant with this protocol or interfere with the interpretation of results
2. The subject or subject's parent or legally authorized representative(s) is unable to comply with the protocol as determined by the Investigator

6 STUDY TREATMENT

6.1 Description of Treatment

No investigational product will be administered in this study.

6.2 Treatments Administered

Not applicable.

6.3 Selection and Timing of Dose for Each Subject

Not applicable.

6.4 Method of Assigning Subjects to Treatment Groups

Not applicable.

6.5 Masking

Not applicable.

6.6 Medications

Any medications administered to the subjects will be collected from the time of informed consent through the 5-year CA visit (or until the subject withdraws or is discontinued). Any investigational product received by subjects will be recorded separately as part of an assessment of subjects' participation in other clinical studies (Section 7.11.1).

6.7 Restrictions

6.7.1 Prior Therapy

There are no restrictions related to prior therapy.

6.7.2 Other Restrictions

There are no restrictions related to fluid or food intake, or subject activity.

6.7.3 Treatment Compliance

Not applicable.

6.7.4 Packaging and Labeling

Not applicable.

6.8 Storage and Accountability

Not applicable

7 STUDY PROCEDURES

Detailed descriptions of subject procedures and evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of the study (see Schedule of Events in Appendix 1).

All data collected are to be recorded on the subject's appropriate eCRF.

Details for study procedures are described in the Operations Manual for this study.

7.1 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).

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 11.4. Documentation and filing of informed consent documents should be completed according to Section 11.4.

7.2 Study Entrance Criteria and Eligibility

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.

7.3 Study Enrollment

Subjects will be considered enrolled in the study once written informed consent has been obtained from the subject's parent(s) or legally authorized representative(s).

7.4 Demographics

Subject demographic information including gender, date of birth, and race will be recorded.

7.5 Growth Parameters: Length (and Height), Weight, and Head Circumference

7.5.1 Length and Height

Body length (supine measurement) will be collected when subjects are 24-months CA or younger. 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 when subjects are older than 24-months CA. 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).

7.5.2 Body Weight

Body weight will be collected. Calibrated scales should be utilized for body weight measures (type of scale will depend upon subject's age). Care should be taken to remove any extraneous clothing prior to measures and shoes should be removed.

The measure should be recorded to the nearest 0.1 kg.

7.5.3 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.

7.6 Efficacy Assessments

7.6.1 Visual Assessments

After corrective lens determination has occurred (Section 7.6.1.2), all visual assessments should be conducted with best-corrected vision, ie, with corrective lenses in place (if required); this applies to 24-month and 5-year visits.

7.6.1.1 Visual Acuity

Visual acuity is a measure of how well a subject sees at different distances. It will be assessed by the methods summarized in Table 7-1; the method employed will be selected based on the subject's age (CA) at the time of the study visit. Visual acuity measurements will be measured and recorded for the left (OS), right (OD) eye, and both eyes (OU).

At ages 6 months and 12 months CA, visual acuity will be assessed with Teller acuity cards. At ages 24 months and 5 years CA an attempt should be made to assess visual acuity by the LEA

Symbols Test and LEA Symbols Chart, respectively. If during this attempt, the examiner determines that it will not be possible to perform an accurate assessment with the relevant LEA tool, visual acuity should be assessed with the Teller acuity cards.

The visual acuity assessments should be performed by an optometrist or ophthalmologist trained in pediatrics.

Table 7-1 Summary of Visual Acuity Assessments

Visual Acuity Assessment Tool	Description	Unit of Measure	Applicable Age/Study Visit (CA)
Teller acuity cards	Resolution acuity – discrimination of a grating optotype from a background with the same mean luminance	cycles per degree	6 months 12 months
LEA Symbols Test	Recognition acuity - tests recognition of 4 optotypes	Snellen fraction (eg, 20/20)	24 months[a]
LEA Symbols (ETDRS-style) chart	Distance visual acuity test	Snellen fraction (eg, 20/20)	5 years[a]

Abbreviations: CA = corrected age; ETDRS = Early Treatment of Diabetic Retinopathy Study

[a] At ages 24 months and 5 years CA an attempt should be made to assess visual acuity by the LEA Symbols Test and LEA Symbols Chart, respectively. If during this attempt, the examiner determines that it will not be possible to perform an accurate assessment with the relevant LEA tool, visual acuity should be assessed with the Teller acuity cards.

7.6.1.2 Corrective Lens Determination

An assessment to determine if the subject requires vision correction with corrective lenses will be performed. This is being performed to ensure the accuracy of subjects' subsequent visual acuity assessments (at the 24-month and 5-year visits). The corrective lens determination will be performed according to the guidelines published by the American Academy of Ophthalmology (AAO).[14]

This assessment should be performed by an optometrist or ophthalmologist trained in pediatrics.

7.6.1.3 Ocular Alignment and Oculomotor Examination (Motility)

Ocular alignment will be assessed in primary gaze by comparing the position of the corneal light reflection in OS and OD (corneal light reflection assessment). Presence or absence of strabismus will be recorded in primary gaze and in as many of the 9 positions of gaze as feasible with the cover test assessment of refixation movement. Extraocular muscle over-action or deficiency will be recorded. The assessment will be performed according to the AAO guidelines.[14]

Presence or absence of nystagmus as observed during the ocular alignment assessments will also be recorded.

The assessment will be performed by a pediatric ophthalmologist or an ophthalmologist trained in the care of pediatric subjects with a history of premature birth. Degree of adherence to the AAO guidelines will be at the discretion of the examining physician in consideration of the need for patient cooperation.

Ocular motility refers to eye movements, which are governed by the 6 extraocular muscles in each eye. It will be assessed by examiner observation of the subject's ability to abduct, adduct, supra, and inferoduct each eye (to assess for strabismus). Any of the observed misalignment (strabismus classifications) will be recorded:

- esotropia
- exotropia
- hypertropia
- hypotropia

The frequency (constant or intermittent) with which any misalignment occurs and whether the turning eye is always the same eye or if it alternates between OS and OD, will be recorded. Extraocular muscle over-action or deficiency will be recorded.

This assessment should be performed by an optometrist or ophthalmologist trained in pediatrics.

7.6.1.4 Refraction with Cycloplegia

Refraction is a measure of the lens power required for a focused image on the retina. Refraction with cycloplegia will be measured and recorded in diopters for each eye individually (OS and OD).

Cycloplegia may be induced according to site standard practice.

This assessment should be performed by an optometrist or ophthalmologist trained in pediatrics.

7.6.1.5 Stereoacuity

Stereoacuity is a measure of depth perception and will be assessed using the Lang Stereotest and performed by certified personnel. The presence or absence of stereopsis will be recorded.

7.6.1.6 [redacted]

[redacted]

[redacted]

7.6.2 Hearing Assessment History

Results of previously completed hearing assessments will be recorded; hearing tests are not being performed as part of this study.

7.6.3 Behavioral Assessments

7.6.3.1 Bayley Scales of Infant and Toddler Development, Third Edition

The BSID-III will be used to assess cognitive, motor, and language skills, and is applicable to children aged 1 to 42 months.

The BSID-III is an assessment tool designed to measure a young child's skills in the 3 core areas of development: cognitive, language, and motor. There are 5 subscales, the cognitive subscale stands alone while 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 examiner's manual.

The BSID-III 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.

7.6.3.2 Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV)

The WPPSI-IV is a measure of general cognitive development in children that has components of both verbal and nonverbal tasks.[19] It is applicable to preschoolers and young children aged 2 years + 6 months to 7 years + 7 months, and is a direct assessment of a child's cognitive skills.

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[20] 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-IV will be administered to the subject by a trained professional. Scores to be recorded are detailed in the Study Operations Manual.

7.6.3.3 Child Behavior Checklist (CBCL)

The CBCL (1 ½ to 5) is a parent-reported outcome measure used to assess behavioral, emotional, and social functioning of toddlers and preschool children aged 18 to 60 months.[21] It is composed of 99 items that are rated on a Likert scale and includes the following 7 syndrome scales arranged under 2 domains (ie, Internalizing and Externalizing Problems):[22]

- Internalizing Problems
- Emotionally Reactive
- Anxious/Depressed
- Somatic Complaints
- Withdrawn
- Sleep Problems
- Attention Problems
- Aggressive Behavior

The questionnaire is widely used and has been employed to assess long-term behavioral outcomes in children born prematurely, aged similarly to the subjects expected in this study population.[22-24] It is associated with well-established normative data;[25] norms may be selected to aid in interpretation of the scale scores.

The CBCL (1 ½ to 5) is a questionnaire that will be administered to 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.

7.6.3.4 Vineland Adaptive Behavior Scales, Second Edition

The VABS-II Expanded Interview Form will be used to measure the personal and social skills of subjects serially over time; these scales are organized within a 3-domain structure: Communication, Daily Living, and Socialization. In addition, the VABS-II offers a Motor Skills Domain and an optional Maladaptive Behavior Index. The VABS-II Expanded Interview Form assesses what a subject actually does, rather than what he or she is able to do.

The VABS-II Expanded Interview Form will be administered to 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.

7.6.3.5 Attention-Deficit/Hyperactivity Disorder Rating Scale-Fourth Edition

The ADHD-RS-IV was developed to measure the behaviors of children with ADHD. The ADHD-RS-IV consists of 18 items designed to reflect current symptomatology of ADHD based on DSM-IV 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-IV,[26] will be completed by the subject's parent(s) or legally authorized representative(s). Scores to be recorded are detailed in the Study Operations Manual.

7.6.3.6 Social Communication Questionnaire – Lifetime Form

The SCQ is a brief instrument that helps evaluate communication skills and social functioning in children[27] that can be used for screening for autism or autism spectrum disorders in the general population.[28]

The SCQ will be completed by the subject's parent(s) or legally authorized representative(s). 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.

7.6.4 Cerebral Palsy Assessment

Comprehensive neurological examination for the diagnosis of cerebral palsy (CP) will be conducted. The Amiel-Tison neurological examination framework[29] will be utilized for this assessment and conducted by trained medical professionals.

7.6.5 Pulmonary Morbidity Assessment

Pulmonary morbidity will be assessed with questions related to family history and smoking status as well as diagnosis of select pulmonary symptoms, conditions and related hospitalizations. The assessment will be administered to the subject's parent(s) or legally authorized representative(s).

7.6.6 Survival Assessment

Survival status will be assessed and recorded.

7.6.7 Health Economic Outcome Research Assessments

7.6.7.1 Health Related Quality of Life

Health-related quality of life (HRQoL) is an important outcome towards improving the health care of pediatric patients as it is that part of a person's overall quality of life that is determined primarily by their health status and which can be influenced by clinical interventions. It is an important concept, which is also used in determining the value of health care services in this population.[30,31] It is a multidimensional construct whose content is guided by the World Health Organization;[32] minimally it includes physical, psychological (including emotional and cognitive), and social health dimensions.

In this study, HRQoL will be assessed via the validated Pediatric Quality of Life Inventory (PedsQL™) Scales appropriate for the child's age of development.[33-35] The development of the PedsQL was based on the delineations of the World Health Organization (WHO) and is a modular approach to assessing HRQoL in the pediatric population. Initially, the PedsQL Generic Scales were developed and continue to be used in children aged 2 to 18 years. More recently Infant Scales have been developed that apply to ages 1 to 24 months.[34]

The following scales will be used in this study:

- Infant Scale for ages 1-12 months (36 Items)
- Infant Scale for ages 13–24 months (45 Items)
- Toddler Scale for 2-4 years of age (21 Items)
- Young Child Scale for 5-7 years of age (23 Items)

The PedsQL will be administered to the subject's parent and may be conducted via telephone by clinical site staff. The scale(s) to be administered at each visit will be specified in the Study Operations Manual.

7.6.8 Health Care Resource Use

To understand the value of the investigational product administered in Study ROPP-2008-01 (Section D), the resource use associated with inpatient visits, outpatient visits, and medical and pharmacy utilization in this study will be recorded.

This assessment may be conducted via telephone by clinical site staff.

7.6.8.1 Health Status Classification System-Preschool

Health status (eg, health utility) will be measured by the Health Status Classification System-Preschool (HSCS-PS), which is a validated instrument adapted for use via parent proxy within the pediatric population age 2.5 to 5 (adapted from the validated Health Utilities Index Mark 2 and 3 [HUI 2/3]).[36] Validity of the HSCS-PS concepts has not been established for ages younger than 2.5 years.

The HSCS-PS was developed to provide a consistent measure of health status in preschool-aged children who had been born prematurely.[36] The system is applicable to children with special needs as may be included in this study; validation cohorts for the system included children with very low birth weight (VLBW), which is congruent with this study population.

The instrument is composed of 12 dimensions (Vision, Hearing, Speech, Mobility, Dexterity, Self-care, Emotion, Learn/remember, Think/problem solve, Pain, General Health, and Behavior) intended to provide a comprehensive assessment of a child's health status as it pertains to health-related quality of life. The individual domains of the instrument will be scored as a mean score, representing the overall state for each concept individually. The global score will be recorded as well as the scores for each of the dimensions.

The HSCS-PS is a questionnaire that will be administered to the subject's parent(s) or legally authorized representative(s) and may be conducted via telephone by clinical site staff.

7.7 Safety Assessments

7.7.1 Abdominal ultrasound

An abdominal ultrasound will be performed to assess the size of the spleen and kidneys. The spleen will be measured in the coronal longitudinal plane and the longest longitudinal length will be measured for each kidney (left and right).[37] Ultrasound results will be assessed by a central reader.

Organ size will be interpreted in the context of reference values established for children.[37,38]

7.7.2 Echocardiogram

Echocardiographic examination (conventional M-mode recording of the left ventricle [LV] parasternal long axis view) will be performed for the evaluation of cardiac size, assessed by measuring the following:

- interventricular septal thickness (during end diastole)
- LV posterior wall thickness
- LV intracavity volume (both in end diastole and end systole)

Echocardiogram results will be assessed by a central reader.

7.7.3 Physical Examination

Physical examinations will include a review of the subject's general appearance, neurological examination, as well as a tonsillar examination (Table 7-2). Any abnormal change in findings will be recorded as an AE.

Table 7-2 Assessments for Physical Examinations

Assessment	Assessment
General appearance	Endocrine
Head and neck	Cardiovascular
Eyes	Abdomen
Ears	Genitourinary
Nose	Skin
Throat	Musculoskeletal
Chest and lungs	Neurological
Tonsils	

7.8 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 7.11.1).

7.9 Adverse Events Assessments

7.9.1 Definitions of Adverse Events, Serious Adverse Events, and Suspected Unexpected Serious Adverse Reactions

7.9.1.1 Adverse Event

An AE is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered investigational product-related. This includes an exacerbation of a pre-existing condition.

Adverse events include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study
- Intercurrent illnesses
- Drug interactions
- Events related to or possibly related to concomitant medications
- Abnormal laboratory values (this includes significant shifts from baseline within the range of normal that the Investigator considers to be clinically important)
- Clinically significant abnormalities in physical examination, vital signs, and weight

In this long-term outcome study in follow-up to Study ROPP-2008-01 (Section D), no investigational product is being administered. However, the relationship to the investigational product (rhIGF-1/rhIGFBP-3) as administered in Study ROPP-2008-01 (Section D) will be assessed.

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

- those considered related to investigational product (rhIGF-1/rhIGFBP-3 as administered in Study ROPP -2008-01, Section D)
- those considered related to procedures performed in this study (Study SHP-607-201)
- specified targeted medical events (Section 7.9.1.3) regardless of causality

Throughout the study, the Investigator must record AEs on the AE electronic case report form (eCRF), regardless of the severity. The Investigator should treat subjects with AEs appropriately and observe them at suitable intervals until the events stabilize or resolve. Adverse events may be discovered through observation or examination of the subject, questioning of the subject, complaint by the subject, or by abnormal clinical laboratory values.

In addition, AEs may also include laboratory values that become significantly out of range. In the event of an out-of-range value, the laboratory test should be repeated until it returns to normal or can be explained and the subject's safety is not at risk.

Additional illnesses present at the time when informed consent is given are regarded as AEs and will be documented on the appropriate pages of the eCRF. Illnesses first occurring or detected during the study, and worsening of a concomitant illness during the study, are to be regarded as AEs and must be documented as such in the eCRF.

7.9.1.2 Serious Adverse Event

An SAE is any AE that results in any of the following outcomes:

- Death
- Is life-threatening
- Requires hospitalization
- Requires prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect

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 one of the outcomes listed in this definition. A life-threatening AE is defined as an AE that placed the

subject, in the view of the initial reporter, at immediate risk of death from the AE as it occurred (ie, it does not include an AE that, had it occurred in a more severe form, might have caused death).

For the purposes of this study only SAE listed in the following will be collected:

- fatal SAEs regardless of causality
- SAEs related to ROP
- SAEs related to congenital malformations not identified at birth which may impact neurocognitive development

7.9.1.3 Suspected Unexpected Serious Adverse Reaction

Suspected unexpected serious adverse reactions (SUSAR) are suspected adverse reactions related to an investigational product (investigational products and comparators [if applicable]), which occur in the concerned study, and that are both serious and unexpected according to the current Investigator's Brochure.

7.9.1.4 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, as appropriate, regardless of relationship to investigational product (rhIGF-1/rhIGFBP-3 as administered in Study ROPP-2008-01, Section D):

- intracranial hypertension
- any abnormality of glucose metabolism (eg, hypoglycemia, hyperglycemia, and diabetes)
- tonsillar hypertrophy (based on tonsil exam [part of the physical exam])
- increased kidney size
- increased cardiac size
- increased spleen size

7.9.2 Classification of Adverse Events and Serious Adverse Events

The severity of AEs will be assessed by the Investigator based on the definition indicated in Table 7-3. The severity of all AEs/SAEs should be recorded on the appropriate eCRF page to a severity of mild, moderate, or severe.

Table 7-3 Adverse Event Severity

Severity	Definition
Mild	No limitation of usual activities.

Table 7-3 Adverse Event Severity

Severity	Definition
Moderate	Some limitation of usual activities.
Severe	Inability to carry out usual activities.

7.9.3 Clarification between Serious and Severe

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) and causality serve as a guide for defining regulatory reporting obligations.

7.9.4 Relatedness of Adverse Events and Serious Adverse Events

Relationship of an AE or SAE to investigational product (rhIGF-1/rhIGFBP-3 as administered in Study ROPP-2008-01, Section D) is to be determined by the Investigator based on the following definitions (See Table 7-4).

Table 7-4 Adverse Event Relatedness

Relationship to Product	Definition
Not Related	Unrelated to investigational product
Possibly Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, but which could also be explained by concurrent disease or other drugs or chemicals.
Probably Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on de-challenge. The association of the clinical event or laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds.
Definitely related	The event follows a reasonable temporal sequence from administration of the investigational product, follows a known or suspected response pattern to the investigational product, is confirmed by improvement upon stopping the investigational product (de-challenge), and reappears upon repeated exposure (re-challenge). Note that this is not to be construed as requiring re-exposure of the subject to investigational product; however, the determination of definitely related can only be used when recurrence of event is observed.

7.9.5 Procedures for Recording and Reporting Adverse Events

7.9.5.1 Adverse Event Monitoring and Period of Observation

Adverse events will be monitored throughout the study.

For the purposes of this study, the period of observation begins from the time at which the subject's parent(s) or legally authorized representative(s) gives informed consent until the subject's final evaluation of the study. When possible, subject's parents or legally authorized representative(s) should be consented at the end of study visit for the ROPP-2008-01. However, if this is not possible, subject's parents or legally authorized representative(s) will be asked to provide consent for any Serious Adverse Events that the subject experiences between ROPP-2008-01 end-of-study visit and the start of the SHP-607-201, to be reported by the Investigator. For safety purposes, the final evaluation will be defined as the last study visit when the subject is 5 years-old in CA.

If the Investigator considers it necessary to report an AE in a study subject after the end of the safety observation period, he or she should contact the Sponsor to determine how the AE should be documented and reported.

7.9.5.2 Reporting Serious Adverse Events

Any SAE meeting the reporting criteria for this study should be recorded by the clinical site on an SAE form. The SAE must be completely described on the subject's eCRF, including the judgment of the Investigator as to the relationship of the SAE to the investigational product. The Investigator will promptly supply all information identified and requested by the Sponsor (or contract research organization [CRO]) regarding the SAE.

The Investigator must report the SAE to the Shire Pharmacovigilance and Risk Management Department AND to the local Shire Medical Monitor on an SAE form. This form must be completed and FAXED or EMAILED within 24 hours of the Investigator's learning of the event to:

Shire Pharmacovigilance and Risk Management Department:

International FAX: [redacted] **(UK) OR United States FAX:** [redacted]

Email: [redacted]

AND

North America	Europe
Shire Medical Monitor: [redacted]	**Shire Medical Monitor:** [redacted]
E-mail: [redacted]	**E-mail:** [redacted]

Any follow-up information must also be completed on an SAE form and faxed or emailed to the same numbers or emails listed above.

In the event of a severe and unexpected, fatal, or life-threatening SAE, the clinical site must contact the Shire Medical Monitor by telephone as soon as possible and within 24 hours of awareness; this is in addition to completing and transmitting the SAE form as stated above. The following provides contact information for the Shire Medical Monitor.

If an SAE is assessed as severe and unexpected, or life-threatening, contact:	
North America [redacted], MD, MPH [redacted] **Shire** **300 Shire Way** **Lexington, MA 02421 USA** **Telephone:** [redacted] **Mobile:** [redacted] **(24-hr access)** **E-mail:** [redacted] **Fax:** [redacted] **(North America)**	**Europe** [redacted], MD, PhD [redacted] **Shire International GmbH** **Zahlerweg 10** **6301 Zug - Switzerland** **Telephone:** [redacted] **Mobile:** [redacted] **(24-hr access)** **E-mail:** [redacted] **Fax:** [redacted] **(Global)**

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

The Sponsor and the CRO are responsible for notifying the relevant regulatory authorities/US central IRBs/European Union (EU) central ECs of related, unexpected SAEs.

For some European regulatory authorities, these reports are submitted directly to Eudravigilance. In case of deaths or life-threatening SUSARs, these must be reported to the relevant regulatory authorities before 7 days have elapsed from that the initial SAE report has reached the Sponsor or its representatives. A full report has to be submitted within another 8 days. For other SUSARs the timelines for reporting are 15 days.

In addition, the CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the rhIGF-1/rhIGFBP-3 program at Shire.

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.

7.10 Removal of Subjects from the Trial

A subject's participation in the study may be discontinued at any time at the discretion of the Investigator. The following may be justifiable reasons for the Investigator to remove a subject from the study:

- Non-compliance, including failure to appear at one or more study visits
- The subject was erroneously included in the study
- The subject develops an exclusion criterion
- The study is terminated by the Sponsor

The subject, the subject's parent(s), or the subject's legally authorized representative acting on behalf of the subject is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment.

If a subject or the subject's parent(s) or the subject's legally authorized representative(s) acting on behalf of the subject, discontinues participation in the study, or the subject is discontinued by the Investigator, reasonable efforts will be made to follow the subject through the end of study assessments. The reason for refusal will be documented on the eCRF. Any AEs experienced up to the point of discontinuation must be documented on the AE eCRF. If AEs are present when the subject withdraws from the study, the subject will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal will be followed until resolution.

7.11 Other Study Procedures

7.11.1 Participation in Other Clinical Studies

Following enrollment, subjects in this study will not be restricted from enrolling in another clinical study that involves 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 being evaluated in the study, and the subject's treatment assignment in the study (if possible).

7.12 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. These are the pulmonary morbidity assessment and the cerebral palsy assessment. In these cases, the tools are either based on validated tools or the current state of knowledge in the literature. For example, the cerebral

palsy assessment is based on the Amiel-Tison neurological examination framework[29] and the pulmonary assessment is based on published research in a similar pediatric population[39,40].

8 STUDY ACTIVITIES

The timing of the visits in this study is based on subjects' corrected age (CA).

8.1 Initial Study Visit (40 weeks CA [term equivalent])

The Initial Visit will occur at 40 weeks CA (ie, term equivalent) or upon discontinuation from Study ROPP-2008-01, Section D or any time up to the visit at 3 months CA.

At the Initial Visit, informed consent will be obtained followed by an assessment of study eligibility criteria and collection of demographic data.

The following AE data, collected as part of Study ROPP-2008-01 (Section D) will be recorded:

- Ongoing targeted medical events regardless of causality
- Ongoing study drug-related AEs, including SAEs

SAEs, as outlined in Section 7.9.1.1 and Section 7.9.1.2, that the subject experiences between the ROPP-2008-01 end-of-study visit and the time of informed consent for the SHIP-607-201 study will be reported by the Investigator, pending permission for subject's parent or legally authorized representative(s), as documented on the informed consent form.

8.2 Study Visits

Study visits for follow-up outcome assessments will take place at the following time points in CA:

- 3 months (±2 weeks) – conducted by telephone
- 6 months (±1 month) – clinical site visit
- 12 months (±3 months) – clinical site visit
- 20 month (-1 months) – clinical site visit
- 24 months (±3 months) – clinical site visit
- 3 years (±3 months) – conducted by telephone
- 4 years (±3 month) – conducted by telephone
- 4.75 years (-1 months) – clinical site visit
- 5 years (+6 months) – clinical site visit

In addition, there will be 2 visits that must occur at least 1 month prior to the 24-month and 5-year CA study visits to assess the need for corrective lenses. The timing of these 2 visits (20 months [-1 month] and 4.75 years [-1 month]) was set to ensure that any prescribed corrective lenses would be worn for at least 1 month prior to the visual assessments at the 24-month and 5-year study visits CA.

The activities at the study visits are described in Sections 8.2.1 and 8.2.2.

8.2.1 Outcome Assessment Visits Conducted by Telephone

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

- HRQoL
- HCRU
- HSCS-PS (3-year and 4-year visits only)
- Medications
- Survival assessment
- Assessment of participation in other clinical studies
- Adverse events (including targeted medical events)

8.2.2 Clinical Site Visits

8.2.2.1 Outcome Assessment Site Visits

The following clinical site visits (in CA) to capture follow-up outcome data will occur at the clinical site:

- 6 months (±1 month)
- 12 months (±3 months)
- 20 months (-1 month)
- 24 months (±3 months)
- 4.75 years (-1 months)
- 5 years (+6 months)

The following assessments will be performed at the 6-month visit:

- Visual acuity
- Refraction with cycloplegia
- Length
- Weight
- Head circumference
- VABS-II
- Physical examination (including tonsil examination)

- Hearing Assessment History (Historical hearing test data may be recorded at any time prior to the 6-month visit)
- Pulmonary morbidity assessment
- Survival assessment
- HRQoL (may be performed by telephone if there are time constraints during this clinical site visit)
- HCRU (may be performed by telephone if there are time constraints during this clinical site visit)
- Abdominal ultrasound
- Echocardiogram
- Assessment of participation in other clinical studies
- Medications
- Adverse events (including targeted medical events)

The following assessments will be performed at the 12-month visit:

- Visual acuity
- Corrective lens determination (including refraction with cycloplegia)
- Ocular alignment and motility
- Length
- Weight
- Head circumference
- BSID-III
- VABS-II
- Physical examination (including tonsil examination)
- Pulmonary morbidity assessment
- Survival assessment
- HRQoL (may be performed by telephone if there are time constraints during this clinical site visit)
- HCRU (may be performed by telephone if there are time constraints during this clinical site visit)
- Assessment of participation in other clinical studies
- Medications
- Adverse events (including targeted medical events)

The following assessments will be performed at the 20-month visit:

- Visual acuity
- Corrective lens determination (including refraction with cycloplegia)
- Assessment of participation in other clinical studies

The following assessments will be performed at the 24-month visit:

- Visual acuity
- Ocular alignment and motility
- Length
- Weight
- Head circumference
- BSID-III
- CBCL
- VABS-II
- Physical examination (including tonsil examination)
- Cerebral Palsy assessment
- Pulmonary morbidity assessment
- Survival assessment
- HRQoL (may be performed by telephone if there are time constraints during this clinical site visit)
- HCRU (may be performed by telephone if there are time constraints during this clinical site visit)
- HSCS-PS (may be performed by telephone if there are time constraints during this clinical site visit)
- Assessment of participation in other clinical studies
- Medications
- Adverse events (including targeted medical events)

The following assessments will be performed at 4.75-year visit:

- Visual acuity
- Corrective lens determination (including refraction with cycloplegia)

The following assessments will be performed at the 5-year visit:

- Visual acuity
- Ocular alignment and motility
- Stereoacuity
- Height
- Weight
- WPPSI-IV
- CBCL
- VABS-II
- ADHD-RS-IV
- SCQ
- Physical examination (including tonsil examination)
- Pulmonary morbidity assessment
- Survival assessment
- [redacted]
- HRQoL (may be performed by telephone if there are time constraints during this clinical site visit)
- HCRU (may be performed by telephone if there are time constraints during this clinical site visit)
- HSCS-PS (may be performed by telephone if there are time constraints during this clinical site visit)
- Assessment of participation in other clinical studies
- Medications
- Adverse events (including targeted medical events)

8.2.2.2 Visits Dedicated to Corrective Lens Determination

The following clinical site visits are dedicated solely to corrective lens determination in preparation for the outcome assessment visits at 24-months and 5-years CA:

- 20 months (-1 month)
- 4.75 years (-1 month)

At these visits, the following will be performed:

- Visual acuity
- Corrective lens determination (includes refraction with cycloplegia)

The 20-month visit and the 4.75-year (4 years, 9 months) visit must occur at least 1 month prior to the 24-month and 5-year visits, respectively. Any prescribed corrective lenses must be worn for at least 1 month prior to the 24 month and 5 year assessments.

8.3 Assessments upon Discontinuation

If a subject discontinues prior to the 5-year CA visit, every attempt will be made to complete the assessments scheduled for the subject's next visit.

9 QUALITY CONTROL AND ASSURANCE

Training will occur at an Investigator meeting or at the site initiation visit or both, and instruction manuals will be provided to aid consistency in data collection and reporting across sites.

Clinical sites will be monitored by the Sponsor or its designee to ensure the accuracy of data against source documents. The required data will be captured in a validated clinical data management system that is compliant with the FDA 21 Code of Federal Regulations (CFR) Part 11 Guidance. The clinical trial database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be trained and given restricted access, based on their role(s) in the study, through a password-protected environment.

Data entered in the system will be reviewed manually for validity and completeness against the source documents by a clinical monitor from the Sponsor or its designee. If necessary, the study site will be contacted for corrections or clarifications; all missing data will be accounted for.

Serious adverse event information captured in the clinical trial database will be reconciled with the information captured in the Pharmacovigilance and Risk Management database.

10 STATISTICAL ANALYSES

10.1 General Methodology

Details regarding the statistical methods and definitions will be provided in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to database lock. All statistical analyses will be performed by the Biometrics department at Shire. Statistical analyses will be performed using Version 9.1 or higher of SAS® (SAS Institute, Cary, NC 27513).

Continuous variables will be summarized using descriptive statistics including the number of observations, 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 2 possible treatment assignments in the antecedent study, ROPP-2008-01, Section D (rhIGF-1/rhIGFBP-3 or standard neonatal care).

For analysis purposes, baseline is defined as the first assessment either in the antecedent study (ROPP-2008-01) or in this study (SHP-607-201). As necessary, relevant data from Study ROPP-2008-01 may be summarized with the data from this study (SHP-607-201).

10.2 Determination of Sample Size

No formal sample size calculation was performed for this study because this is a follow-up study to Section D of Study ROPP-2008-01. Any subjects enrolled in Study ROPP-2008-01 are eligible to enroll in this study. There are up to 120 subjects who will be eligible to enroll in this long-term developmental outcome study.

10.3 Method of Assigning Study Subjects to Treatment Groups

Not applicable.

10.4 Population Description

10.4.1 Analysis Populations

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

Safety Population- the Safety Population will consist of the subjects in the Enrolled Population who have safety follow-up data in this long-term outcome study.

10.4.2 Subject Disposition

Subjects who complete the study and subjects who prematurely discontinue from the study will be summarized by treatment group using descriptive statistics. In addition, for subjects who

prematurely discontinue from the study, the reasons for discontinuation will be summarized by treatment group.

10.4.3 Protocol Violations and Deviations

Protocol violations and deviations will be listed. Details of the criteria for deviations and violations will be provided in the SAP.

10.4.4 Demographics and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group for the Enrolled Population.

Demographics and baseline characteristics will be examined to assess the comparability of the treatment groups. Continuous variables such as age (including corrected age), weight, and length/height will be summarized using number of observations, mean, standard deviation, median, minimum and maximum values. Categorical variables, like gender and race, will be summarized using number of observations and percentages.

Medical history, including maternal and perinatal history, (as obtained from the antecedent study, ROPP-2008-01) will be summarized by treatment group using the number of observations and percentages of subjects reporting each category.

10.5 Efficacy Analysis

All efficacy analyses will be performed using the Enrolled Population.

10.5.1 Primary Efficacy Analysis

The primary efficacy endpoints consist of the following:

- Visual Acuity: Visual acuity will be categorized as the following:
  - normal (measurable acuity ≥20/40),
  - below normal (20/200≤ measurable acuity <20/40),
  - poor (measurable acuity ≤20/200)
  - blind/low vision (only the ability to detect the 2.2 cm wide stripes on the low-vision Teller acuity card and at any location in the visual field).

  The number and proportion of patients within each category listed above will be summarized by treatment group and visit. In addition, acuity results in the normal and below normal categories will be classified as favorable outcomes, and acuity results in the poor and blind/low-vision categories will be classified as unfavorable outcomes. Tabular summaries by treatment group and visit will include the frequency and the percentage for each visual acuity category. In addition, shift tables of favorable outcomes from baseline (first assessment during this study) to each of the subsequent assessments, including the last assessment, will be presented by treatment group.

- Ocular Alignment and Oculomotor Exam (Motility): Findings from the ocular motility assessment will be either presence or absence of strabismus (esotropia, exotropia, hypertropia, or hypotropia). Tabular summaries by treatment group and visit will include the frequency and the percentage in each category. In addition, shift tables from baseline (first assessment during this study) to the last assessment will be provided by treatment group.
- Nystagmus: Presence or absence of nystagmus will be summarized by treatment group and visit
- Refraction with Cycloplegia: Findings from the refraction with cycloplegia will be summarized by treatment group and visit
- Stereoacuity: Presence or absence of stereopsis will be summarized by treatment group and visit

10.5.2 Secondary Efficacy Analysis

- Growth Parameters (body weight, body length [and height], and head circumference): A standard Z-score, utilizing WHO child growth standards, will be calculated for each assessment by adjusting age- and sex- matched means and standard deviations (norm). The descriptive statistics of the Z-score for each of these parameters will be summarized at each assessment and the corresponding change from baseline. When appropriate, a 95% CI for the corresponding mean change within each group and the difference in the mean change between the 2 treatment groups and the corresponding 95% CI will be presented as appropriate. If the parametric assumption for the distribution of the above endpoints cannot be justified, a non-parametric approach will be utilized to estimate the treatment difference (ie, median difference or Hodges-Lehmann estimator and the corresponding confidence intervals)
- BSID-III and WPPSI-IV: The raw score for each domain within each questionnaire will be summarized by treatment group and visit using descriptive statistics.
- ADHD-RS-IV: ADHD-RS-IV total score and subscales (Hyperactivity/Impulsivity and Inattentiveness) will be summarized by treatment group and visit using descriptive statistics.
- SCQ: The SCQ subscales (communication and social) will be summarized by treatment group and visit using descriptive statistics
- VABS-II: The raw score for each domain of the scale will be summarized by treatment group and visit using descriptive statistics.
- CBCL: The raw score and change from baseline for each domain of the scale will be summarized by treatment group and visit using descriptive statistics.
- Pulmonary morbidity assessment: The binary response of each question will be by treatment group and visit using descriptive statistics.
- Survival: For subjects who have an event (ie, death), the event time will be calculated as the length of time from the subject's date of birth to death during the study due to

any cause. Subjects who do not have an event (ie, death) during the study will be censored at the end of the study. The survival endpoint will be analyzed by treatment group using Kaplan-Meier methods.

10.5.3 Subset Analyses

Subgroup analyses may be explored based on factors that may have influence on the efficacy or safety endpoints. Subgroup analyses will be specified in the SAP.

10.5.4 Exploratory Analyses

[redacted]

10.6 Health Economics and Outcomes Research Analyses

For PedsQL, descriptive statistics will be provided for summary scores by treatment group 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 and at each time point.

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.

10.7 Analysis of Safety

Safety summaries will be based on all assessments post-baseline. The safety data will be assessed by AE monitoring, change in cardiac size, and kidney and spleen size over time.

Adverse events will be summarized by system organ class and preferred term for each treatment group and overall, the number and percentage of subjects having any AE, having an AE in each body system and having each individual AE. In addition, those events which resulted in death, or were otherwise classified as serious will be presented in a separate listing. In addition, the summary of AEs will be presented by severity and relationship to trial medication.

The change in cardiac size, and size of kidney and spleen will be assessed at the 6-month CA visit via echocardiogram and abdominal ultrasound, respectively. These data will be analyzed as a binary response (ie, normal/abnormal) and summarized using frequency count. The number and proportion of patients with each category (ie, normal/abnormal) for each of these safety endpoints will be summarized by treatment group. In addition, the 2-sided 95% CI for the proportion of patients with a normal status for each of the endpoints will be estimated by treatment group.

Physical examinations findings will be summarized descriptively.

10.8 Statistical/Analytical Issues

10.8.1 Adjustment for Covariates

If any baseline data are imbalanced and are considered to be clinically relevant, between-group comparisons for efficacy outcomes will be adjusted for covariates and detailed in the SAP.

10.8.2 Handling of Dropouts or Missing Data

Handling of missing data rules will be described in the SAP.

10.8.3 Interim Analyses and Data Monitoring

An interim analysis will be performed after all data from all enrolled subjects in this study have either completed 2-year follow-up (24-month visit) assessments or have prematurely withdrawn from the study (before completing 2 years of follow-up) has been entered into the database, queried and discrepancies resolved. A full 2-year study report based on these data, including efficacy and safety endpoint analyses, will be completed.

Additionally, descriptive analyses of the data at other time points before study completion may be performed for safety monitoring, regulatory reporting or general planning purposes.

10.8.4 Multiple Comparisons/Multiplicity

Not applicable.

10.8.5 Sensitivity Analyses

Sensitivity analyses for the efficacy outcomes will be detailed in the SAP, as necessary.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

Before initiation of the study, the Investigators must provide the Sponsor with a completed Form FDA 1572 and Investigator Agreement. Curriculum vitae must be provided for the Investigators and sub-investigators listed on Form FDA 1572 or Investigator Agreement.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, and their study related duties and functions. The Investigator must maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study related duties.

11.2 Institutional Review Board or Independent Ethics Committee Approval

Before initiation of the study, the Investigator must provide the Sponsor with a copy of the written IRB/IEC/REB approval of the protocol and the informed consent form. This approval must refer to the informed consent form and to the study title, study number, and version and date of issue of the study protocol, as given by the Sponsor on the cover page of the protocol.

Status reports must be submitted to the IRB/IEC/REB at least once per year. The IRB/IEC/REB must be notified of completion of the study. Within 3 months of study completion or termination, a final report must be provided to the IRB/IECREB. A copy of these reports will be sent to the study clinical monitor. The Investigators must maintain an accurate and complete record of all submissions made to the IRB/IEC, including a list of all reports and documents submitted. AEs which are reported to the US (FDA or other Regulatory agencies (Safety Reports) must be submitted promptly to the IRB/IEC/REB.

11.3 Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigators abide by good clinical practice (GCP) as described in the 21 CFR Parts 50, 56, and 312 and the International Conference on Harmonization (ICH) GCP Guidelines Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

11.4 Subject Information and Consent

Before enrolling in the clinical study, the subject or the subject's parent(s) or legally authorized representative(s) must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her.

An informed consent form (assent form if applicable) that includes information about the study will be prepared and given to the subject or the subject's parent(s) or legally authorized representative(s). This document will contain all FDA and ICH-required elements. The informed consent (or assent) form must be in a language understandable to the subject or the subject's

parent(s) or legally authorized representative(s) and must specify who informed the subject, the subject's parent(s), or the subject's legally authorized representative(s).

After reading the informed consent document, the subject or the subject's parent(s) or legally authorized representative(s) must give consent in writing. Consent must be confirmed at the time of consent by the personally dated signature of the subject, the subject's parent(s) or the subject's legally authorized representative(s) and by the personally dated signature of the person conducting the informed consent discussions.

If the subject or the subject's parent(s) or legally authorized representative(s) is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the subject or by a local legally recognized alternative (eg, the subject's thumbprint or mark) or by the personally dated signature of the subject's parent(s) or the subject's legally authorized representative. The witness and the person conducting the informed consent discussions must also sign and personally date the informed consent document. It should also be recorded and dated in the source document that consent was given.

A copy of the signed and dated consent document(s) must be given to the subject or the subject's parent(s) or legal representative(s). The original signed and dated consent document will be retained by the Investigator.

The Investigator will not undertake any measures specifically required solely for the clinical study until valid consent has been obtained.

A model of the informed consent form to be used in this study will be provided to the sites separately from this protocol.

11.5 Subject Confidentiality

Subject names will not be supplied to the Sponsor. Only the subject number - will be recorded in the eCRF, and if the subject name appears on any other document, it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be told that representatives of the Sponsor, a designated CRO, the IRB/IEC/REB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. The Investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

11.6 Study Monitoring

Monitoring procedures that comply with current Good Clinical Practice (GCP) guidelines will be followed. Review of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by the Sponsor or its designee. Monitoring will be performed by a representative of the Sponsor (Clinical Study Monitor) who will review the eCRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and communications (letter, telephone, and facsimile).

11.7 Case Report Forms and Study Records

11.7.1 Case Report Forms

Electronic case report forms (eCRFs) are provided for each subject. All forms must be filled out by authorized study personnel. All corrections to the original eCRF entry must indicate the reason for change. The Investigator is required to sign the eCRF after all data have been captured for each subject. If corrections are made after review and signature by the Investigator, he or she must be made aware of the changes, and his or her awareness documented by resigning the eCRF.

11.7.2 Critical Documents

Before the Sponsor initiates the trial (ie, obtains informed consent from the first subject), it is the responsibility of the Investigator to ensure that the following documents are available to Sponsor or their designee:

- Completed FDA Form 1572 (Statement of Investigator), signed, dated, and accurate
- Curricula vitae of Investigator and sub-investigator(s) (current, dated and signed within 12 months of study initiation)
- Copy of Investigator and sub-investigator(s) current medical license (indicating license number and expiration date)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/IEC/REB clearly identifying the documents reviewed by name, number and date of approval or re approval: protocol, any amendments, Subject Information/Informed Consent Form, and any other written information to be provided regarding subject recruitment procedures
- Copy of IRB/IEC/REB approved Subject Information/Informed Consent Form/any other written information/advertisement (with IRB approval stamp and date of approval)
- Current list of IRB/IEC/REB Committee members/constitution (dated within 12 months prior to study initiation)
- Financial Disclosure Form signed by Investigator and sub-investigator(s)
- Current laboratory reference ranges (if applicable)
- Certification/QA scheme/other documentation (if applicable)

Regulatory approval and notification as required must also be available; these are the responsibility of Shire.

11.8 Data Monitoring Committee

Given that any long-term safety signal observed in this study could impact the safety profile of rhIGF-1/rhIGFBP-3 as administered in premature neonates being enrolled in the antecedent study (ROPP-2008-01, Section D), the Data Monitoring Committee (DMC) for Study ROPP-2008-01 will review safety data from this long-term outcome study.

11.9 Protocol Violations/Deviations

The Investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the IRB/IEC/REB and the appropriate regulatory authorities, where applicable, have given approval/favorable opinion. Modifications to the protocol will not be made without agreement of the Sponsor. Changes to the protocol will require written IRB/IEC/REB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB/IEC/REB may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC/REB. The Sponsor will submit all protocol modifications to the regulatory authorities, where applicable, in accordance with the governing regulations.

A record of subjects screened, but not entered into the study, is also to be maintained. No protocol exemption will be granted for this study.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Sponsor or its designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will need to be reviewed by the medical monitor and may also be required to be submitted to the IRB/IEC/REB.

Protocol modifications will only be initiated by the Sponsor and must be approved by the IRB/IEC/REB and submitted to the FDA or other applicable international regulatory authority before initiation, if applicable.

11.10 Premature Closure of the Study

If the Sponsor, Investigator, or regulatory authorities discover conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable subject risk, the study may be terminated after appropriate consultation between the Sponsor and the Investigator(s). In addition, a decision on the part of the Sponsor to suspend or discontinue development of the investigational product may be made at any time. Conditions that may warrant termination of the study or site include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study
- Failure of the Investigator to comply with pertinent global regulations
- Submission of knowingly false information from the study site to the Sponsor or other pertinent regulatory authorities
- Insufficient adherence by the Investigator to protocol requirements

11.11 Access to Source Documentation

Regulatory authorities, the IRB/IEC/REB, or the Sponsor may request access to all source documents, eCRFs, and other study documentation for onsite audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Monitoring and auditing procedures that comply with current GCP guidelines will be followed. On-site review of the eCRFs for completeness and clarity, crosschecking with source documents, and clarification of administrative matters may be performed.

11.12 Data Generation and Analysis

The clinical database will be developed and maintained by a contract research organization or an electronic data capture technology provider as designated by the Sponsor. The Sponsor or its designee will be responsible for performing study data management activities.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medication will be coded using WHO-Drug Dictionary (WHO-DD). Central reads will be employed as described in the study manual to aid in consistent measurement of abdominal ultrasound and echocardiogram parameters.

11.13 Retention of Data

Essential documents should be retained until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The Sponsor will notify the Investigator if these documents must be retained for a longer period of time. It is the responsibility of the Sponsor to inform the Investigator or institution as to when these documents no longer need to be retained.

11.14 Financial Disclosure

The Investigator should disclose any financial interests in the Sponsor as described in 21 CFR Part 54 prior to beginning this study. The appropriate form will be provided to the Investigator by the Sponsor, which will be signed and dated by the Investigator, prior to the start of the study.

11.15 Publication and Disclosure Policy

All information concerning the study material, such as patent applications, manufacturing processes, basic scientific data, and formulation information supplied by the Sponsor and not previously published are considered confidential and will remain the sole property of the Sponsor. The Investigator agrees to use this information only in accomplishing this study and will not use it for other purposes.

It is understood by the Investigator that the information developed in the clinical study may be disclosed as required to the authorized regulatory authorities and governmental agencies. In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the Sponsor with complete test results and all data developed in the study in a timely manner.

The Investigator and any other clinical personnel associated with this study will not publish the results of the study, in whole or in part, at any time, unless they have consulted with the Sponsor, provided the Sponsor a copy of the draft document intended for publication, and obtained the Sponsor's written consent for such publication. All information obtained during the conduct of this study will be regarded as confidential.

12 LIST OF REFERENCES

1. Maida JM, Mathers K, Alley CL. Pediatric ophthalmology in the developing world. Current opinion in ophthalmology 2008;19:403-8.
2. O'Connor AR, Stephenson TJ, Johnson A, et al. Visual function in low birthweight children. The British journal of ophthalmology 2004;88:1149-53.
3. Keith CG, Kitchen WH. Ocular morbidity in infants of very low birth weight. The British journal of ophthalmology 1983;67:302-5.
4. Laws D, Shaw DE, Robinson J, Jones HS, Ng YK, Fielder AR. Retinopathy of prematurity: a prospective study. Review at six months. Eye 1992;6:477-83.
5. O'Connor AR, Stephenson T, Johnson A, et al. Long-term ophthalmic outcome of low birth weight children with and without retinopathy of prematurity. Pediatr 2002;109:12-8.
6. Schaffer DB, Quinn GE, Johnson L. Sequelae of arrested mild retinopathy of prematurity. Archives of ophthalmology 1984;102:373-6.
7. Cats BP, Tan KE. Prematures with and without regressed retinopathy of prematurity: comparison of long-term (6-10 years) ophthalmological morbidity. Journal of pediatric ophthalmology and strabismus 1989;26:271-5.
8. Chard T. Insulin-like growth factors and their binding proteins in normal and abnormal human fetal growth. Growth Regul 1994;4:91-100.
9. Hansen-Pupp I, Lofqvist C, Polberger S, et al. Influence of insulin-like growth factor I and nutrition during phases of postnatal growth in very preterm infants. Pediatr Res 2011;69:448-53.
10. Ohkawa N, Shoji H, Kitamura T, et al. IGF-I, leptin and active ghrelin levels in very low birth weight infants during the first 8 weeks of life. Acta Paediatr 2010;99:37-41.
11. Lofqvist C, Hellgren G, Niklasson A, Engstrom E, Ley D, Hansen-Pupp I. Low postnatal serum IGF-I levels are associated with bronchopulmonary dysplasia (BPD). Acta Paediatr 2012;101:1211-6.
12. Ishii DN, Glazner GW, Whalen LR. Regulation of peripheral nerve regeneration by insulin-like growth factors. Annals of the New York Academy of Sciences 1993;692:172-82.
13. Lewis ME, Neff NT, Contreras PC, et al. Insulin-like growth factor-I: potential for treatment of motor neuronal disorders. Experimental neurology 1993;124:73-88.
14. Pediatric Ophthalmology/Strabismus Preferred Practice Pattern Development Process and Participants. Pediatric Eye Evaluations: American Academy of OphthalmologyPediatric Ophthalmology/Strabismus Preferred Practice Pattern Panel; 2012.

[redacted]

19. Wechsler D. Wechsler preschool and primary scale of intelligence 4th ed. Bloomington, MN: Pearson; 2012.

20. Wechsler D. Technical and Interpretive Manual Supplement: Special Group Validity Studies With Other Measures2012.

21. Achenbach T, Rescorla L. Manual for the ASEBA preschool forms and profiles. Burlington, VT: University of Vermont; 2000.

22. Vinall J, Miller SP, Synnes AR, Grunau RE. Parent behaviors moderate the relationship between neonatal pain and internalizing behaviors at 18 months corrected age in children born very prematurely. Pain 2013;154:1831-9.

23. Scott MN, Taylor HG, Fristad MA, et al. Behavior disorders in extremely preterm/extremely low birth weight children in kindergarten. J Dev Behav Pediatr 2012;33:202-13.

24. Wu YC, Leng CH, Hsieh WS, et al. A randomized controlled trial of clinic-based and home-based interventions in comparison with usual care for preterm infants: Effects and mediators. Res Dev Disabil 2014;35:2384-93.

25. Ebesutani C, Bernstein A, Nakamura BJ, Chorpita BF, Higa-McMillan CK, Weisz JR. Concurrent Validity of the Child Behavior Checklist DSM-Oriented Scales: Correspondence with DSM Diagnoses and Comparison to Syndrome Scales. Journal of psychopathology and behavioral assessment 2010;32:373-84.

26. DuPaul G, Power T, Anastopoulos A, Reed R. The ADHD rating scale IV: checklists, norms and clinical interpretation. New York: Guilford Press; 1998.

27. Rutter M, Bailey A, Lord C. Manual for the Social Communication Questionnaire2003.

28. Chandler S, Charman T, Baird G, et al. Validation of the social communication questionnaire in a population cohort of children with autism spectrum disorders. Journal of the American Academy of Child and Adolescent Psychiatry 2007;46:1324-32.

29. Gosselin J, Amiel-Tison C. Neurological Assessment from Birth to 6 Years. 2nd ed. Montreal: CHU Sainte-Justine; 2011.

30. Matza LS, Swensen AR, Flood EM, Secnik K, Leidy NK. Assessment of health-related quality of life in children: a review of conceptual, methodological, and regulatory issues. Value Health 2004;7:79-92.

31. Varni JW, Burwinkle TM, Lane MM. Health-related quality of life measurement in pediatric clinical practice: an appraisal and precept for future research and application. Health Qual Life Outcomes 2005;3:34.

32. Constitution of the World Health Organization: basic document. Geneva, Switzerland: World Health Organization; 1948.

33. Varni JW, Limbers CA. The pediatric quality of life inventory: measuring pediatric health-related quality of life from the perspective of children and their parents. Pediatr Clin North Am 2009;56:843-63.

34. Varni JW, Limbers CA, Neighbors K, et al. The PedsQL Infant Scales: feasibility, internal consistency reliability, and validity in healthy and ill infants. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2011;20:45-55.

35. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Medical care 2001;39:800-12.

36. Saigal S, Rosenbaum P, Stoskopf B, et al. Development, reliability and validity of a new measure of overall health for pre-school children. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2005;14:243-57.

37. Rosenbaum DM, Korngold E, Teele RL. Sonographic assessment of renal length in normal children. Am J Roentgenol 1984;142:467-9.

38. Rosenberg HK, Markowitz RI, Kolberg H, Park C, Hubbard A, Bellah RD. Normal splenic size in infants and children: sonographic measurements. Am J Roentgenol 1991;157:119-21.

39. Stevens TP, Finer NN, Carlo WA, et al. Respiratory Outcomes of the Surfactant Positive Pressure and Oximetry Randomized Trial (SUPPORT). J Pediatr 2014;165:240-9.e4.

40. Zivanovic S, Peacock J, Alcazar-Paris M, et al. Late outcomes of a randomized trial of high-frequency oscillation in neonates. N Engl J Med 2014;370:1121-30.

Appendix 1 Study Schedule of Events

Procedures	Initial Study Visit[e]	Months (CA)					Years (CA)			
	40 weeks (CA)/term equivalent	3[f] ± 2 wks	6 ± 1 mth	12 ± 3 mths	20 -1 mth[g]	24 ± 3 mth	3[f] ± 3 mths	4[f] ± 3 mths	4.75 -1 mth[g]	5 + 6 mths
Informed Consent	•									
Eligibility Criteria	•									
Demographics	•									
Visual acuity[a]			•	•	•	•			•	•
Corrective lens determination[h]				•	•[g]				•[g]	
Ocular alignment and motility				•		•				•
Refraction with cycloplegia[h]			•							
Stereoacuity										•
Length			•	•		•				
Height										•
Weight			•	•		•				•
Head Circumference			•	•		•				
BSID-III				•		•				
WPPSI-IV										•
CBCL						•				•
VABS-II			•	•		•				•
ADHD-RS-IV										•
SCQ										•
Physical Examination including tonsil examination			•	•		•				•
Cerebral Palsy Assessment						•				
Hearing Assessment History[b]			•							
Pulmonary Morbidity Assessment			•	•		•				•
Survival assessment		•	•	•		•	•	•		•
[redacted]		[redacted]								
HRQoL[c]		•	•[1]	•[1]		•[1]	•	•		•[1]
HCRU		•	•[1]	•[1]		•[1]	•	•		•[1]
HSCS-PS						•[1]	•	•		•[1]
Abdominal Ultrasound			•							
Echocardiogram			•							
Assessment of Participation in Other Clinical Studies		•	•	•		•	•	•		•

Procedures	Initial Study Visit[e]	Months (CA)					Years (CA)			
	40 weeks (CA)/term equivalent	3[f] ± 2 wks	6 ± 1 mth	12 ± 3 mths	20 -1 mth[g]	24 ± 3 mth	3[f] ± 3 mths	4[f] ± 3 mths	4.75 -1 mth[g]	5 + 6 mths
Medications		•	•	•		•	•	•		•
Adverse events[d]	•[j]	•	•	•		•	•	•		•

Abbreviations: ADHD-RS-IV = Attention-Deficit/Hyperactivity Disorder Rating Scale-fourth edition; BSID-III = Bayley Scales of Infant and Toddler Development-Third Edition, CBCL = Child Behavior Checklist; CA = corrected age; HCRU = health care resource use; HRQoL = health-related quality of life; HSCS-PS = Health Status Classification System; mth(s) = months; [redacted]; PedsQL = Pediatric Quality of Life Inventory; SCQ = Social Communication Questionnaire; VABS-II = Vineland Adaptive Behavior Scales, Second Edition; wks = weeks; WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition

[a] The tools used to assess visual acuity will change as the subject ages during their participation in the study. The tools that will be used in this study and are summarized by applicable study visit in Table 12-1.

[b] Historical hearing test data may be recorded at any time during the study prior to the 6-month visit.

[c] HRQoL will be assessed via the validated PedsQL™ scales appropriate for the child's age of development as specified in the Study Operations Manual

[d] Adverse event collection will include an assessment of the specified targeted medical events

[e] The Initial Visit may be performed prior to 40 weeks CA for any subject who discontinued from Study ROPP-2008-01 and, for all subjects, any time after 40 weeks CA, up to the study visit to occur at 3 months CA.

[f] Visits at 3 months, 3 years, and 4 years CA will be conducted by telephone.

[g] The 20-month visit and the 4.75-year (4 years, 9 months) visit must occur at least 1 month prior to the 24-month and 5-year visits, respectively. Any prescribed corrective lenses must be worn for at least 1 month prior to the 24-month and 5-year assessments.

[h] Refraction with cycloplegia will be performed as part of the corrective lens determination procedure.

[i] The HRQoL, HCRU, and HSCS-PS assessments for the 6-month, 12-month, 24-month and 5-year visits may be performed through clinical site staff if there are time constraints during the on-site visit. At the 3-month, 3-year, and 4-year visits, these assessments will be performed through clinical site staff and may be performed at any time within the visit window.

[j] The following, collected as part of the ROPP-2008-01 study, will be used as part of this study (SHP-607-201): any ongoing targeted medical events regardless of causality and any ongoing study drug-related AEs, including SAEs.

Table 12-1 Summary of Visual Acuity Assessments

Visual Acuity Assessment Tool	Description	Unit of Measure	Applicable Age/Study Visit (CA)
Teller acuity cards	Resolution acuity – discrimination of a grating optotype from a background with the same mean luminance	cycles per degree	6 months 12 months
LEA Symbols Test	Recognition acuity - tests recognition of 4 optotypes	Snellen fraction (eg, 20/20)	24 months[a]
LEA Symbols (ETDRS-style) chart	Distance visual acuity test	Snellen fraction (eg, 20/20)	5 years[a]

Abbreviations: CA = corrected age; ETDRS = Early Treatment of Diabetic Retinopathy Study

[a] At ages 24 months and 5 years CA an attempt should be made to assess visual acuity by the LEA Symbols Test and LEA Symbols Chart, respectively. If during this attempt, the examiner determines that it will not be possible to perform an accurate assessment with the relevant LEA tool, visual acuity should be assessed with the Teller acuity cards.

Appendix 2 Summary of Changes

Description of Change	Section(s)
Eliminate repetitive study procedures – the Refraction with Cycloplegia assessment is completed as part of the corrective lens determination that occurs at the 20 month and the 4.75 year visits. This procedure is removed from the 24 month and the 5year visits. Added visual acuity to 20 month visit and 4.75 year visit. Added assessment of participation in other clinical studies to 20 month visit. Removed "Refraction with cycloplegia" from assessment performed at the 20 month and the 4.75 years visits.	Section 4.1– Figure 4-1 Section 8.2 Section 8.2.2.1 Section 8.2.2.2 Appendix 1
The 20 month visit was added with the following assessments: • Visual acuity • Corrective lens determination (including refraction with cycloplegia) • Assessment of participation in other clinical studies The 4.75 year visit was added with the following assessments: • Visual acuity • Corrective lens determination (including refraction with cycloplegia)	Section 8.2.2
Clarify by using the term "Pulmonary Morbidity Assessment" throughout the protocol for consistency. Replaced "Questionnaire" with "Assessment"	Section 7.6.5 Section 10.5.2
All phone contacts are performed by site staff, no call center was set up for the study. Replace "call center" to "by clinical site staff"	Section 7.6.7.1 Section 7.6.8 Section 7.6.8.1 Appendix 1

Description of Change	Section(s)
The overall list of Target Medical Events to be captured in the study was reassessed and updated to ensure all any events with a potential impact to the primary and secondary endpoint are tracked. For this study only the following AEs will be collected: • those considered related to investigational product (rhIGF-1/rhIGFBP-3 as administered in Study ROPP 2008 01, Section D) • those considered related to procedures performed in this study (Study SHP 607 201) • specified targeted medical events (Section 7.9.1.3) regardless of causality Only the following SAEs will be collected: • Fatal SAEs regardless of causality • SAEs related to ROP • SAEs related to congenital malformations not identified at birth which may impact neurocognitive development	Section 7.9.1.1 Section 7.9.1.2
Capture SAE from the end-of–study visit in ROPP-2008-01 Section D and the start of the SHP-607-201 study for safety purpose. Added “When possible, subject’s parents or legally authorized representative(s) should be consented at the end of study visit for the ROPP-2008-01.However, Serious Adverse Events that the subject experiences between ROPP-2008-001 end-of-study visit and the start of the SHP-607-201, will be reported by the Investigator.” in Section 7.9.5.1 Added “SAEs that the subject experiences between ROPP-2008-001 end-of-study visit and the start of the SHP-607-201 will be reported by the Investigator.” in Section 8.1	Section 7.9.5.1 Section 8.1

Description of Change	Section(s)
Administrative changes Update Medical Monitor information as follow: North America [redacted], MD, MPH Shire 300 Shire Way Lexington, MA 02421 USA Telephone: [redacted] Mobile: [redacted] (24-hr access) E-mail: [redacted] Fax: [redacted] (North America) Europe [redacted], MD, PhD Shire International GmbH Zahlerweg 10 6301 Zug - Switzerland Telephone: [redacted] Mobile: [redacted] (24-hr access) E-mail: [redacted] Fax: [redacted] (Global)	Title Page Section 7.9.5.2
Ensure patient PHI are protected – removed "and subject initials"	Section 11.5
Administrative errors were corrected throughout the protocol.	Section 7.6.1.1 Section 10.8.3

Appendix 3 Protocol Signature Page

Study Title:	Long-term Outcome of Children Enrolled in Study ROPP-2008-01 Previously Treated with rhIGF-1/rhIGFBP-3 for the Prevention of Retinopathy of Prematurity (ROP) or Who Received Standard Neonatal Care
Study Number:	SHP-607-201
Final Date:	19 February 2016
Version	Amendment 1

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.
Signatory:

Investigator

_____
Signature **Date**

_____
Printed Name

I have read and approve the protocol described above.
Signatory:

Shire Medical Monitor North America

_____
Signature **Date**

[redacted] MD, MPH
Printed Name

I have read and approve the protocol described above.
Signatory:

Shire Medical Monitor Europe

_____
Signature **Date**

[redacted] MD, PhD
Printed Name

Clinical Trial Protocol: SHP-607-201

Study Title:	Long-term Outcome of Children Enrolled in Study ROPP-2008-01 Previously Treated with rhIGF-1/rhIGFBP-3 for the Prevention of Retinopathy of Prematurity (ROP) or Who Received Standard Neonatal Care
Study Number:	SHP-607-201
Study Phase:	II
Product Name:	Mecasermin rinfabate (rhIGF-1/rhIGFBP-3)
IND Number:	121698
EUDRACT Number	2014-003556-31
Indication:	Retinopathy of Prematurity
Investigators:	Multicenter
Sponsor:	Premacure AB, A Member of the Shire Group of Companies
Sponsor Contact:	300 Shire Way Lexington, MA 02421 USA
Medical Monitor:	[redacted], MD, MPH

	Date
Original Protocol:	27 August 2014
Amendment 1	19 February 2016
Amendment 2	21 February 2017

Confidentiality Statement

SYNOPSIS

Sponsor:

Premacure AB, A Member of the Shire Group of Companies

Name of Finished Product:

Mecasermin rinfabate (rhIGF-1/rhIGFBP-3)

Study Title:

Long-term Outcome of Children Enrolled in Study ROPP-2008-01 Previously Treated with rhIGF-1/rhIGFBP-3 for the Prevention of Retinopathy of Prematurity (ROP) or Who Received Standard Neonatal Care

Study Number:

SHP-607-201

Study Phase: II

Investigational Product, Dose, and Mode of Administration:
Not applicable.

Primary Objectives

The primary objectives of this study are:

- To evaluate the long-term efficacy outcomes following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D) as assessed by ROP associated visual outcomes
- To evaluate the long-term safety outcomes following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D)

Secondary Objectives

The secondary objectives of this study are to evaluate the effect following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D) on:

- Growth parameters
- Cognitive development
- Physical development
- Child behavior
- Pulmonary morbidity
- Survival
- Health-related quality of life (HRQoL)
- Health utility
- Health care resource use (HCRU)

Exploratory Objective

[redacted]

Study Endpoints

The primary efficacy endpoints of this study are:

- Visual acuity as assessed by an age appropriate method
- Ocular alignment and ocular motor examination in primary gaze and in as many of 9 positions of gaze as possible as assessed by corneal light reflex and by the cover test
- Assessment of nystagmus by observation
- Refraction as assessed by retinoscopy with cycloplegia
- Stereoacuity as assessed with the Lang Stereotest

The secondary efficacy endpoints of this study are:

- Growth parameters including body weight, body length (or height), and head circumference
- Cognitive development as assessed by the following standardized, age-appropriate tools:
    - Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)
    - Wechsler Preschool and Primary Scale of Intelligence (WPPSI)
- Physical development as assessed by the following standardized, age appropriate tools:
    - Physical exam
    - Neurological examination for assessment of cerebral palsy
    - Hearing assessment
    - Blood pressure, heart rate, and respiratory rate
    - Cerebral magnetic resonance imaging (MRI)
- Child behavior as assessed by the following:
    - Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
    - Child Behavior Checklist (CBCL; 1 ½ to 5)
    - Attention Deficit/Hyperactivity Disorder Rating Scale (ADHD RS) for the assessment of symptoms of attention deficit/hyperactivity disorder (ADHD)
    - Social Communication Questionnaire (SCQ) for screening of Autism Spectrum Disorder (ASD)
- Pulmonary morbidity data (eg, hospitalizations, emergency room [ER] visits, pulmonary medications)
- Survival as assessed by death during the study due to any cause

The health economic outcome research endpoints of this study are:

- Health-related quality of life (HRQoL) 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, respectively)

- Health status (eg, health utility) will be measured by the Health Status Classification System-Preschool (HSCS-PS)
- Resource use associated with inpatient visits, outpatient visits, medical utilization and pharmacy utilization will be assessed

The safety endpoints of this study are:

- Physical examination including tonsil examination
- Adverse events (AEs), as follows:
  - those considered related to rhIGF-1/rhIGFBP-3 (as administered in Study ROPP-2008-01, Section D)
  - those considered related to procedures performed in this study (Study SHP-607-201)
  - specified targeted medical events regardless of causality
  - fatal SAEs regardless of causality
- Cardiac size as assessed by echocardiogram
- Kidney and spleen size and any other gross abnormalities as assessed by abdominal ultrasound

Exploratory Endpoints:

[redacted]

Study Population:

Subjects randomized in Study ROPP-2008-01, Section D are eligible to enroll in this study; completion of Study ROPP-2008-01 Section D is not required. Subjects in Study ROPP-2008-01 are premature infants (gestational age of 23 weeks + 0 days to 27 weeks + 6 days) who are randomized to receive either treatment with rhIGF-1/rhIGFBP-3 or standard neonatal care. Up to 120 subjects are planned to be randomized into Study ROPP-2008-01 Section D.

Study Design:

This is a Phase II, multicenter, long-term developmental outcome study enrolling subjects who were randomized in Section D of Study ROPP-2008-01. Enrolled subjects in this study will be followed through age 5 years corrected age (CA). This study will enroll both subjects who were in the treated (received rhIGF-1/rhIGFBP-3) and control (received standard neonatal care) groups of Study ROPP-2008-01 (Section D) to enable assessment of rhIGF-1/rhIGFBP-3 long-term efficacy and safety outcomes versus standard neonatal care. No investigational product will be administered in this study.

Study Duration:

Duration for an individual subject's participation in the study will vary depending upon age at enrollment, but subjects will not be followed beyond age 5.5 years corrected age (CA).

Study Inclusion and Exclusion Criteria:

Subjects randomized in Study ROPP-2008-01, Section D are eligible to enroll in this study. Subjects will not be excluded from participating in other clinical studies.

Efficacy Assessments:

Efficacy will be assessed by visual outcomes, growth parameters, cognitive development, physical development, child behavior, pulmonary morbidity, and survival.

Safety Assessments:

Safety will be assessed by physical examination (including tonsil examination), AEs (as specified), echocardiogram, and abdominal ultrasound.

Statistical Methods

Details regarding the statistical methods and definitions will be provided in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to database lock. All statistical analyses will be performed by the sponsor or CRO after the database is locked. Statistical analyses will be performed using Version 9.1 or higher of SAS® (SAS Institute, Cary, NC 27513).

Continuous variables will be summarized using descriptive statistics including the number of observations, 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 2 possible treatment assignments in the antecedent study, ROPP-2008-01, Section D (rhIGF-1/rhIGFBP-3 or standard neonatal care).

For analysis purposes, baseline is defined as the first assessment either in the antecedent study (ROPP-2008-01) or in this study (SHP-607-201). As necessary, relevant data from Study ROPP-2008-01 may be summarized with the data from this study (SHP-607-201).

Date of Original Protocol: 27 August 2014

Date of Amendment 1: 19 February 2016

Date of Amendment 2: 21 February 2017

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AAO	American Academy of Ophthalmology
ADHD	attention-deficit hyperactivity disorder
ADHD-RS	Attention-Deficit/Hyperactivity Disorder Rating Scale
AE	adverse event
ASD	Autism Spectrum Disorder
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
CBCL	Child Behavior Checklist (1 ½ to 5)
CFR	Code of Federal Regulations
CA	corrected age
CI	confidence interval
CRF	case report form (electronic)
CRO	contract research organization
DMC	data monitoring committee
eCRF	electronic case report form
EOS	end of study
ETDRS	Early Treatment of Diabetic Retinopathy Study
ER	emergency room
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GH	growth hormone
HRQoL	health-related quality of life
HSCS-PS	Health Status Classification System-Preschool
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IGF	insulin-like growth factor
IGFBP-3	insulin-like growth factor binding protein-3
IND	Investigational New Drug application
IRB	institutional review board
LV	left ventricle
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
[redacted]	[redacted]

Abbreviation	Definition
OD	right eye
OS	left eye
OU	both eyes
PedsQL	Pediatric Quality of Life Inventory
REB	research ethics board
ROP	retinopathy of prematurity
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System©
SCQ	Social Communication Questionnaire
SD	standard deviation
SOE	schedule of events
SUSAR	suspected unexpected serious adverse reaction
UK	United Kingdom
US	United States
VABS-II	Vineland Adaptive Behavior Scales, Second Edition
VLBW	very low birth weight
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

1 INTRODUCTION

Retinopathy of prematurity (ROP) is a rare disorder of the developing retinal blood vessels and retinal neurons of the preterm infant and is one of the leading causes of preventable blindness in children.[1]

Visual acuity is decreased in infants with a history of ROP.[2] In addition to acuity, other aspects of eye health are also significantly impacted by ROP. Strabismus and myopia are clearly increased in patients with a history of ROP.[3-6] Additionally, more than half of patients at 6 to 10 years of age with a history of Stage 1 and Stage 2 ROP were reported to have ongoing visual issues.[7]

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. During fetal life, IGF-1 is available through placental absorption and ingestion from amniotic fluid.[8] Deprivation of such factors is likely to cause inhibition or improper stimulation of important pathways, which in the eye may cause abnormal retinal vascular development, the hallmark of ROP.

The finding in both a mouse model of ROP and preterm infants that development of ROP is associated with low levels of IGF-1 after premature birth, indicates a possible role for replacement of IGF-1 to levels found in utero as a strategy to potentially decrease abnormal retinal vascularization and abnormal retinal neural development, and ultimately, ROP.

Mecasermin rinfabate (rhIGF-1/rhIGFBP-3) is the human recombinant form of the naturally occurring protein complex of IGF-1 and insulin-like growth factor binding protein-3 (IGFBP-3). rhIGF-1/rhIGFBP-3 was developed to enhance the systemic exposure of administered rhIGF-1 and to improve the safety profile of rhIGF-1 therapy. rhIGF-1/rhIGFBP-3 was approved by the Food and Drug Administration (FDA) in 2005 for the treatment of growth failure in children with severe primary IGF-1 deficiency or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.

The pharmacokinetics and safety of rhIGF-1/rhIGFBP-3 have been evaluated in a Phase I study (ROPP-2005-01) and pharmacokinetics, safety, and efficacy are being evaluated in the ongoing phase II study (ROPP-2008-01). Sections A-C of the ROPP-2008-01 study are complete. Section D of the ROPP-2008-01 study is currently being conducted to assess pharmacokinetics, safety and efficacy of rhIGF-1/rhIGFBP-3 for the prevention of ROP in premature infants (up to a corrected age [CA] of 40 weeks [± 4 days]). Subjects in Study ROPP-2008-01are randomly assigned to receive rhIGF-1/rhIGFBP-3 or standard neonatal care. The target dose of rhIGF-1/rhIGFBP-3 for Study Section D is 250 µg/kg/24 hours to be administered via continuous infusion starting on Study Day 0 (day of birth) and continuing through postmenstrual age (gestational age + time elapsed from birth) 29 weeks + 6 days.

Although the rhIGF-1/rhIGFBP-3 therapy in Section D of the Phase II study (Study ROPP-2008-01) represents a short-term exposure (< 2 months for each subject), rhIGF-1/rhIGFBP-3 may have long-lasting effects on visual outcomes as well as other potential

outcomes related to complications of prematurity such as neurodevelopment, pulmonary function, and growth. In addition, it is critical to understand any long term safety effects from short term exposure to rhIGF-1/rhIGFBP-3.

The long-term outcomes assessed in this study will require utilization of different assessment tools than are utilized in the Phase II study, ROPP-2008-01 Section D, given the changes in physical and cognitive development that will occur in the subjects as they age during their participation in this study.

Please refer to the current edition of the Investigator's Brochure for further information concerning the safety and clinical development of rhIGF-1/rhIGFBP-3.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are:

- To evaluate the long-term efficacy outcomes following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D) as assessed by ROP-associated visual outcomes
- To evaluate the long-term safety outcomes following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D)

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate the effect following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D) on:

- Growth parameters
- Cognitive development
- Physical development
- Child behavior
- Pulmonary morbidity
- Survival
- Health-related quality of life (HRQoL)
- Health utility
- Health care resource use (HCRU)

2.3 Exploratory Objective

[redacted]

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

3.1.1 Primary Efficacy Endpoints

- Visual acuity as assessed by an age-appropriate method
- Ocular alignment and ocular motor examination in primary gaze and in as many of 9 positions of gaze as possible as assessed by corneal light reflex and by the cover test
- Assessment of nystagmus by observation
- Refraction as assessed by retinoscopy with cycloplegia
- Stereoacuity as assessed with the Lang Stereotest

3.1.2 Secondary Efficacy Endpoints

- Growth parameters including body weight, body length (or height), and head circumference
- Cognitive development as assessed by the following standardized, age-appropriate tools:
    - Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)
    - Wechsler Preschool and Primary Scale of Intelligence (WPPSI)
- Physical development as assessed by standardized, age appropriate tools including physical examination, neurological examination for assessment of cerebral palsy, and hearing assessment
- Child behavior as assessed by the following:
    - Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
    - Child Behavior Checklist (CBCL; 1 ½ to 5)
    - Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS) for the assessment of symptoms of attention-deficit/hyperactivity disorder (ADHD)
    - Social Communication Questionnaire (SCQ) for screening of Autism Spectrum Disorder (ASD)
- Pulmonary morbidity data (eg, hospitalizations, emergency room [ER] visits, pulmonary medications)
- Survival as assessed by death during the study due to any cause

3.2 Health Economic Outcome Research Endpoints

- Health Related Quality of Life (HRQoL) 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, respectively)

- Health status (eg, health utility) will be measured by the Health Status Classification System-Preschool (HSCS-PS)
- Resource use associated with inpatient visits, outpatient visits, medical utilization and pharmacy utilization will be assessed

3.3 Safety Endpoints

- Physical examination including tonsil examination
- Adverse events (AEs), as follows:
  - those considered related to rhIGF-1/rhIGFBP-3 (as administered in Study ROPP-2008-01, Section D)
  - those considered related to procedures performed in this study (SHP-607-201)
  - specified targeted medical events regardless of causality
  - fatal serious adverse events (SAEs) regardless of causality
- Cardiac size as assessed by echocardiogram
- Kidney and spleen size and any other gross abnormalities as assessed by abdominal ultrasound

3.4 Exploratory Endpoints

[redacted]

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase II, multicenter, long-term developmental outcome study enrolling subjects who were randomized in Section D of Study ROPP-2008-01 to receive either rhIGF-1/rhIGFBP-3 (treated) or standard neonatal care (control). Enrolled subjects in this study will be followed through age 5 years CA. This study will enroll both subjects who were in the treated (received rhIGF-1/rhIGFBP-3) and control (received standard neonatal care) groups of Study ROPP-2008-01 (Section D) to enable assessment of rhIGF-1/rhIGFBP-3 long-term efficacy and safety outcomes versus standard neonatal care. No investigational product will be administered in this study.

In this study, the Initial Visit will occur at 40 weeks CA (ie, term equivalent) or upon discontinuation from Study ROPP-2008-01 or may occur any time up to the visit at 3 months CA. Subjects in Study ROPP-2008-01 are premature infants enrolling at gestational age of 23 weeks + 0 days to 27 weeks + 6 days.

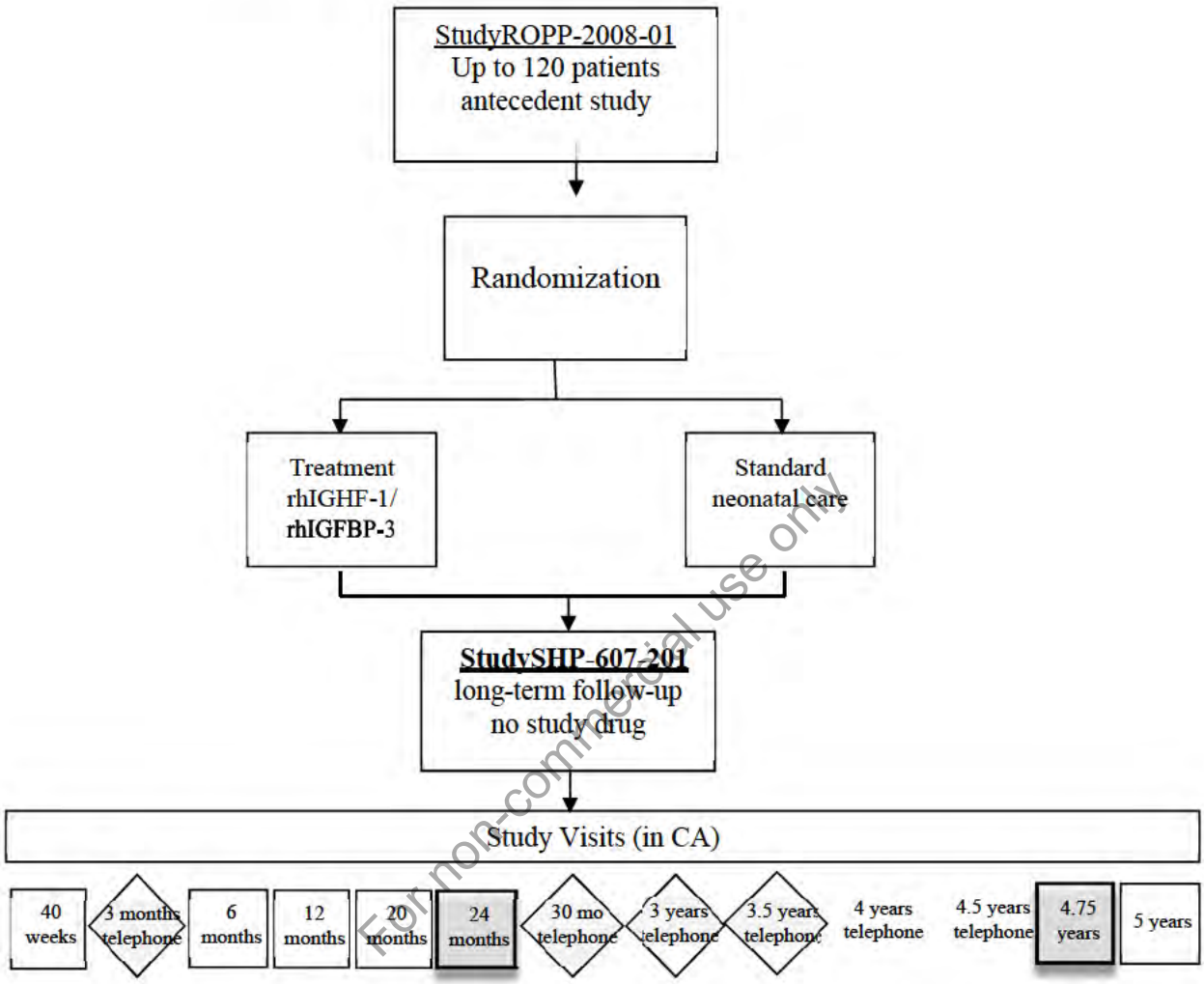
Time points for assessments have been chosen based on standard premature infant follow-up periods and represent important developmental ages for premature infant follow-up. Both telephone and clinical site visits are included to help maintain contact with subjects throughout the 5-year duration of the study.

Subjects will be evaluated at appropriate follow-up site locations with expertise in the assessment of the developmental outcomes of premature infants. Pediatric ophthalmology expertise will also be required.

See Appendix 1 for the Study Schedule of Events table.

The overall study design is outlined in Figure 4-1.

Figure 4-1 Overview of Study Design, Study SHP-607-201



Abbreviations: CA = corrected age

Note: Visits conducted by telephone are indicated with a diamond shape. Visits conducted at the study site are indicated with rectangles. Visit windows are provided in the Schedule of Events (Appendix 1).

4.2 Rationale for Study Design

The only approved therapies for ROP are ablative (cryotherapy or laser therapy). To date, there are no commercially available preventative treatments for ROP.

Although treatment with rhIGF-1/rhIGFBP-3 in ROPP-2008-01 (Section D) after premature birth is limited to less than 2 months of therapy, it remains important to assess the long-term outcomes of treatment on both efficacy and safety. Thus, this long-term follow-up study to Study ROPP-2008 01 (Section D) has been designed to assess long-term efficacy and safety outcomes following short-term exposure to rhIGF-1/rhIGFBP-3.

Insulin-like growth factor-1 (IGF-1) mediates its primary actions by binding to its specific receptor, the insulin-like growth factor 1 receptor (IGF-1R), which is present on many cell types in many tissues. Binding to its receptor initiates intracellular signaling including via the AKT signaling pathway. This pathway is involved in stimulation of cell division, growth and differentiation and inhibits programmed cell death. Specifically regarding premature infants, IGF-1 is an important mediator of fetal growth and has been shown to play a role in early postnatal growth following pre-term delivery.[9,10]

Insulin-like growth factor-1 (IGF-1) has also been shown to play a role in pulmonary development[11] and neural development.[12,13] Given the potential role for IGF-1 in the development of multiple systems, this study has been designed to evaluate the long-term effects of rhIGF-1/rhIGFBP-3, both from a safety and efficacy perspective, on the development of the premature infant.

4.3 Study Duration

Duration for an individual subject's participation in the study will vary depending upon age at enrollment, but subjects will not be followed beyond age 5.5 years CA.

5 STUDY POPULATION SELECTION

5.1 Study Population

Subjects randomized in Study ROPP-2008-01, Section D are eligible to enroll in this study; completion of Study ROPP-2008-01 Section D is not required. Subjects in Study ROPP-2008-01 are premature infants (gestational age of 23 weeks + 0 days to 27 weeks + 6 days) who are randomized to receive either treatment with rhIGF-1/rhIGFBP-3 or standard neonatal care. Up to 120 subjects are planned to be randomized in Study ROPP-2008-01 Section D.

5.2 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study.

1. Subject was randomized in Study ROPP-2008-01, Section D
2. Subject's parent or legally authorized representative(s) must provide written informed consent prior to performing any study-related activities. Study-related activities are any procedures that would not have been performed during normal management of the subject.

5.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study.

1. Any other condition or therapy that, in the Investigator's opinion, may pose a risk to the subject or interfere with the subject's ability to be compliant with this protocol or interfere with the interpretation of results
2. The subject or subject's parent or legally authorized representative(s) is unable to comply with the protocol as determined by the Investigator

6 STUDY TREATMENT

6.1 Description of Treatment

No investigational product will be administered in this study.

6.2 Treatments Administered

Not applicable.

6.3 Selection and Timing of Dose for Each Subject

Not applicable.

6.4 Method of Assigning Subjects to Treatment Groups

Not applicable.

6.5 Masking

Not applicable.

6.6 Medications

Any medications administered to the subjects will be collected from the time of informed consent through the 5-year CA visit (or until the subject withdraws or is discontinued). Any investigational product received by subjects will be recorded separately as part of an assessment of subjects' participation in other clinical studies (Section 7.11.1).

6.7 Restrictions

6.7.1 Prior Therapy

There are no restrictions related to prior therapy.

6.7.2 Other Restrictions

There are no restrictions related to fluid or food intake, or subject activity.

6.7.3 Treatment Compliance

Not applicable.

6.7.4 Packaging and Labeling

Not applicable.

6.8 Storage and Accountability

Not applicable

7 STUDY PROCEDURES

Detailed descriptions of subject procedures and evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of the study (see Schedule of Events in Appendix 1).

All data collected are to be recorded on the subject's appropriate eCRF.

Details for study procedures are described in the Operations Manual for this study.

7.1 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).

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 11.4. Documentation and filing of informed consent documents should be completed according to Section 11.4.

7.2 Study Entrance Criteria and Eligibility

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 informed consent is not obtained at or before the 3-month visit in Study ROPP-2008-01 for inclusion in this study (SHP607-201), the subject may still be enrolled until they turn 2 years CA +3 months. Subjects are no longer eligible to participate in this study after they turn 2 years CA +3 months.

7.3 Study Enrollment

Subjects will be considered enrolled in the study once written informed consent has been obtained from the subject's parent(s) or legally authorized representative(s).

7.4 Demographics

Subject demographic information including gender, date of birth, and race will be recorded.

7.5 Growth Parameters: Length (and Height), Weight, and Head Circumference

7.5.1 Length and Height

Body length (supine measurement) will be collected when subjects are 24-months CA or younger. 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 when subjects are older than 24-months CA. 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).

7.5.2 Body Weight

Body weight will be collected. Calibrated scales should be utilized for body weight measures (type of scale will depend upon subject's age). Care should be taken to remove any extraneous clothing prior to measures and shoes should be removed.

The measure should be recorded to the nearest 0.1 kg.

7.5.3 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.

7.6 Efficacy Assessments

7.6.1 Visual Assessments

After corrective lens determination has occurred (Section 7.6.1.2), all visual assessments should be conducted with best-corrected vision, ie, with corrective lenses in place (if required); this applies to 24-month and 5-year visits.

7.6.1.1 Visual Acuity

Visual acuity is a measure of how well a subject sees at different distances. It will be assessed by the methods summarized in Table 7-1; the method employed will be selected based on the subject's age (CA) at the time of the study visit. Visual acuity measurements will be measured and recorded for the left (OS), right (OD) eye, and both eyes (OU).

At ages 6 months and 12 months CA, visual acuity will be assessed with Teller acuity cards. At ages 24 months and 5 years CA an attempt should be made to assess visual acuity by the LEA Symbols Test and LEA Symbols Chart, respectively. If during this attempt, the examiner determines that it will not be possible to perform an accurate assessment with the relevant LEA tool, visual acuity should be assessed with the Teller acuity cards.

The visual acuity assessments should be performed by an optometrist or ophthalmologist trained in pediatrics.

Table 7-1 Summary of Visual Acuity Assessments

Visual Acuity Assessment Tool	Description	Unit of Measure	Applicable Age/Study Visit (CA)
Teller acuity cards	Resolution acuity – discrimination of a grating optotype from a background with the same mean luminance	cycles per degree	6 months 12 months
LEA Symbols Test	Recognition acuity - tests recognition of 4 optotypes	Snellen fraction (eg, 20/20)	24 months[a]
LEA Symbols (ETDRS-style) chart	Distance visual acuity test	Snellen fraction (eg, 20/20)	5 years[a]

Abbreviations: CA = corrected age; ETDRS = Early Treatment of Diabetic Retinopathy Study

[a] At ages 24 months and 5 years CA an attempt should be made to assess visual acuity by the LEA Symbols Test and LEA Symbols Chart, respectively. If during this attempt, the examiner determines that it will not be possible to perform an accurate assessment with the relevant LEA tool, visual acuity should be assessed with the Teller acuity cards.

7.6.1.2 Corrective Lens Determination

An assessment to determine if the subject requires vision correction with corrective lenses will be performed. This is being performed to ensure the accuracy of subjects' subsequent visual acuity assessments (at the 24-month and 5-year visits). The corrective lens determination will be performed according to the guidelines published by the American Academy of Ophthalmology (AAO).[14]

This assessment should be performed by an optometrist or ophthalmologist trained in pediatrics.

7.6.1.3 Ocular Alignment and Oculomotor Examination (Motility)

Ocular alignment will be assessed in primary gaze by comparing the position of the corneal light reflection in OS and OD (corneal light reflection assessment). Presence or absence of strabismus will be recorded in primary gaze and in as many of the 9 positions of gaze as feasible with the cover test assessment of refixation movement. Extraocular muscle over-action or deficiency will be recorded. The assessment will be performed according to the AAO guidelines.[14]

Presence or absence of nystagmus as observed during the ocular alignment assessments will also be recorded.

The assessment will be performed by a pediatric ophthalmologist or an ophthalmologist trained in the care of pediatric subjects with a history of premature birth. Degree of adherence to the AAO guidelines will be at the discretion of the examining physician in consideration of the need for patient cooperation.

Ocular motility refers to eye movements, which are governed by the 6 extraocular muscles in each eye. It will be assessed by examiner observation of the subject's ability to abduct, adduct, supra, and inferoduct each eye (to assess for strabismus). Any of the observed misalignment (strabismus classifications) will be recorded:

- esotropia
- exotropia
- hypertropia
- hypotropia

The frequency (constant or intermittent) with which any misalignment occurs and whether the turning eye is always the same eye or if it alternates between OS and OD, will be recorded. Extraocular muscle over-action or deficiency will be recorded.

This assessment should be performed by an optometrist or ophthalmologist trained in pediatrics.

7.6.1.4 Refraction with Cycloplegia

Refraction is a measure of the lens power required for a focused image on the retina. Refraction with cycloplegia will be measured and recorded in diopters for each eye individually (OS and OD).

Cycloplegia may be induced according to site standard practice.

This assessment should be performed by an optometrist or ophthalmologist trained in pediatrics.

7.6.1.5 Stereoacuity

Stereoacuity is a measure of depth perception and will be assessed using the Lang Stereotest and performed by certified personnel. The presence or absence of stereopsis will be recorded.

7.6.1.6 [redacted]

[redacted]

7.6.2 Hearing Assessment History

Results of previously completed hearing assessments will be recorded at the 5-year CA visit; hearing tests are not being performed as part of this study.

7.6.3 Behavioral Assessments

7.6.3.1 Bayley Scales of Infant and Toddler Development, Third Edition

The BSID-III will be used to assess cognitive, motor, and language skills, and is applicable to children aged 1 to 42 months.

The BSID-III is an assessment tool designed to measure a young child's skills in the 3 core areas of development: cognitive, language, and motor. There are 5 subscales, the cognitive subscale stands alone while 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 examiner's manual.

The BSID-III 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.

7.6.3.2 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.[19] It is applicable to preschoolers and young children aged 2 years + 6 months to 7 years + 7 months, and is a direct assessment of a child's cognitive skills.

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[20] 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. Scores to be recorded are detailed in the Study Operations Manual.

7.6.3.3 Child Behavior Checklist (CBCL)

The CBCL (1 ½ to 5) is a parent-reported outcome measure used to assess behavioral, emotional, and social functioning of toddlers and preschool children aged 18 to 60 months.[21] It is composed of 99 items that are rated on a Likert scale and includes the following 7 syndrome scales arranged under 2 domains (ie, Internalizing and Externalizing Problems):[22]

- Internalizing Problems
- Emotionally Reactive
- Anxious/Depressed
- Somatic Complaints
- Withdrawn
- Sleep Problems
- Attention Problems
- Aggressive Behavior

The questionnaire is widely used and has been employed to assess long-term behavioral outcomes in children born prematurely, aged similarly to the subjects expected in this study population.[22-24] It is associated with well-established normative data;[25] norms may be selected to aid in interpretation of the scale scores.

The CBCL (1 ½ to 5) is a questionnaire that will be administered to 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.

7.6.3.4 Vineland Adaptive Behavior Scales, Second Edition

The VABS-II Expanded Interview Form will be used to measure the personal and social skills of subjects serially over time; these scales are organized within a 3-domain structure: Communication, Daily Living, and Socialization. In addition, the VABS-II offers a Motor Skills Domain and an optional Maladaptive Behavior Index. The VABS-II Expanded Interview Form assesses what a subject actually does, rather than what he or she is able to do.

The VABS-II Expanded Interview Form will be administered to 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.

7.6.3.5 Attention-Deficit/Hyperactivity Disorder Rating Scale

The ADHD-RS was developed to measure the behaviors of children with ADHD. The ADHD-RS consists of 18 items designed to reflect current symptomatology of ADHD based on DSM-IV 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,[26] will be completed by the subject's parent(s) or legally authorized representative(s). Scores to be recorded are detailed in the Study Operations Manual.

7.6.3.6 Social Communication Questionnaire – Lifetime Form

The SCQ is a brief instrument that helps evaluate communication skills and social functioning in children[27] that can be used for screening for autism or autism spectrum disorders in the general population.[28]

The SCQ will be completed by the subject's parent(s) or legally authorized representative(s). 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.

7.6.4 Cerebral Palsy Assessment

Comprehensive neurological examination for the diagnosis of cerebral palsy (CP) will be conducted. The Amiel-Tison neurological examination framework[29] will be utilized for this assessment and conducted by trained medical professionals.

7.6.5 Pulmonary Morbidity Assessment

Pulmonary morbidity will be assessed with questions related to family history and smoking status as well as diagnosis of select pulmonary symptoms, conditions and related hospitalizations. The assessment will be administered to the subject's parent(s) or legally authorized representative(s). Assessments will be performed as outlined in the Schedule of Events (see Appendix 1).Questionnaires that will be used for these assessments at clinical site visits are provided in Appendix 2 for the 6-month and 12-month CA visits and Appendix 3 for the 24-month and 5-year CA visits. The questionnaire that will be used for these assessments during phone interviews at the 30-month, 3-year, 3.5-year, 4-year, and 4.5-year CA visits is provided in Appendix 4.

7.6.6 Cerebral Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) of the brain will be performed. The MRI should be performed without sedation. If the scan is unsuccessful, a second attempt should be made. 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.

7.6.7 Survival Assessment

Survival status will be assessed and recorded.

7.6.8 Health Economic Outcome Research Assessments

7.6.8.1 Health Related Quality of Life

Health-related quality of life (HRQoL) is an important outcome towards improving the health care of pediatric patients as it is that part of a person's overall quality of life that is determined

primarily by their health status and which can be influenced by clinical interventions. It is an important concept, which is also used in determining the value of health care services in this population.[30,31] It is a multidimensional construct whose content is guided by the World Health Organization;[32] minimally it includes physical, psychological (including emotional and cognitive), and social health dimensions.

In this study, HRQoL will be assessed via the validated Pediatric Quality of Life Inventory (PedsQL™) Scales appropriate for the child's age of development.[33-35] The development of the PedsQL was based on the delineations of the World Health Organization (WHO) and is a modular approach to assessing HRQoL in the pediatric population. Initially, the PedsQL Generic Scales were developed and continue to be used in children aged 2 to 18 years. More recently Infant Scales have been developed that apply to ages 1 to 24 months.[34]

The following scales will be used in this study:

- Infant Scale for ages 1-12 months (36 Items)
- Infant Scale for ages 13–24 months (45 Items)
- Toddler Scale for 2-4 years of age (21 Items)
- Young Child Scale for 5-7 years of age (23 Items)

The PedsQL will be administered to the subject's parent and may be conducted via telephone by clinical site staff. The scale(s) to be administered at each visit will be specified in the Study Operations Manual.

7.6.9 Health Care Resource Use

To understand the value of the investigational product administered in Study ROPP-2008-01 (Section D), the resource use associated with inpatient visits, outpatient visits, and medical and pharmacy utilization in this study will be recorded.

This assessment may be conducted via telephone by clinical site staff.

7.6.9.1 Health Status Classification System-Preschool

Health status (eg, health utility) will be measured by the Health Status Classification System-Preschool (HSCS-PS), which is a validated instrument adapted for use via parent proxy within the pediatric population age 2.5 to 5 (adapted from the validated Health Utilities Index Mark 2 and 3 [HUI 2/3]).[36] Validity of the HSCS-PS concepts has not been established for ages younger than 2.5 years.

The HSCS-PS was developed to provide a consistent measure of health status in preschool-aged children who had been born prematurely.[36] The system is applicable to children with special needs as may be included in this study; validation cohorts for the system included children with very low birth weight (VLBW), which is congruent with this study population.

The instrument is composed of 12 dimensions (Vision, Hearing, Speech, Mobility, Dexterity, Self-care, Emotion, Learn/remember, Think/problem solve, Pain, General Health, and Behavior) intended to provide a comprehensive assessment of a child's health status as it pertains to health-related quality of life. The individual domains of the instrument will be scored as a mean score, representing the overall state for each concept individually. The global score will be recorded as well as the scores for each of the dimensions.

The HSCS-PS is a questionnaire that will be administered to the subject's parent(s) or legally authorized representative(s) and may be conducted via telephone by clinical site staff.

7.7 Safety Assessments

7.7.1 Abdominal ultrasound

An abdominal ultrasound will be performed to assess the size of the spleen and kidneys. The spleen will be measured in the coronal longitudinal plane and the longest longitudinal length will be measured for each kidney (left and right).[37] Ultrasound results will be assessed by a central reader.

Organ size will be interpreted in the context of reference values established for children.[37,38]

7.7.2 Echocardiogram

Echocardiographic examination (conventional M-mode recording of the left ventricle [LV] parasternal long axis view) will be performed for the evaluation of cardiac size, assessed by measuring the following:

- interventricular septal thickness (during end diastole)
- LV posterior wall thickness
- LV intracavity volume (both in end diastole and end systole)

Echocardiogram results will be assessed by a central reader.

7.7.3 Physical Examination

Physical examinations will include a review of the subject's general appearance, neurological examination, as well as a tonsillar examination (Table 7-2). Any abnormal change in findings will be recorded as an AE.

Table 7-2 Assessments for Physical Examinations

Assessment	Assessment
General appearance	Endocrine
Head and neck	Cardiovascular
Eyes	Abdomen
Ears	Genitourinary
Nose	Skin

Table 7-2 Assessments for Physical Examinations

Assessment	Assessment
Throat	Musculoskeletal
Chest and lungs	Neurological
Tonsils	

7.7.4 Blood Pressure, Heart Rate, and Respiratory Rate

Blood pressure, heart rate, and respiratory will be measured at the 5-year CA visit.

7.8 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 7.11.1).

7.9 Adverse Events Assessments

7.9.1 Definitions of Adverse Events, Serious Adverse Events, and Suspected Unexpected Serious Adverse Reactions

7.9.1.1 Adverse Event

An AE is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered investigational product-related. This includes an exacerbation of a pre-existing condition.

Adverse events include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study
- Intercurrent illnesses
- Drug interactions
- Events related to or possibly related to concomitant medications
- Abnormal laboratory values (this includes significant shifts from baseline within the range of normal that the Investigator considers to be clinically important)
- Clinically significant abnormalities in physical examination, vital signs, and weight

In this long-term outcome study in follow-up to Study ROPP-2008-01 (Section D), no investigational product is being administered. However, the relationship to the investigational product (rhIGF-1/rhIGFBP-3) as administered in Study ROPP-2008-01 (Section D) will be assessed.

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

- those considered related to investigational product (rhIGF-1/rhIGFBP-3 as administered in Study ROPP -2008-01, Section D)
- those considered related to procedures performed in this study (Study SHP-607-201)
- specified targeted medical events (Section 7.9.1.3) regardless of causality

Throughout the study, the Investigator must record AEs on the AE electronic case report form (eCRF), regardless of the severity. The Investigator should treat subjects with AEs appropriately and observe them at suitable intervals until the events stabilize or resolve. Adverse events may be discovered through observation or examination of the subject, questioning of the subject, complaint by the subject, or by abnormal clinical laboratory values.

In addition, AEs may also include laboratory values that become significantly out of range. In the event of an out-of-range value, the laboratory test should be repeated until it returns to normal or can be explained and the subject's safety is not at risk.

Additional illnesses present at the time when informed consent is given are regarded as AEs and will be documented on the appropriate pages of the eCRF. Illnesses first occurring or detected during the study, and worsening of a concomitant illness during the study, are to be regarded as AEs and must be documented as such in the eCRF.

7.9.1.2 Serious Adverse Event

An SAE is any AE that results in any of the following outcomes:

- Death
- Is life-threatening
- Requires hospitalization
- Requires prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect

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 one of the outcomes listed in this definition. A life-threatening AE is defined as an AE that placed the subject, in the view of the initial reporter, at immediate risk of death from the AE as it occurred (ie, it does not include an AE that, had it occurred in a more severe form, might have caused death).

For the purposes of this study only SAE listed in the following will be collected:

- fatal SAEs regardless of causality
- SAEs related to ROP
- SAEs related to congenital malformations not identified at birth which may impact neurocognitive development

7.9.1.3 Suspected Unexpected Serious Adverse Reaction

Suspected unexpected serious adverse reactions (SUSAR) are suspected adverse reactions related to an investigational product (investigational products and comparators [if applicable]), which occur in the concerned study, and that are both serious and unexpected according to the current Investigator's Brochure.

7.9.1.4 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, as appropriate, regardless of relationship to investigational product (rhIGF-1/rhIGFBP-3 as administered in Study ROPP-2008-01, Section D):

- intracranial hypertension
- any abnormality of glucose metabolism (eg, hypoglycemia, hyperglycemia, and diabetes)
- tonsillar hypertrophy (based on tonsil exam [part of the physical exam])
- increased kidney size
- increased cardiac size
- increased spleen size

7.9.2 Classification of Adverse Events and Serious Adverse Events

The severity of AEs will be assessed by the Investigator based on the definition indicated in Table 7-3. The severity of all AEs/SAEs should be recorded on the appropriate eCRF page to a severity of mild, moderate, or severe.

Table 7-3 Adverse Event Severity

Severity	Definition
Mild	No limitation of usual activities.
Moderate	Some limitation of usual activities.
Severe	Inability to carry out usual activities.

7.9.3 Clarification between Serious and Severe

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) and causality serve as a guide for defining regulatory reporting obligations.

7.9.4 Relatedness of Adverse Events and Serious Adverse Events

Relationship of an AE or SAE to investigational product (rhIGF-1/rhIGFBP-3 as administered in Study ROPP-2008-01, Section D) is to be determined by the Investigator based on the following definitions (See Table 7-4).

Table 7-4 Adverse Event Relatedness

Relationship to Product	Definition
Not Related	Unrelated to investigational product
Possibly Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, but which could also be explained by concurrent disease or other drugs or chemicals.
Probably Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on de-challenge. The association of the clinical event or laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds.
Definitely related	The event follows a reasonable temporal sequence from administration of the investigational product, follows a known or suspected response pattern to the investigational product, is confirmed by improvement upon stopping the investigational product (de-challenge), and reappears upon repeated exposure (re-challenge). Note that this is not to be construed as requiring re-exposure of the subject to investigational product; however, the determination of definitely related can only be used when recurrence of event is observed.

7.9.5 Procedures for Recording and Reporting Adverse Events

7.9.5.1 Adverse Event Monitoring and Period of Observation

Adverse events will be monitored throughout the study.

For the purposes of this study, the period of observation begins from the time at which the subject's parent(s) or legally authorized representative(s) gives informed consent until the subject's final evaluation of the study. When possible, subject's parents or legally authorized representative(s) should be consented at the end of study visit for the ROPP-2008-01. However, if this is not possible, subject's parents or legally authorized representative(s) will be asked to provide consent for any Serious Adverse Events that the subject experiences between

ROPP-2008-01 end-of-study visit and the start of the SHP-607-201, to be reported by the Investigator. For safety purposes, the final evaluation will be defined as the last study visit when the subject is 5 years-old in CA.

If the Investigator considers it necessary to report an AE in a study subject after the end of the safety observation period, he or she should contact the Sponsor to determine how the AE should be documented and reported.

7.9.5.2 Reporting Serious Adverse Events

Any SAE meeting the reporting criteria for this study should be recorded by the clinical site on an SAE form. The SAE must be completely described on the subject's eCRF, including the judgment of the Investigator as to the relationship of the SAE to the investigational product. The Investigator will promptly supply all information identified and requested by the Sponsor (or contract research organization [CRO]) regarding the SAE.

The Investigator must report the SAE to the Shire Pharmacovigilance and Risk Management Department AND to the local Shire Medical Monitor on an SAE form. This form must be completed and FAXED or EMAILED within 24 hours of the Investigator's learning of the event to:

Shire Pharmacovigilance and Risk Management Department:

International FAX: [redacted] **(UK) OR United States FAX:** [redacted]

Email: [redacted]

AND

Shire Medical Monitor: [redacted], **MD, MPH**
E-mail: [redacted]

Any follow-up information must also be completed on an SAE form and faxed or emailed to the same numbers or emails listed above.

In the event of a severe and unexpected, fatal, or life-threatening SAE, the clinical site must contact the Shire Medical Monitor by telephone as soon as possible and within 24 hours of awareness; this is in addition to completing and transmitting the SAE form as stated above. The following provides contact information for the Shire Medical Monitor.

If an SAE is assessed as severe and unexpected, or life-threatening, contact:
[redacted], MD, MPH [redacted] Shire 300 Shire Way Lexington, MA 02421 USA Telephone: [redacted] Mobile: [redacted] (24-hr access) E-mail: [redacted] Fax: [redacted] (North America)

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

The Sponsor and the CRO are responsible for notifying the relevant regulatory authorities/US central IRBs/European Union (EU) central ECs of related, unexpected SAEs.

For some European regulatory authorities, these reports are submitted directly to Eudravigilance. In case of deaths or life-threatening SUSARs, these must be reported to the relevant regulatory authorities before 7 days have elapsed from that the initial SAE report has reached the Sponsor or its representatives. A full report has to be submitted within another 8 days. For other SUSARs the timelines for reporting are 15 days.

In addition, the CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the rhIGF-1/rhIGFBP-3 program at Shire.

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.

7.10 Removal of Subjects from the Trial

A subject's participation in the study may be discontinued at any time at the discretion of the Investigator. The following may be justifiable reasons for the Investigator to remove a subject from the study:

- Non-compliance, including failure to appear at one or more study visits
- The subject was erroneously included in the study
- The subject develops an exclusion criterion
- The study is terminated by the Sponsor

The subject, the subject's parent(s), or the subject's legally authorized representative acting on behalf of the subject is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment.

If a subject or the subject's parent(s) or the subject's legally authorized representative(s) acting on behalf of the subject, discontinues participation in the study, or the subject is discontinued by the Investigator, reasonable efforts will be made to follow the subject through the end of study assessments. The reason for refusal will be documented on the eCRF. Any AEs experienced up to the point of discontinuation must be documented on the AE eCRF. If AEs are present when the subject withdraws from the study, the subject will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal will be followed until resolution.

7.11 Other Study Procedures

7.11.1 Participation in Other Clinical Studies

Following enrollment, subjects in this study will not be restricted from enrolling in another clinical study that involves 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 being evaluated in the study, and the subject's treatment assignment in the study (if possible).

7.12 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. These are the pulmonary morbidity assessment and the cerebral palsy assessment. In these cases, the tools are either based on validated tools or the current state of knowledge in the literature. For example, the cerebral palsy assessment is based on the Amiel-Tison neurological examination framework[29] and the pulmonary assessment is based on published research in a similar pediatric population.[39,40]

8 STUDY ACTIVITIES

The timing of the visits in this study is based on subjects' corrected age (CA).

8.1 Initial Study Visit (40 weeks CA [term equivalent])

The Initial Visit will occur at 40 weeks CA (ie, term equivalent) or upon discontinuation from Study ROPP-2008-01, Section D or any time up to the visit at 3 months CA.

For subjects enrolled between the ages of 9 months CA and 2 years +3 months CA, missed procedures such as neurocognitive assessments, abdominal ultrasounds, and echocardiograms are not required.

At the Initial Visit, informed consent will be obtained followed by an assessment of study eligibility criteria and collection of demographic data.

The following AE data, collected as part of Study ROPP-2008-01 (Section D) will be recorded:

- Ongoing targeted medical events regardless of causality
- Ongoing study drug-related AEs, including SAEs

SAEs, as outlined in Section 7.9.1.1 and Section 7.9.1.2, that the subject experiences between the ROPP-2008-01 end-of-study visit and the time of informed consent for the SHIP-607-201 study will be reported by the Investigator, pending permission for subject's parent or legally authorized representative(s), as documented on the informed consent form.

8.2 Study Visits

Study visits for follow-up outcome assessments will take place at the following time points in CA:

- 3 months (±2 weeks) – conducted by telephone
- 6 months (±1 month) – clinical site visit
- 12 months (±3 months) – clinical site visit
- 20 months (-1 months) – clinical site visit
- 24 months (±3 months) – clinical site visit
- 30 months (±3 months) – conducted by telephone
- 3 years (±3 months) – conducted by telephone
- 3.5 years (±3 months) – conducted by telephone
- 4 years (±3 month) – conducted by telephone
- 4.5 years (±3 month) – conducted by telephone
- 4.75 years (-1 months) – clinical site visit
- 5 years (+6 months) – clinical site visit

In addition, there will be 2 visits that must occur at least 1 month prior to the 24-month and 5-year CA study visits to assess the need for corrective lenses. The timing of these 2 visits (20 months [-1 month] and 4.75 years [-1 month]) was set to ensure that any prescribed corrective lenses would be worn for at least 1 month prior to the visual assessments at the 24-month and 5-year study visits CA.

The activities at the study visits are described in Sections 8.2.1 and 8.2.2.

8.2.1 Outcome Assessment Visits Conducted by Telephone

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

- HRQoL (3-month, 3-year, and 4-year visits)
- HCRU (3-month, 3-year, and 4-year visits)
- HSCS-PS (3-year and 4-year visits)
- Pulmonary morbidity assessment (30-month, 3-year, 3.5-year, 4-year, and 4.5-year visits)
- Medications (3-month, 3-year, and 4-year visits)
- Survival assessment (3-month, 3-year, and 4-year visits)
- Assessment of participation in other clinical studies (3-month, 3-year, and 4-year visits)
- Adverse events, including targeted medical events (3-month, 3-year, and 4-year visits)

8.2.2 Clinical Site Visits

8.2.2.1 Outcome Assessment Site Visits

The following clinical site visits (in CA) to capture follow-up outcome data will occur at the clinical site:

- 6 months (±1 month)
- 12 months (±3 months)
- 20 months (-1 month)
- 24 months (±3 months)
- 4.75 years (-1 months)
- 5 years (+6 months)

The following assessments will be performed at the 6-month visit:

- Visual acuity
- Refraction with cycloplegia

- Length
- Weight
- Head circumference
- VABS-II
- Physical examination (including tonsil examination)
- Hearing Assessment History (Historical hearing test data may be recorded at any time prior to the 6-month visit)
- Pulmonary morbidity assessment
- Survival assessment
- HRQoL (may be performed by telephone if there are time constraints during this clinical site visit)
- HCRU (may be performed by telephone if there are time constraints during this clinical site visit)
- Abdominal ultrasound
- Echocardiogram
- Assessment of participation in other clinical studies
- Medications
- Adverse events (including targeted medical events)

The following assessments will be performed at the 12-month visit:

- Visual acuity
- Corrective lens determination (including refraction with cycloplegia)
- Ocular alignment and motility
- Length
- Weight
- Head circumference
- BSID-III
- VABS-II
- Physical examination (including tonsil examination)
- Pulmonary morbidity assessment
- Survival assessment
- HRQoL (may be performed by telephone if there are time constraints during this clinical site visit)

- HCRU (may be performed by telephone if there are time constraints during this clinical site visit)
- Assessment of participation in other clinical studies
- Medications
- Adverse events (including targeted medical events)

The following assessments will be performed at the 20-month visit:

- Visual acuity
- Corrective lens determination (including refraction with cycloplegia)
- Assessment of participation in other clinical studies

The following assessments will be performed at the 24-month visit:

- Visual acuity
- Ocular alignment and motility
- Length
- Weight
- Head circumference
- BSID-III
- CBCL
- VABS-II
- Physical examination (including tonsil examination)
- Cerebral Palsy assessment
- Pulmonary morbidity assessment
- Survival assessment
- HRQoL (may be performed by telephone if there are time constraints during this clinical site visit)
- HCRU (may be performed by telephone if there are time constraints during this clinical site visit)
- HSCS-PS (may be performed by telephone if there are time constraints during this clinical site visit)
- Assessment of participation in other clinical studies
- Medications
- Adverse events (including targeted medical events)

The following assessments will be performed at 4.75-year visit:

- Visual acuity
- Corrective lens determination (including refraction with cycloplegia)

The following assessments will be performed at the 5-year visit:

- Visual acuity
- Ocular alignment and motility
- Stereoacuity
- Height
- Weight
- WPPSI
- CBCL
- VABS-II
- ADHD-RS
- SCQ
- Physical examination (including tonsil examination)
- Blood pressure, heart rate, and respiratory rate
- Pulmonary morbidity assessment
- Hearing assessment history
- Survival assessment
- [redacted]
- Cerebral MRI
- HRQoL (may be performed by telephone if there are time constraints during this clinical site visit)
- HCRU (may be performed by telephone if there are time constraints during this clinical site visit)
- HSCS-PS (may be performed by telephone if there are time constraints during this clinical site visit)
- Assessment of participation in other clinical studies
- Medications
- Adverse events (including targeted medical events)

8.2.2.2 Visits Dedicated to Corrective Lens Determination

The following clinical site visits are dedicated solely to corrective lens determination in preparation for the outcome assessment visits at 24-months and 5-years CA:

- 20 months (-1 month)
- 4.75 years (-1 month)

At these visits, the following will be performed:

- Visual acuity
- Corrective lens determination (includes refraction with cycloplegia)

The 20-month visit and the 4.75-year (4 years, 9 months) visit must occur at least 1 month prior to the 24-month and 5-year visits, respectively. Any prescribed corrective lenses must be worn for at least 1 month prior to the 24 month and 5 year assessments.

8.3 Assessments upon Discontinuation

If a subject discontinues prior to the 5-year CA visit, every attempt will be made to complete the assessments scheduled for the subject's next visit.

9 QUALITY CONTROL AND ASSURANCE

Training will occur at an Investigator meeting or at the site initiation visit or both, and instruction manuals will be provided to aid consistency in data collection and reporting across sites.

Clinical sites will be monitored by the Sponsor or its designee to ensure the accuracy of data against source documents. The required data will be captured in a validated clinical data management system that is compliant with the FDA 21 Code of Federal Regulations (CFR) Part 11 Guidance. The clinical trial database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be trained and given restricted access, based on their role(s) in the study, through a password-protected environment.

Data entered in the system will be reviewed manually for validity and completeness against the source documents by a clinical monitor from the Sponsor or its designee. If necessary, the study site will be contacted for corrections or clarifications; all missing data will be accounted for.

Serious adverse event information captured in the clinical trial database will be reconciled with the information captured in the Pharmacovigilance and Risk Management database.

10 STATISTICAL ANALYSES

10.1 General Methodology

Details regarding the statistical methods and definitions will be provided in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to database lock. All statistical analyses will be performed by the Biometrics department at Shire. Statistical analyses will be performed using Version 9.1 or higher of SAS® (SAS Institute, Cary, NC 27513).

Continuous variables will be summarized using descriptive statistics including the number of observations, 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 2 possible treatment assignments in the antecedent study, ROPP-2008-01, Section D (rhIGF-1/rhIGFBP-3 or standard neonatal care).

For analysis purposes, baseline is defined as the first assessment either in the antecedent study (ROPP-2008-01) or in this study (SHP-607-201). As necessary, relevant data from Study ROPP-2008-01 may be extracted and summarized with the data from this study (SHP-607-201). For consented patients, additional biomarker analysis may be performed on prior collected blood samples from Study ROPP-2008-01.

10.2 Determination of Sample Size

No formal sample size calculation was performed for this study because this is a follow-up study to Section D of Study ROPP-2008-01. Any subjects enrolled in Study ROPP-2008-01 are eligible to enroll in this study. There are up to 120 subjects who will be eligible to enroll in this long-term developmental outcome study.

10.3 Method of Assigning Study Subjects to Treatment Groups

Not applicable.

10.4 Population Description

10.4.1 Analysis Populations

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

Safety Population- the Safety Population will consist of the subjects in the Enrolled Population who have safety follow-up data in this long-term outcome study.

10.4.2 Subject Disposition

Subjects who complete the study and subjects who prematurely discontinue from the study will be summarized by treatment group using descriptive statistics. In addition, for subjects who prematurely discontinue from the study, the reasons for discontinuation will be summarized by treatment group.

10.4.3 Protocol Violations and Deviations

Protocol violations and deviations will be listed. Details of the criteria for deviations and violations will be provided in the SAP.

10.4.4 Demographics and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group for the Enrolled Population.

Demographics and baseline characteristics will be examined to assess the comparability of the treatment groups. Continuous variables such as age (including corrected age), weight, and length/height will be summarized using number of observations, mean, standard deviation, median, minimum and maximum values. Categorical variables, like gender and race, will be summarized using number of observations and percentages.

Medical history, including maternal and perinatal history, (as obtained from the antecedent study, ROPP-2008-01) will be summarized by treatment group using the number of observations and percentages of subjects reporting each category.

10.5 Efficacy Analysis

All efficacy analyses will be performed using the Enrolled Population.

10.5.1 Primary Efficacy Analysis

The primary efficacy endpoints consist of the following:

- Visual Acuity: Visual acuity will be categorized as the following:
    - normal (measurable acuity ≥20/40),
    - below normal (20/200≤ measurable acuity <20/40),
    - poor (measurable acuity ≤20/200)
    - blind/low vision (only the ability to detect the 2.2 cm wide stripes on the low-vision Teller acuity card and at any location in the visual field).

  The number and proportion of patients within each category listed above will be summarized by treatment group and visit. In addition, acuity results in the normal and below normal categories will be classified as favorable outcomes, and acuity results in the poor and blind/low-vision categories will be classified as unfavorable outcomes. Tabular summaries by treatment group and visit will include the frequency and the percentage for each visual acuity category.

In addition, shift tables of favorable outcomes from baseline (first assessment during this study) to each of the subsequent assessments, including the last assessment, will be presented by treatment group.

- Ocular Alignment and Oculomotor Exam (Motility): Findings from the ocular motility assessment will be either presence or absence of strabismus (esotropia, exotropia, hypertropia, or hypotropia). Tabular summaries by treatment group and visit will include the frequency and the percentage in each category. In addition, shift tables from baseline (first assessment during this study) to the last assessment will be provided by treatment group.
- Nystagmus: Presence or absence of nystagmus will be summarized by treatment group and visit
- Refraction with Cycloplegia: Findings from the refraction with cycloplegia will be summarized by treatment group and visit
- Stereoacuity: Presence or absence of stereopsis will be summarized by treatment group and visit

10.5.2 Secondary Efficacy Analysis

- Growth Parameters (body weight, body length [and height], and head circumference): A standard Z-score, utilizing WHO child growth standards, will be calculated for each assessment by adjusting age- and sex- matched means and standard deviations (norm). The descriptive statistics of the Z-score for each of these parameters will be summarized at each assessment and the corresponding change from baseline. When appropriate, a 95% CI for the corresponding mean change within each group and the difference in the mean change between the 2 treatment groups and the corresponding 95% CI will be presented as appropriate. If the parametric assumption for the distribution of the above endpoints cannot be justified, a non-parametric approach will be utilized to estimate the treatment difference (ie, median difference or Hodges-Lehmann estimator and the corresponding confidence intervals)
- BSID-III and WPPSI: The raw score for each domain within each questionnaire will be summarized by treatment group and visit using descriptive statistics.
- ADHD-RS: ADHD-RS total score and subscales (Hyperactivity/Impulsivity and Inattentiveness) will be summarized by treatment group and visit using descriptive statistics.
- SCQ: The SCQ subscales (communication and social) will be summarized by treatment group and visit using descriptive statistics
- VABS-II: The raw score for each domain of the scale will be summarized by treatment group and visit using descriptive statistics.
- CBCL: The raw score and change from baseline for each domain of the scale will be summarized by treatment group and visit using descriptive statistics.

- Pulmonary morbidity assessment: The binary response of each question will be by treatment group and visit using descriptive statistics.
- Survival: For subjects who have an event (ie, death), the event time will be calculated as the length of time from the subject's date of birth to death during the study due to any cause. Subjects who do not have an event (ie, death) during the study will be censored at the end of the study. The survival endpoint will be analyzed by treatment group using Kaplan-Meier methods.

10.5.3 Subset Analyses

Subgroup analyses may be explored based on factors that may have influence on the efficacy or safety endpoints. Subgroup analyses will be specified in the SAP.

10.5.4 Exploratory Analyses

[redacted]

10.6 Health Economics and Outcomes Research Analyses

For PedsQL, descriptive statistics will be provided for summary scores by treatment group 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 and at each time point.

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.

10.7 Analysis of Safety

Safety summaries will be based on all assessments post-baseline. The safety data will be assessed by AE monitoring, change in cardiac size, and kidney and spleen size over time.

Adverse events will be summarized by system organ class and preferred term for each treatment group and overall, the number and percentage of subjects having any AE, having an AE in each body system and having each individual AE. In addition, those events which resulted in death, or were otherwise classified as serious will be presented in a separate listing. In addition, the summary of AEs will be presented by severity and relationship to trial medication.

The change in cardiac size, and size of kidney and spleen will be assessed at the 6-month CA visit via echocardiogram and abdominal ultrasound, respectively. These data will be analyzed as a binary response (ie, normal/abnormal) and summarized using frequency count. The number and proportion of patients with each category (ie, normal/abnormal) for each of these safety endpoints will be summarized by treatment group.

In addition, the 2-sided 95% CI for the proportion of patients with a normal status for each of the endpoints will be estimated by treatment group.

Physical examinations findings will be summarized descriptively.

10.8 Statistical/Analytical Issues

10.8.1 Adjustment for Covariates

If any baseline data are imbalanced and are considered to be clinically relevant, between-group comparisons for efficacy outcomes will be adjusted for covariates and detailed in the SAP.

10.8.2 Handling of Dropouts or Missing Data

Handling of missing data rules will be described in the SAP.

10.8.3 Interim Analyses and Data Monitoring

An interim analysis will be performed after all data from all enrolled subjects in this study have either completed 2-year follow-up (24-month visit) assessments or have prematurely withdrawn from the study (before completing 2 years of follow-up) has been entered into the database, queried and discrepancies resolved. A full 2-year study report based on these data, including efficacy and safety endpoint analyses, will be completed.

Additionally, descriptive analyses of the data at other time points before study completion may be performed for safety monitoring, regulatory reporting or general planning purposes.

10.8.4 Multiple Comparisons/Multiplicity

Not applicable.

10.8.5 Sensitivity Analyses

Sensitivity analyses for the efficacy outcomes will be detailed in the SAP, as necessary.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

Before initiation of the study, the Investigators must provide the Sponsor with a completed Form FDA 1572 and Investigator Agreement. Curriculum vitae must be provided for the Investigators and sub-investigators listed on Form FDA 1572 or Investigator Agreement.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, and their study related duties and functions. The Investigator must maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study related duties.

11.2 Institutional Review Board or Independent Ethics Committee Approval

Before initiation of the study, the Investigator must provide the Sponsor with a copy of the written IRB/IEC/REB approval of the protocol and the informed consent form. This approval must refer to the informed consent form and to the study title, study number, and version and date of issue of the study protocol, as given by the Sponsor on the cover page of the protocol.

Status reports must be submitted to the IRB/IEC/REB at least once per year. The IRB/IEC/REB must be notified of completion of the study. Within 3 months of study completion or termination, a final report must be provided to the IRB/IECREB. A copy of these reports will be sent to the study clinical monitor. The Investigators must maintain an accurate and complete record of all submissions made to the IRB/IEC, including a list of all reports and documents submitted. AEs which are reported to the US (FDA or other Regulatory agencies (Safety Reports) must be submitted promptly to the IRB/IEC/REB.

11.3 Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigators abide by good clinical practice (GCP) as described in the 21 CFR Parts 50, 56, and 312 and the International Conference on Harmonization (ICH) GCP Guidelines Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

11.4 Subject Information and Consent

Before enrolling in the clinical study, the subject or the subject's parent(s) or legally authorized representative(s) must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her.

An informed consent form (assent form if applicable) that includes information about the study will be prepared and given to the subject or the subject's parent(s) or legally authorized representative(s). This document will contain all FDA and ICH-required elements. The informed consent (or assent) form must be in a language understandable to the subject or the subject's

parent(s) or legally authorized representative(s) and must specify who informed the subject, the subject's parent(s), or the subject's legally authorized representative(s).

After reading the informed consent document, the subject or the subject's parent(s) or legally authorized representative(s) must give consent in writing. Consent must be confirmed at the time of consent by the personally dated signature of the subject, the subject's parent(s) or the subject's legally authorized representative(s) and by the personally dated signature of the person conducting the informed consent discussions.

If the subject or the subject's parent(s) or legally authorized representative(s) is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the subject or by a local legally recognized alternative (eg, the subject's thumbprint or mark) or by the personally dated signature of the subject's parent(s) or the subject's legally authorized representative. The witness and the person conducting the informed consent discussions must also sign and personally date the informed consent document. It should also be recorded and dated in the source document that consent was given.

A copy of the signed and dated consent document(s) must be given to the subject or the subject's parent(s) or legal representative(s). The original signed and dated consent document will be retained by the Investigator.

The Investigator will not undertake any measures specifically required solely for the clinical study until valid consent has been obtained.

A model of the informed consent form to be used in this study will be provided to the sites separately from this protocol.

11.5 Subject Confidentiality

Subject names will not be supplied to the Sponsor. Only the subject number - will be recorded in the eCRF, and if the subject name appears on any other document, it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be told that representatives of the Sponsor, a designated CRO, the IRB/IEC/REB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. The Investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

11.6 Study Monitoring

Monitoring procedures that comply with current Good Clinical Practice (GCP) guidelines will be followed. Review of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by the Sponsor or its designee. Monitoring will be performed by a representative of the Sponsor (Clinical Study Monitor) who will review the eCRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and communications (letter, telephone, and facsimile).

11.7 Case Report Forms and Study Records

11.7.1 Case Report Forms

Electronic case report forms (eCRFs) are provided for each subject. All forms must be filled out by authorized study personnel. All corrections to the original eCRF entry must indicate the reason for change. The Investigator is required to sign the eCRF after all data have been captured for each subject. If corrections are made after review and signature by the Investigator, he or she must be made aware of the changes, and his or her awareness documented by resigning the eCRF.

11.7.2 Critical Documents

Before the Sponsor initiates the trial (ie, obtains informed consent from the first subject), it is the responsibility of the Investigator to ensure that the following documents are available to Sponsor or their designee:

- Completed FDA Form 1572 (Statement of Investigator), signed, dated, and accurate
- Curricula vitae of Investigator and sub-investigator(s) (current, dated and signed within 12 months of study initiation)
- Copy of Investigator and sub-investigator(s) current medical license (indicating license number and expiration date)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/IEC/REB clearly identifying the documents reviewed by name, number and date of approval or re approval: protocol, any amendments, Subject Information/Informed Consent Form, and any other written information to be provided regarding subject recruitment procedures
- Copy of IRB/IEC/REB approved Subject Information/Informed Consent Form/any other written information/advertisement (with IRB approval stamp and date of approval)
- Current list of IRB/IEC/REB Committee members/constitution (dated within 12 months prior to study initiation)
- Financial Disclosure Form signed by Investigator and sub-investigator(s)
- Current laboratory reference ranges (if applicable)
- Certification/QA scheme/other documentation (if applicable)

Regulatory approval and notification as required must also be available; these are the responsibility of Shire.

11.8 Data Monitoring Committee

Given that any long-term safety signal observed in this study could impact the safety profile of rhIGF-1/rhIGFBP-3 as administered in premature neonates being enrolled in the antecedent study (ROPP-2008-01, Section D), the Data Monitoring Committee (DMC) for Study ROPP-2008-01 will review safety data from this long-term outcome study.

11.9 Protocol Violations/Deviations

The Investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the IRB/IEC/REB and the appropriate regulatory authorities, where applicable, have given approval/favorable opinion. Modifications to the protocol will not be made without agreement of the Sponsor. Changes to the protocol will require written IRB/IEC/REB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB/IEC/REB may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC/REB. The Sponsor will submit all protocol modifications to the regulatory authorities, where applicable, in accordance with the governing regulations.

A record of subjects screened, but not entered into the study, is also to be maintained. No protocol exemption will be granted for this study.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Sponsor or its designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will need to be reviewed by the medical monitor and may also be required to be submitted to the IRB/IEC/REB.

Protocol modifications will only be initiated by the Sponsor and must be approved by the IRB/IEC/REB and submitted to the FDA or other applicable international regulatory authority before initiation, if applicable.

11.10 Premature Closure of the Study

If the Sponsor, Investigator, or regulatory authorities discover conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable subject risk, the study may be terminated after appropriate consultation between the Sponsor and the Investigator(s). In addition, a decision on the part of the Sponsor to suspend or discontinue development of the investigational product may be made at any time. Conditions that may warrant termination of the study or site include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study
- Failure of the Investigator to comply with pertinent global regulations
- Submission of knowingly false information from the study site to the Sponsor or other pertinent regulatory authorities
- Insufficient adherence by the Investigator to protocol requirements

11.11 Access to Source Documentation

Regulatory authorities, the IRB/IEC/REB, or the Sponsor may request access to all source documents, eCRFs, and other study documentation for onsite audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Monitoring and auditing procedures that comply with current GCP guidelines will be followed. On-site review of the eCRFs for completeness and clarity, crosschecking with source documents, and clarification of administrative matters may be performed.

11.12 Data Generation and Analysis

The clinical database will be developed and maintained by a contract research organization or an electronic data capture technology provider as designated by the Sponsor. The Sponsor or its designee will be responsible for performing study data management activities.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medication will be coded using WHO-Drug Dictionary (WHO-DD). Central reads will be employed as described in the study manual to aid in consistent measurement of abdominal ultrasound and echocardiogram parameters.

11.13 Retention of Data

Essential documents should be retained until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The Sponsor will notify the Investigator if these documents must be retained for a longer period of time. It is the responsibility of the Sponsor to inform the Investigator or institution as to when these documents no longer need to be retained.

11.14 Financial Disclosure

The Investigator should disclose any financial interests in the Sponsor as described in 21 CFR Part 54 prior to beginning this study. The appropriate form will be provided to the Investigator by the Sponsor, which will be signed and dated by the Investigator, prior to the start of the study.

11.15 Publication and Disclosure Policy

All information concerning the study material, such as patent applications, manufacturing processes, basic scientific data, and formulation information supplied by the Sponsor and not previously published are considered confidential and will remain the sole property of the Sponsor. The Investigator agrees to use this information only in accomplishing this study and will not use it for other purposes.

It is understood by the Investigator that the information developed in the clinical study may be disclosed as required to the authorized regulatory authorities and governmental agencies. In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the Sponsor with complete test results and all data developed in the study in a timely manner.

The Investigator and any other clinical personnel associated with this study will not publish the results of the study, in whole or in part, at any time, unless they have consulted with the Sponsor, provided the Sponsor a copy of the draft document intended for publication, and obtained the Sponsor's written consent for such publication. All information obtained during the conduct of this study will be regarded as confidential.

12 LIST OF REFERENCES

1. Maida JM, Mathers K, Alley CL. Pediatric ophthalmology in the developing world. Current opinion in ophthalmology 2008;19:403-8.

2. O'Connor AR, Stephenson TJ, Johnson A, et al. Visual function in low birthweight children. The British journal of ophthalmology 2004;88:1149-53.

3. Keith CG, Kitchen WH. Ocular morbidity in infants of very low birth weight. The British journal of ophthalmology 1983;67:302-5.

4. Laws D, Shaw DE, Robinson J, Jones HS, Ng YK, Fielder AR. Retinopathy of prematurity: a prospective study. Review at six months. Eye (London, England) 1992;6:477-83.

5. O'Connor AR, Stephenson T, Johnson A, et al. Long-term ophthalmic outcome of low birth weight children with and without retinopathy of prematurity. Pediatrics 2002;109:12-8.

6. Schaffer DB, Quinn GE, Johnson L. Sequelae of arrested mild retinopathy of prematurity. Archives of ophthalmology 1984;102:373-6.

7. Cats BP, Tan KE. Prematures with and without regressed retinopathy of prematurity: comparison of long-term (6-10 years) ophthalmological morbidity. Journal of pediatric ophthalmology and strabismus 1989;26:271-5.

8. Chard T. Insulin-like growth factors and their binding proteins in normal and abnormal human fetal growth. Growth Regul 1994;4:91-100.

9. Hansen-Pupp I, Lofqvist C, Polberger S, et al. Influence of insulin-like growth factor I and nutrition during phases of postnatal growth in very preterm infants. Pediatric research 2011;69:448-53.

10. Ohkawa N, Shoji H, Kitamura T, et al. IGF-I, leptin and active ghrelin levels in very low birth weight infants during the first 8 weeks of life. Acta paediatrica (Oslo, Norway : 1992) 2010;99:37-41.

11. Lofqvist C, Hellgren G, Niklasson A, Engstrom E, Ley D, Hansen-Pupp I. Low postnatal serum IGF-I levels are associated with bronchopulmonary dysplasia (BPD). Acta paediatrica (Oslo, Norway : 1992) 2012;101:1211-6.

12. Ishii DN, Glazner GW, Whalen LR. Regulation of peripheral nerve regeneration by insulin-like growth factors. Annals of the New York Academy of Sciences 1993;692:172-82.

13. Lewis ME, Neff NT, Contreras PC, et al. Insulin-like growth factor-I: potential for treatment of motor neuronal disorders. Experimental neurology 1993;124:73-88.

14. Pediatric Ophthalmology/Strabismus Preferred Practice Pattern Development Process and Participants. Pediatric Eye Evaluations: American Academy of Ophthalmology Pediatric Ophthalmology/Strabismus Preferred Practice Pattern Panel; 2012.

[redacted]

19. Wechsler D. Wechsler preschool and primary scale of intelligence 4th ed. Bloomington, MN: Pearson; 2012.

20. Wechsler D. Technical and Interpretive Manual Supplement: Special Group Validity Studies With Other Measures2012.

21. Achenbach T, Rescorla L. Manual for the ASEBA preschool forms and profiles. Burlington, VT: University of Vermont; 2000.

22. Vinall J, Miller SP, Synnes AR, Grunau RE. Parent behaviors moderate the relationship between neonatal pain and internalizing behaviors at 18 months corrected age in children born very prematurely. Pain 2013;154:1831-9.

23. Scott MN, Taylor HG, Fristad MA, et al. Behavior disorders in extremely preterm/extremely low birth weight children in kindergarten. Journal of developmental and behavioral pediatrics : JDBP 2012;33:202-13.

24. Wu YC, Leng CH, Hsieh WS, et al. A randomized controlled trial of clinic-based and home-based interventions in comparison with usual care for preterm infants: Effects and mediators. Res Dev Disabil 2014;35:2384-93.

25. Ebesutani C, Bernstein A, Nakamura BJ, Chorpita BF, Higa-McMillan CK, Weisz JR. Concurrent Validity of the Child Behavior Checklist DSM-Oriented Scales: Correspondence with DSM Diagnoses and Comparison to Syndrome Scales. J Psychopathol Behav Assess 2010;32:373-84.

26. DuPaul G, Power T, Anastopoulos A, Reed R. The ADHD rating scale IV: checklists, norms and clinical interpretation. New York: Guilford Press; 1998.

27. Rutter M, Bailey A, Lord C. Manual for the Social Communication Questionnaire2003.

28. Chandler S, Charman T, Baird G, et al. Validation of the social communication questionnaire in a population cohort of children with autism spectrum disorders. Journal of the American Academy of Child and Adolescent Psychiatry 2007;46:1324-32.

29. Gosselin J, Amiel-Tison C. Neurological Assessment from Birth to 6 Years. 2nd ed. Montreal: CHU Sainte-Justine; 2011.

30. Matza LS, Swensen AR, Flood EM, Secnik K, Leidy NK. Assessment of health-related quality of life in children: a review of conceptual, methodological, and regulatory issues. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2004;7:79-92.

31. Varni JW, Burwinkle TM, Lane MM. Health-related quality of life measurement in pediatric clinical practice: an appraisal and precept for future research and application. Health and quality of life outcomes 2005;3:34.

32. Constitution of the World Health Organization: basic document. Geneva, Switzerland: World Health Organization; 1948.

33. Varni JW, Limbers CA. The pediatric quality of life inventory: measuring pediatric health-related quality of life from the perspective of children and their parents. Pediatric clinics of North America 2009;56:843-63.

34. Varni JW, Limbers CA, Neighbors K, et al. The PedsQL Infant Scales: feasibility, internal consistency reliability, and validity in healthy and ill infants. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2011;20:45-55.

35. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Medical care 2001;39:800-12.

36. Saigal S, Rosenbaum P, Stoskopf B, et al. Development, reliability and validity of a new measure of overall health for pre-school children. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2005;14:243-57.

37. Rosenbaum DM, Korngold E, Teele RL. Sonographic assessment of renal length in normal children. AJR Am J Roentgenol 1984;142:467-9.

38. Rosenberg HK, Markowitz RI, Kolberg H, Park C, Hubbard A, Bellah RD. Normal splenic size in infants and children: sonographic measurements. AJR Am J Roentgenol 1991;157:119-21.

39. Stevens TP, Finer NN, Carlo WA, et al. Respiratory Outcomes of the Surfactant Positive Pressure and Oximetry Randomized Trial (SUPPORT). The Journal of pediatrics 2014;165:240-9.e4.

40. Zivanovic S, Peacock J, Alcazar-Paris M, et al. Late outcomes of a randomized trial of high-frequency oscillation in neonates. The New England journal of medicine 2014;370:1121-30.

13 APPENDICES

Appendix 1 Study Schedule of Events

Procedures	Initial Study Visit[e]	Months (CA)						Years (CA)					
	40 weeks (CA)/term equivalent	3[f] ± 2 wks	6 ± 1 mth	12 ± 3 mths	20 -1 mth[g]	24 ± 3 mth	30 ± 3 mth	3[f] ± 3 mths	3.5 ± 3 mth	4[f] ± 3 mths	4.5 ± 3 mth	4.75 -1 mth[g]	5 + 6 mths
Informed Consent	•												
Eligibility Criteria	•												
Demographics	•												
Visual acuity[a]			•	•	•	•						•	•
Corrective lens determination[h]				•	•[g]							•[g]	
Ocular alignment and motility				•		•							•
Refraction with cycloplegia[h]			•										
Stereoacuity													•
Length			•	•		•							
Height													•
Weight			•	•		•							•
Head Circumference			•	•		•							
BSID-III				•		•							
WPPSI													•
CBCL						•							•
VABS-II			•	•		•							•
ADHD-RS													•
SCQ													•
Physical Examination including tonsil examination			•	•		•							•
Blood Pressure, Heart Rate, and Respiratory Rate													•
Cerebral Palsy Assessment						•							
Hearing Assessment History[b]			•										•
Pulmonary Morbidity Assessment 1			•	•									
Pulmonary Morbidity Assessment 2 (clinical site visit)						•							•
Pulmonary Morbidity Assessment (phone interview)							•	•	•	•	•		

Procedures	Initial Study Visit[e]	Months (CA)						Years (CA)					
	40 weeks (CA)/term equivalent	3[f] ± 2 wks	6 ± 1 mth	12 ± 3 mths	20 -1 mth[g]	24 ± 3 mth	30 ± 3 mth	3[f] ± 3 mths	3.5 ± 3 mth	4[f] ± 3 mths	4.5 ± 3 mth	4.75 -1 mth[g]	5 + 6 mths
Survival assessment		•	•	•		•		•		•			•
[redacted]													[redacted]
Cerebral MRI													•
HRQoL[c]		•	•[i]	•[i]		•[i]		•		•			•[i]
HCRU		•	•[i]	•[i]		•[i]		•		•			•[i]
HSCS-PS						•[i]		•		•			•[i]
Abdominal Ultrasound			•										
Echocardiogram			•										
Assessment of Participation in Other Clinical Studies		•	•	•		•		•		•			•
Medications		•	•	•		•		•		•			•
Adverse events[d]	•[j]	•	•	•		•		•		•			•

Abbreviations: ADHD-RS = Attention-Deficit/Hyperactivity Disorder Rating Scale; BSID-III = Bayley Scales of Infant and Toddler Development-Third Edition, CBCL = Child Behavior Checklist; CA = corrected age; HCRU = health care resource use; HRQoL = health-related quality of life; HSCS-PS = Health Status Classification System; mth(s) = months; [redacted]; PedsQL = Pediatric Quality of Life Inventory; SCQ = Social Communication Questionnaire; VABS-II = Vineland Adaptive Behavior Scales, Second Edition; wks = weeks; WPPSI = Wechsler Preschool and Primary Scale of Intelligence

[a] The tools used to assess visual acuity will change as the subject ages during their participation in the study. The tools that will be used in this study and are summarized by applicable study visit in Table 13-1.

[b] Historical hearing test data may be recorded at any time during the study prior to the 6-month visit.

[c] HRQoL will be assessed via the validated PedsQL™ scales appropriate for the child's age of development as specified in the Study Operations Manual

[d] Adverse event collection will include an assessment of the specified targeted medical events

[e] The Initial Visit may be performed prior to 40 weeks CA for any subject who discontinued from Study ROPP-2008-01 and, for all subjects, any time after 40 weeks CA, up to the study visit to occur at 3 months CA.

[f] Visits at 3 months, 3 years, and 4 years CA will be conducted by telephone.

[g] The 20-month visit and the 4.75-year (4 years, 9 months) visit must occur at least 1 month prior to the 24-month and 5-year visits, respectively. Any prescribed corrective lenses must be worn for at least 1 month prior to the 24-month and 5-year assessments.

[h] Refraction with cycloplegia will be performed as part of the corrective lens determination procedure.

[i] The HRQoL, HCRU, and HSCS-PS assessments for the 6-month, 12-month, 24-month and 5-year visits may be performed through clinical site staff if there are time constraints during the on-site visit. At the 3-month, 3-year, and 4-year visits, these assessments will be performed through clinical site staff and may be performed at any time within the visit window.

Procedures	Initial Study Visit[e]	Months (CA)						Years (CA)					
	40 weeks (CA)/term equivalent	3[f] ± 2 wks	6 ± 1 mth	12 ± 3 mths	20 -1 mth[g]	24 ± 3 mth	30 ± 3 mth	3[f] ± 3 mths	3.5 ± 3 mth	4[f] ± 3 mths	4.5 ± 3 mth	4.75 -1 mth[g]	5 + 6 mths

[j] The following, collected as part of the ROPP-2008-01 study, will be used as part of this study (SHP-607-201): any ongoing targeted medical events regardless of causality and any ongoing study drug-related AEs, including SAEs.

Table 13-1 Summary of Visual Acuity Assessments

Visual Acuity Assessment Tool	Description	Unit of Measure	Applicable Age/Study Visit (CA)
Teller acuity cards	Resolution acuity – discrimination of a grating optotype from a background with the same mean luminance	cycles per degree	6 months 12 months
LEA Symbols Test	Recognition acuity - tests recognition of 4 optotypes	Snellen fraction (eg, 20/20)	24 months[a]
LEA Symbols (ETDRS-style) chart	Distance visual acuity test	Snellen fraction (eg, 20/20)	5 years[a]

Abbreviations: CA = corrected age; ETDRS = Early Treatment of Diabetic Retinopathy Study

[a] At ages 24 months and 5 years CA an attempt should be made to assess visual acuity by the LEA Symbols Test and LEA Symbols Chart, respectively. If during this attempt, the examiner determines that it will not be possible to perform an accurate assessment with the relevant LEA tool, visual acuity should be assessed with the Teller acuity cards.

Appendix 2 Pulmonary Morbidity Assessment (Clinical Site Visits at 6 and 12 Months CA)

Subject Name _____ **Subject Number** _____

The SHP-607-201 Protocol refers to a "Pulmonary Morbidity Questionnaire" however; there is no formal questionnaire for the pulmonary morbidity assessment. These questions are built into the pulmonary morbidity eCRF page, which will be completed after obtaining this information at the 6mo, 12movisits. The data will be captured in EDC, not through MedAvante and will not scored in any way.

To assist with capturing these data, Pulmonary Morbidity Assessment Site Source Document has been developed for your use.

1. Was the Pulmonary Morbidity Assessment done? ☐ YES ☐ NO

   If NO, please explain why not: _____

2. Date of Examination: Month _____ Day _____ Year _____

FAMILY HISTORY

3. Does anyone living in the same home with subject smoke? ☐ YES ☐ NO
4. Have any immediate family members (parents or siblings) of the subject been diagnosed with asthma or wheezing? ☐ YES ☐ NO
5. Have the parents/family of the subject had to change their plans because the subject's breathing problems or pulmonary health in the last six months? ☐ YES ☐ NO

PATIENT DATA

6. Has the subject had asthma, wheezing, or bronchopulmonary dysplasia (BPD) exacerbation or flare-up in the last six months? ☐ YES ☐ NO

   If YES, how many episodes in the last six months? _____
7. Has the subject had bronchiolitis, bronchitis, or pneumonia diagnosed in the last six months? ☐ YES ☐ NO

   If YES, how many episodes in the last six months? _____
8. Has the subject had to use oxygen at home during the last six months? ☐ YES ☐ NO

   If YES, how many days did the subject use oxygen in the last month? _____
9. Has the subject had to visit an emergency room or urgent care for respiratory or pulmonary problems in the last six months? ☐ YES ☐ NO

   If YES, how many times in the last six months? _____
10. Has the subject had to stay in a hospital overnight for respiratory or pulmonary problems in the last six months? ☐ YES ☐ NO

    If yes, how many overnights has the subject spent in the hospital? _____

Appendix 3 Pulmonary Morbidity Assessment 2 (Clinical Site Visits at 24 Months and 5 Years CA)

Subject Name _____ **Subject Number** _____

The SHP-607-201 Protocol refers to a "Pulmonary Morbidity Assessment – In Person Interview". These questions are built into the pulmonary morbidity assessment in person interview eCRF page. It will be completed at M24 and Year 5. The questions will be administrated to the child caregiver during study visit by site personnel. The data will be captured in EDC on eCRF pages, no scoring is required.

1. Was the Pulmonary Morbidity Assessment done? ☐ YES ☐ NO

   If NO, please explain why not: _____

2. Date of Examination: Month _____ Day _____ Year _____
3. This questionnaire was administered to: _____
4. Was this questionnaire administered to the same responder as last time? ☐ YES ☐ NO
5. Has the child been with this caregiver during the six months ☐ YES ☐ NO

HOME ENVIRONMENT

6. Does anyone living in the same home with subject smoke? ☐ YES ☐ NO
7. If YES, which of the following three statements best describes the situation regarding smoking in the child's home?

   ☐ Smoking is allowed in any common room of the home

   ☐ Smoking is limited to part of the house where the child rarely goes

   ☐ There is no smoking inside

   Are there any exceptions to this situation? ☐ YES ☐ NO

   If YES, under what circumstances are the exceptions allowed? _____

8. Which of the following five statement best describes the situation regarding smoking in the car the child usually rides in? (check only one below)

   ☐ Do not have a car

   ☐ Smoking is usually or always allowed

   ☐ Smoking is sometimes allowed

   ☐ Smoking occurs in the car only when the child is not inside

   ☐ There is no smoking inside the car

9. How often has the baby's mother or primary caretaker smoked since the child was born

☐ Never ☐ Occasionally ☐ Daily ☐ Don't know

10. Altogether, how many people who live in the child's home smoke, even if they smoke outside? _____

11. Approximately how many hours per week does the child spend at a babysitters home or daycare _____ hours

12. Is smoking permitted at the child's daycare facility ☐ YES ☐ NO

How frequent is the smoke exposure at the babysitter or daycare?

☐ Never ☐ Occasionally ☐ Daily ☐ Don't know

Approximately how many children beside your child are in the daycare? _____

13. How many children under 12 live in the house? (including subject) _____

14. Is there a pet inside the home ☐ YES ☐ NO

If YES, how many dogs? _____

How many cats? _____

How many other pets? _____

Specify other pets _____

PATIENT MEDICAL HISTORY DATA

15. Has the child had any medical office visit during the past six month ☐ YES ☐ NO

If YES, how many visit in the last six months? _____

If YES, how many of these visits were because of wheezing or breathing problems? _____

16. For what other reason did the child have a medical visit?

_____

17. Has the child visited the urgent care during the past six months? ☐ YES ☐ NO

If YES, is this urgent care part of your doctor's office? ☐ YES ☐ NO

If YES, how many visit in the last six months? _____

If YES, how many of these visits were because of wheezing or breathing problems? _____

18. Has the child visited the emergency room during the past six months? ☐ YES ☐ NO

If YES, how many visit in the last six months? _____

If YES, how many of these visits were because of wheezing or breathing problems? _____

19. Has the child stayed in the hospital during the past six months? ☐ YES ☐ NO

    If YES, how many visit in the last six months? _____

    If YES, how many of these visits were because of wheezing or breathing problems? _____

    If YES, what was the diagnosis? _____

20. How many colds has the child had in the last six months

21. Has the child's breathing sounded wheezy or whistling in the last six months? ☐ YES ☐ NO

    If YES, has this occurred with colds? ☐ YES ☐ NO

22. During what month did your child's chest first sound wheezy or whistling?

    ☐ January ☐ February ☐ March ☐ April ☐ May ☐ June
    ☐ July ☐ August ☐ September ☐ October ☐ November ☐ December
    ☐ Not Sure ☐ Don't Know Year: _____

23. On average how often has your child's chest sounded wheezy or whistling during the day time? (check only one below)

    ☐ Never ☐ Twice a week or less ☐ More than two times a week but not every day
    ☐ Every day but not all the time ☐ Everyday all the time ☐ Don't know

    During night time? (check only one below)

    ☐ Never ☐ once every two weeks or less ☐ Once a week
    ☐ Two or more times a week ☐ More than three nights a week/ Frequently ☐ Don't know

    During the worst two week period, how often has your child's chest sounded wheezy or whistling during the daytime? (check only one below)

    ☐ Never ☐ Twice a week or less ☐ More than two times a week but not every day
    ☐ Every day but not all the time ☐ Everyday all the time ☐ Don't know

24. Has your child been diagnosed with wheezing by a doctor? ☐ YES ☐ NO

25. Has your child had a cough for more than three days when he/she did not have a cold? ☐ YES ☐ NO

    What time of the day has this cough usually occurred?

    ☐ In the morning shortly after rising ☐ Later in the day
    ☐ During the night ☐ No relation to time of day

26. Has your child coughed on most days for as much as 2 to 3 months? ☐ YES ☐ NO

During what month did your child first develop the cough? (Check only one below)

☐ January ☐ February ☐ March ☐ April ☐ May ☐ June
☐ July ☐ August ☐ September ☐ October ☐ November ☐ December
☐ Not Sure ☐ Don't Know Year: _____

27. Has your child's chest ever sounded wheezy or whistling with episodes of coughing? ☐ YES ☐ NO

28. On average how often has your child had coughing during the daytime in the past six months? (check only one below)

☐ Don't know ☐ Twice a week or less ☐ More than two times a week but not every day
☐ Never ☐ Everyday all the time ☐ Every day but not all the time

During the worst two week period, how often has your child's had coughing during the daytime in the past six month? (check only one below)

☐ Don't know ☐ Twice a week or less ☐ More than two times a week but not every day
☐ Never ☐ Everyday all the time ☐ Every day but not all the time

29. Has your child ever had breathing problems that has caused you to change your plans and stay home with your child? ☐ YES ☐ NO

On average, how many days per month did you have to change your daytime or evening plans becauase of your child's breathing problems? (check only one below)

☐ none, we never had to change plans ☐ 7 or more days ☐ 3-6 days
☐ More than none but less than 3 days ☐ Don't know

During the worst two week period, how many days did you have to change your daytime or evening plans because of your child's breathing problems? (check only one below)

☐ none, we never had to change plans ☐ 7 or more days ☐ 3-6 days
☐ More than none but less than 3 days ☐ Don't know

30. Has the child had any of the following diagnosed by a doctor in the past six month? (check all that apply)

☐ Asthmas ☐ Reactive airway disease ☐ BPD flare-up ☐ Bronchiolitis
☐ Bronchitis ☐ Pneumonia ☐ Croup

31. Does the child have other medical problems? ☐ YES ☐ NO

If YES, list other medical problems _____

32. Please mark any medications your child is taking

☐ Brochiodilators ☐ Inhaled Steriods ☐ Oral Steriods ☐ Antibiotics
☐ Diuretics ☐ Synagis ☐ Other, specify _____

33. Has the child ever had shots to prevent Respiratory Synsytial Virus (palivizxumab, or RSV shot)? ☐ YES ☐ NO
34. Has the child had a flu shot? ☐ YES ☐ NO
35. Has the child had to use oxygen therapy at home during the last six months? ☐ YES ☐ NO

    If YES, how many days did the child use oxygen in the last month? _____

    Is the oxygen administered by nasal canula? ☐ YES ☐ NO

    If YES, what is the FiOx _____ mmHg

    Liter per minutes (LPM)?: (check only one below)

    ☐ < 0.25 ☐ 0.25 ☐ 0.5 ☐ 0.75 ☐ 1 ☐ 1.25
    ☐ 2 ☐ 2.25 ☐ 2.5 ☐ 2.75 ☐ 3 ☐ >3

36. Is your baby in an oxygen hood or tent? ☐ YES ☐ NO
37. Is your baby on a ventilator or CPAP? ☐ YES ☐ NO

    If YES, what are the ventilator settings? _____

38. Has the child taken any medication during the past six months? ☐ YES ☐ NO

☐ Albuterol ☐ Proventil ☐ Serevent ☐ Ventolin ☐ Volmax ☐ Xopenex
☐ Cromolyn (Intal) ☐ Flovent ☐ Advair ☐ Aerobid ☐ Azmacort ☐ Beclovent
☐ Nedocromil (Tilade) ☐ Vanceril ☐ Pulmicort ☐ Decadron ☐ Prednisone ☐ Prednisolone
☐ Accolate ☐ Diuril ☐ Lasix ☐ Aldactixide ☐ Aldactone ☐ Nebulizer
☐ Theophylline ☐ Singulair

Does your child take that medicine every day, sometimes or only when sick? (check all that apply below)

☐ Every Day Medication: _____
☐ Sometimes Medication: _____
☐ Only when sick Medication: _____

PATIENT FAMILY DATA

39. Have the parents/family of the child had to change their plans because the child's breathing problems or pulmonary health in the last six months? ☐ YES ☐ NO
40. Did mother smoke during pregnancy? ☐ YES ☐ NO
41. Did father smoke during pregnancy? ☐ YES ☐ NO

42. Family history of atopy: (Check all that apply below)

Mother	☐ Asthma	☐ Eczema	☐ Seasonal Allergies
Father	☐ Asthma	☐ Eczema	☐ Seasonal Allergies
Siblings	☐ Asthma	☐ Eczema	☐ Seasonal Allergies

43. Does your child frequently have a stuffy nose or runny nose? ☐ YES ☐ NO

    If YES, how many infections has your child had for which antibiotics were prescribed since the last interview six months ago. _____

    What area of the body was infected? (check all that apply below)

    ☐ Nose ☐ Lungs ☐ Throat ☐ Eye ☐ Skin

    ☐ Mouth ☐ Genitals ☐ urinary tract ☐ Other, (Specify) _____

44. Does your child take a daily vitamin? ☐ YES ☐ NO

45. Does your child take daily iron (separate or in the vitamin)? ☐ YES ☐ NO

Appendix 4 Pulmonary Morbidity Assessment (Phone Interviews at 30 Months, 3 Years, 3.5 Years, 4 Years, and 4.5 Years CA)

Subject Name _____ **Subject Number** _____

The SHP-607-201 Protocol refers to a "Pulmonary Morbidity Assessment- phone interview". These questions are built into the pulmonary morbidity eCRF page. It will be completed every 6 months after the M24 visit. The questions are administered to the child's caregiver over the phone by site personnel. The data will be captured in EDC, no scoring is required.

1. Was the Pulmonary Morbidity Assessment done? ☐ YES ☐ NO

   If NO, please explain: _____

2. Date of Examination: Month _____ Day _____ Year _____
3. This questionnaire was administered to: _____
4. Was this questionnaire administered to the same responder as last time? ☐ YES ☐ NO
5. Has the child been with this caregiver during the six months _____
6. Since the last contact, has the smoking status of anyone in the child's home or the child's day care provider changed? ☐ YES ☐ NO

   If YES, please explain:

_____

_____

_____

PATIENT DATA

7. Has the child had any medical office visit during the past six month ☐ YES ☐ NO

   If YES, how many visit in the last six months? _____

   If YES, were any of these visits for respiratory symptoms?
   (Cold, wheezing or other breathing problems) _____

   If YES, what was the diagnosis? _____

   If YES, did the doctor prescribe any medication _____

   If YES, what was the medication _____

8. Has the child visited an urgent care facility in the past six month? ☐ YES ☐ NO

   If YES, were any of these visits related to respiratory symptoms?
   (colds, wheezing or other breathing problems?) ☐ YES ☐ NO

   If YES, what was the diagnosis? _____

   If YES, did the doctor prescribe any medication _____

If YES, what was the medication _____

9. Has the child visited the emergency room facility in the past six months? ☐ YES ☐ NO

If YES, is this urgent care part of the doctor's office? ☐ YES ☐ NO

If YES, were any of these visits related to respiratory symptoms? (colds, wheezing or other breathing problems?) ☐ YES ☐ NO

If YES, what was the diagnosis? _____

If YES, did the doctor prescribe any medication _____

If YES, what was the medication _____

10. Has the child had to stay in a hospital overnight in the last six months? ☐ YES ☐ NO

If YES, how many overnights in the last six months _____

If YES, were any of these visits related to respiratory symptoms? (colds, wheezing or other breathing problems) ☐ YES ☐ NO

If YES, what was the diagnosis?

11. Has the child had a flu shot? ☐ YES ☐ NO

12. Has the child had to use oxygen therapy at home during the last six months?

If YES, how many days did the child use oxygen in the last month? _____

Is the oxygen administered by nasal canula? ☐ YES ☐ NO

If YES, what is the FiO2 _____

Liter per minutes (LPM)?: (check only one below) _____

☐ < 0.25 ☐ 0.25 ☐ 0.5 ☐ 0.75 ☐ 1 ☐ 1.25
☐ 2 ☐ 2.25 ☐ 2.5 ☐ 2.75 ☐ 3 ☐ >3

13. Is your child in an oxygen hood or tent? ☐ YES ☐ NO

14. Is your child on a ventilator or CPAP? ☐ YES ☐ NO

If YES, what are the ventilator settings? _____

15. Has your child taken any medication during the past six months? ☐ YES ☐ NO

☐ Albuterol ☐ Proventil ☐ Serevent ☐ Ventolin ☐ Volmax ☐ Xopenex
☐ Cromolyn (Intal) ☐ Flovent ☐ Advair ☐ Aerobid ☐ Azmacort ☐ Beclovent
☐ Nedocromil (Tilade) ☐ Vanceril ☐ Pulmicort ☐ Decadron ☐ Prednisone ☐ Prednisolone
☐ Accolate ☐ Diuril ☐ Lasix ☐ Aldactixide ☐ Aldactone ☐ Nebulizer
☐ Theophylline ☐ Singulair

Appendix 5 Summary of Changes

Description of Change	Section(s)
Added pulmonary morbidity assessments which will be conducted during phone interviews at the 30-month, 3-year, 3.5-year, 4-year, and 4.5-year CA visits. Provided the pulmonary morbidity assessments at clinical site visits (Appendix 2 for the 6-month and 12-month CA visits; Appendix 3 for the 24-month and 5-year CA visits) and phone interviews (Appendix 4 for the 30-month, 3-year, 3.5-year, 4-year, and 4.5-year CA visits).	Section 4.1, Figure 4-1 Section 7.6.5 Section 8.2 Section 8.2.1 Appendix 1 Appendix 2 Appendix 3 Appendix 4
Added cerebral magnetic resonance imaging (MRI) to the 5-year CA visit.	Section 7.6.6 Section 8.2.2.1 Appendix 1
Added hearing assessment history at the 5-year CA visits.	Section 7.6.2 Section 8.2.2.1 Appendix 1
Added blood pressure, heart rate, and respiratory rate measurements at the 5-year CA visit.	Section 7.7.4 Section 8.2.2.1 Appendix 1
Clarified that if informed consent is not obtained at or before the 3-month visit in Study ROPP-2008-01 for inclusion in this study (SHP607-201), the subject may still be enrolled until they turn 2 years +3 months CA.	Section 7.2
Clarified that for subjects enrolled between the ages of 9 months CA and 2 years +3 months CA, missed procedures such as neurocognitive assessments, abdominal ultrasounds, and echocardiograms are not required.	Section 8.1
Clarified that for consented patients, additional biomarker analysis may be performed on prior collected blood samples from Study ROPP-2008-01.	Section 10.1

Description of Change	Section(s)
Updated Medical Monitor information as follows: [redacted], MD, MPH Shire 300 Shire Way Lexington, MA 02421 USA Telephone: [redacted] Mobile: [redacted] (24-hr access) E-mail: [redacted] Fax: [redacted] (North America)	Title Page Section 7.9.5.2
Administrative errors were corrected throughout the protocol.	All sections

Appendix 6 Protocol Signature Page

Study Title:	Long-term Outcome of Children Enrolled in Study ROPP-2008-01 Previously Treated with rhIGF-1/rhIGFBP-3 for the Prevention of Retinopathy of Prematurity (ROP) or Who Received Standard Neonatal Care
Study Number:	SHP-607-201
Final Date:	21 February 2017
Version	Amendment 2

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.
Signatory:

Investigator

_____
Signature **Date**

_____
Printed Name

I have read and approve the protocol described above.
Signatory:

Shire Medical Monitor

_____
Signature **Date**

[redacted], MD, MPH
Printed Name

Clinical Trial Protocol: SHP-607-201

Study Title:	Long-term Outcome of Children Enrolled in Study ROPP-2008-01 Previously Treated with rhIGF-1/rhIGFBP-3 for the Prevention of Retinopathy of Prematurity (ROP) or Who Received Standard Neonatal Care
Study Number:	SHP-607-201
Study Phase:	II
Product Name:	Mecasermin rinfabate (rhIGF-1/rhIGFBP-3)
IND Number:	121698
EUDRACT Number	2014-003556-31
Indication:	Retinopathy of Prematurity
Investigators:	Multicenter
Sponsor:	Premacure AB, A Member of the Shire Group of Companies
Sponsor Contact:	300 Shire Way Lexington, MA 02421 USA
Medical Monitor:	[redacted], MD, MPH

	Date
Original Protocol:	27 August 2014
Amendment 1	19 February 2016
Amendment 2	21 February 2017
Amendment 3	11 May 2017

Confidentiality Statement

SYNOPSIS

Sponsor:

Premacure AB, A Member of the Shire Group of Companies

Name of Finished Product:

Mecasermin rinfabate (rhIGF-1/rhIGFBP-3)

Study Title:

Long-term Outcome of Children Enrolled in Study ROPP-2008-01 Previously Treated with rhIGF-1/rhIGFBP-3 for the Prevention of Retinopathy of Prematurity (ROP) or Who Received Standard Neonatal Care

Study Number:

SHP-607-201

Study Phase: II

Investigational Product, Dose, and Mode of Administration:
Not applicable.

Primary Objectives

The primary objectives of this study are:

- To evaluate the long-term efficacy outcomes following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D) as assessed by ROP associated visual outcomes
- To evaluate the long-term safety outcomes following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D)

Secondary Objectives

The secondary objectives of this study are to evaluate the effect following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D) on:

- Growth parameters
- Cognitive development
- Physical development
- Child behavior
- Pulmonary morbidity
- Survival
- Health-related quality of life (HRQoL)
- Health utility
- Health care resource use (HCRU)

Exploratory Objective

[redacted]

Study Endpoints

The primary efficacy endpoints of this study are:

- Visual acuity as assessed by an age appropriate method
- Ocular alignment and ocular motor examination in primary gaze and in as many of 9 positions of gaze as possible as assessed by corneal light reflex and by the cover test
- Assessment of nystagmus by observation
- Refraction as assessed by retinoscopy with cycloplegia
- Stereoacuity as assessed with the Lang Stereotest

The secondary efficacy endpoints of this study are:

- Growth parameters including body weight, body length (or height), and head circumference
- Cognitive development as assessed by the following standardized, age-appropriate tools:
  - Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)
  - Wechsler Preschool and Primary Scale of Intelligence (WPPSI)
- Physical development as assessed by the following standardized, age appropriate tools:
  - Physical exam
  - Neurological examination for assessment of cerebral palsy
  - Hearing assessment
  - Blood pressure, heart rate, and respiratory rate
  - Cerebral magnetic resonance imaging (MRI)
- Child behavior as assessed by the following:
  - Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
  - Child Behavior Checklist (CBCL; 1 ½ to 5)
  - Attention Deficit/Hyperactivity Disorder Rating Scale (ADHD RS) for the assessment of symptoms of attention deficit/hyperactivity disorder (ADHD)
  - Social Communication Questionnaire (SCQ) for screening of Autism Spectrum Disorder (ASD)
- Pulmonary morbidity data (eg, hospitalizations, emergency room [ER] visits, pulmonary medications)
- Survival as assessed by death during the study due to any cause

The health economic outcome research endpoints of this study are:

- Health-related quality of life (HRQoL) 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, respectively)

- Health status (eg, health utility) will be measured by the Health Status Classification System-Preschool (HSCS-PS)
- Resource use associated with inpatient visits, outpatient visits, medical utilization and pharmacy utilization will be assessed

The safety endpoints of this study are:

- Physical examination including tonsil examination
- Adverse events (AEs), as follows:
  - those considered related to rhIGF-1/rhIGFBP-3 (as administered in Study ROPP-2008-01, Section D)
  - those considered related to procedures performed in this study (Study SHP-607-201)
  - specified targeted medical events regardless of causality
  - fatal SAEs regardless of causality
- Cardiac size as assessed by echocardiogram
- Kidney and spleen size and any other gross abnormalities as assessed by abdominal ultrasound

Exploratory Endpoints:

[redacted]

Study Population:

Subjects randomized in Study ROPP-2008-01, Section D are eligible to enroll in this study; completion of Study ROPP-2008-01 Section D is not required. Subjects in Study ROPP-2008-01 are premature infants (gestational age of 23 weeks + 0 days to 27 weeks + 6 days) who are randomized to receive either treatment with rhIGF-1/rhIGFBP-3 or standard neonatal care. Up to 120 subjects are planned to be randomized into Study ROPP-2008-01 Section D.

Study Design:

This is a Phase II, multicenter, long-term developmental outcome study enrolling subjects who were randomized in Section D of Study ROPP-2008-01. Enrolled subjects in this study will be followed through age 5 years corrected age (CA). This study will enroll both subjects who were in the treated (received rhIGF-1/rhIGFBP-3) and control (received standard neonatal care) groups of Study ROPP-2008-01 (Section D) to enable assessment of rhIGF-1/rhIGFBP-3 long-term efficacy and safety outcomes versus standard neonatal care. No investigational product will be administered in this study.

Study Duration:

Duration for an individual subject's participation in the study will vary depending upon age at enrollment, but subjects will not be followed beyond age 5.5 years corrected age (CA).

Study Inclusion and Exclusion Criteria:

Subjects randomized in Study ROPP-2008-01, Section D are eligible to enroll in this study. Subjects will not be excluded from participating in other clinical studies.

Efficacy Assessments:

Efficacy will be assessed by visual outcomes, growth parameters, cognitive development, physical development, child behavior, pulmonary morbidity, and survival.

Safety Assessments:

Safety will be assessed by physical examination (including tonsil examination), AEs (as specified), echocardiogram, and abdominal ultrasound.

Statistical Methods

Details regarding the statistical methods and definitions will be provided in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to database lock. All statistical analyses will be performed by the sponsor or CRO after the database is locked. Statistical analyses will be performed using Version 9.1 or higher of SAS® (SAS Institute, Cary, NC 27513).

Continuous variables will be summarized using descriptive statistics including the number of observations, 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 2 possible treatment assignments in the antecedent study, ROPP-2008-01, Section D (rhIGF-1/rhIGFBP-3 or standard neonatal care).

For analysis purposes, baseline is defined as the first assessment either in the antecedent study (ROPP-2008-01) or in this study (SHP-607-201). As necessary, relevant data from Study ROPP-2008-01 may be summarized with the data from this study (SHP-607-201).

Date of Original Protocol: 27 August 2014

Date of Amendment 1: 19 February 2016

Date of Amendment 2: 21 February 2017

Date of Amendment 3: 11 May 2017

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AAO	American Academy of Ophthalmology
ADHD	attention-deficit hyperactivity disorder
ADHD-RS	Attention-Deficit/Hyperactivity Disorder Rating Scale
AE	adverse event
ASD	Autism Spectrum Disorder
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
CBCL	Child Behavior Checklist (1 ½ to 5)
CFR	Code of Federal Regulations
CA	corrected age
CI	confidence interval
CRF	case report form (electronic)
CRO	contract research organization
DMC	data monitoring committee
eCRF	electronic case report form
EOS	end of study
ETDRS	Early Treatment of Diabetic Retinopathy Study
ER	emergency room
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GH	growth hormone
HRQoL	health-related quality of life
HSCS-PS	Health Status Classification System-Preschool
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IGF	insulin-like growth factor
IGFBP-3	insulin-like growth factor binding protein-3
IND	Investigational New Drug application
IRB	institutional review board
LV	left ventricle
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
[redacted]	[redacted]

Abbreviation	Definition
OD	right eye
OS	left eye
OU	both eyes
PedsQL	Pediatric Quality of Life Inventory
REB	research ethics board
ROP	retinopathy of prematurity
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System©
SCQ	Social Communication Questionnaire
SD	standard deviation
SOE	schedule of events
SUSAR	suspected unexpected serious adverse reaction
UK	United Kingdom
US	United States
VABS-II	Vineland Adaptive Behavior Scales, Second Edition
VLBW	very low birth weight
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

1 INTRODUCTION

Retinopathy of prematurity (ROP) is a rare disorder of the developing retinal blood vessels and retinal neurons of the preterm infant and is one of the leading causes of preventable blindness in children.[1]

Visual acuity is decreased in infants with a history of ROP.[2] In addition to acuity, other aspects of eye health are also significantly impacted by ROP. Strabismus and myopia are clearly increased in patients with a history of ROP.[3-6] Additionally, more than half of patients at 6 to 10 years of age with a history of Stage 1 and Stage 2 ROP were reported to have ongoing visual issues.[7]

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. During fetal life, IGF-1 is available through placental absorption and ingestion from amniotic fluid.[8] Deprivation of such factors is likely to cause inhibition or improper stimulation of important pathways, which in the eye may cause abnormal retinal vascular development, the hallmark of ROP.

The finding in both a mouse model of ROP and preterm infants that development of ROP is associated with low levels of IGF-1 after premature birth, indicates a possible role for replacement of IGF-1 to levels found in utero as a strategy to potentially decrease abnormal retinal vascularization and abnormal retinal neural development, and ultimately, ROP.

Mecasermin rinfabate (rhIGF-1/rhIGFBP-3) is the human recombinant form of the naturally occurring protein complex of IGF-1 and insulin-like growth factor binding protein-3 (IGFBP-3). rhIGF-1/rhIGFBP-3 was developed to enhance the systemic exposure of administered rhIGF-1 and to improve the safety profile of rhIGF-1 therapy. rhIGF-1/rhIGFBP-3 was approved by the Food and Drug Administration (FDA) in 2005 for the treatment of growth failure in children with severe primary IGF-1 deficiency or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.

The pharmacokinetics and safety of rhIGF-1/rhIGFBP-3 have been evaluated in a Phase I study (ROPP-2005-01) and pharmacokinetics, safety, and efficacy are being evaluated in the ongoing phase II study (ROPP-2008-01). Sections A-C of the ROPP-2008-01 study are complete. Section D of the ROPP-2008-01 study is currently being conducted to assess pharmacokinetics, safety and efficacy of rhIGF-1/rhIGFBP-3 for the prevention of ROP in premature infants (up to a corrected age [CA] of 40 weeks [± 4 days]). Subjects in Study ROPP-2008-01 are randomly assigned to receive rhIGF-1/rhIGFBP-3 or standard neonatal care. The target dose of rhIGF-1/rhIGFBP-3 for Study Section D is 250 µg/kg/24 hours to be administered via continuous infusion starting on Study Day 0 (day of birth) and continuing through postmenstrual age (gestational age + time elapsed from birth) 29 weeks + 6 days.

Although the rhIGF-1/rhIGFBP-3 therapy in Section D of the Phase II study (Study ROPP-2008-01) represents a short-term exposure (< 2 months for each subject), rhIGF-1/rhIGFBP-3 may have long-lasting effects on visual outcomes as well as other potential outcomes related to complications of prematurity such as neurodevelopment, pulmonary function, and growth. In addition, it is critical to understand any long term safety effects from short term exposure to rhIGF-1/rhIGFBP-3.

The long-term outcomes assessed in this study will require utilization of different assessment tools than are utilized in the Phase II study, ROPP-2008-01 Section D, given the changes in physical and cognitive development that will occur in the subjects as they age during their participation in this study.

Please refer to the current edition of the Investigator's Brochure for further information concerning the safety and clinical development of rhIGF-1/rhIGFBP-3.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are:

- To evaluate the long-term efficacy outcomes following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D) as assessed by ROP-associated visual outcomes
- To evaluate the long-term safety outcomes following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D)

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate the effect following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D) on:

- Growth parameters
- Cognitive development
- Physical development
- Child behavior
- Pulmonary morbidity
- Survival
- Health-related quality of life (HRQoL)
- Health utility
- Health care resource use (HCRU)

2.3 Exploratory Objective

[redacted]

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

3.1.1 Primary Efficacy Endpoints

- Visual acuity as assessed by an age-appropriate method
- Ocular alignment and ocular motor examination in primary gaze and in as many of 9 positions of gaze as possible as assessed by corneal light reflex and by the cover test
- Assessment of nystagmus by observation
- Refraction as assessed by retinoscopy with cycloplegia
- Stereoacuity as assessed with the Lang Stereotest

3.1.2 Secondary Efficacy Endpoints

- Growth parameters including body weight, body length (or height), and head circumference
- Cognitive development as assessed by the following standardized, age-appropriate tools:
    - Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)
    - Wechsler Preschool and Primary Scale of Intelligence (WPPSI)
- Physical development as assessed by standardized, age appropriate tools including physical examination, neurological examination for assessment of cerebral palsy, and hearing assessment
- Child behavior as assessed by the following:
    - Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
    - Child Behavior Checklist (CBCL; 1 ½ to 5)
    - Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS) for the assessment of symptoms of attention-deficit/hyperactivity disorder (ADHD)
    - Social Communication Questionnaire (SCQ) for screening of Autism Spectrum Disorder (ASD)
- Pulmonary morbidity data (eg, hospitalizations, emergency room [ER] visits, pulmonary medications)
- Survival as assessed by death during the study due to any cause

3.2 Health Economic Outcome Research Endpoints

- Health Related Quality of Life (HRQoL) 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, respectively)
- Health status (eg, health utility) will be measured by the Health Status Classification System-Preschool (HSCS-PS)
- Resource use associated with inpatient visits, outpatient visits, medical utilization and pharmacy utilization will be assessed

3.3 Safety Endpoints

- Physical examination including tonsil examination
- Adverse events (AEs), as follows:
  - those considered related to rhIGF-1/rhIGFBP-3 (as administered in Study ROPP-2008-01, Section D)
  - those considered related to procedures performed in this study (SHP-607-201)
  - specified targeted medical events regardless of causality
  - fatal serious adverse events (SAEs) regardless of causality
- Cardiac size as assessed by echocardiogram
- Kidney and spleen size and any other gross abnormalities as assessed by abdominal ultrasound

3.4 Exploratory Endpoints

[redacted]

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase II, multicenter, long-term developmental outcome study enrolling subjects who were randomized in Section D of Study ROPP-2008-01 to receive either rhIGF-1/rhIGFBP-3 (treated) or standard neonatal care (control). Enrolled subjects in this study will be followed through age 5 years CA. This study will enroll both subjects who were in the treated (received rhIGF-1/rhIGFBP-3) and control (received standard neonatal care) groups of Study ROPP-2008-01 (Section D) to enable assessment of rhIGF-1/rhIGFBP-3 long-term efficacy and safety outcomes versus standard neonatal care. No investigational product will be administered in this study.

In this study, the Initial Visit will occur at 40 weeks CA (ie, term equivalent) or upon discontinuation from Study ROPP-2008-01 or may occur any time up to the visit at 3 months CA. Subjects in Study ROPP-2008-01 are premature infants enrolling at gestational age of 23 weeks + 0 days to 27 weeks + 6 days.

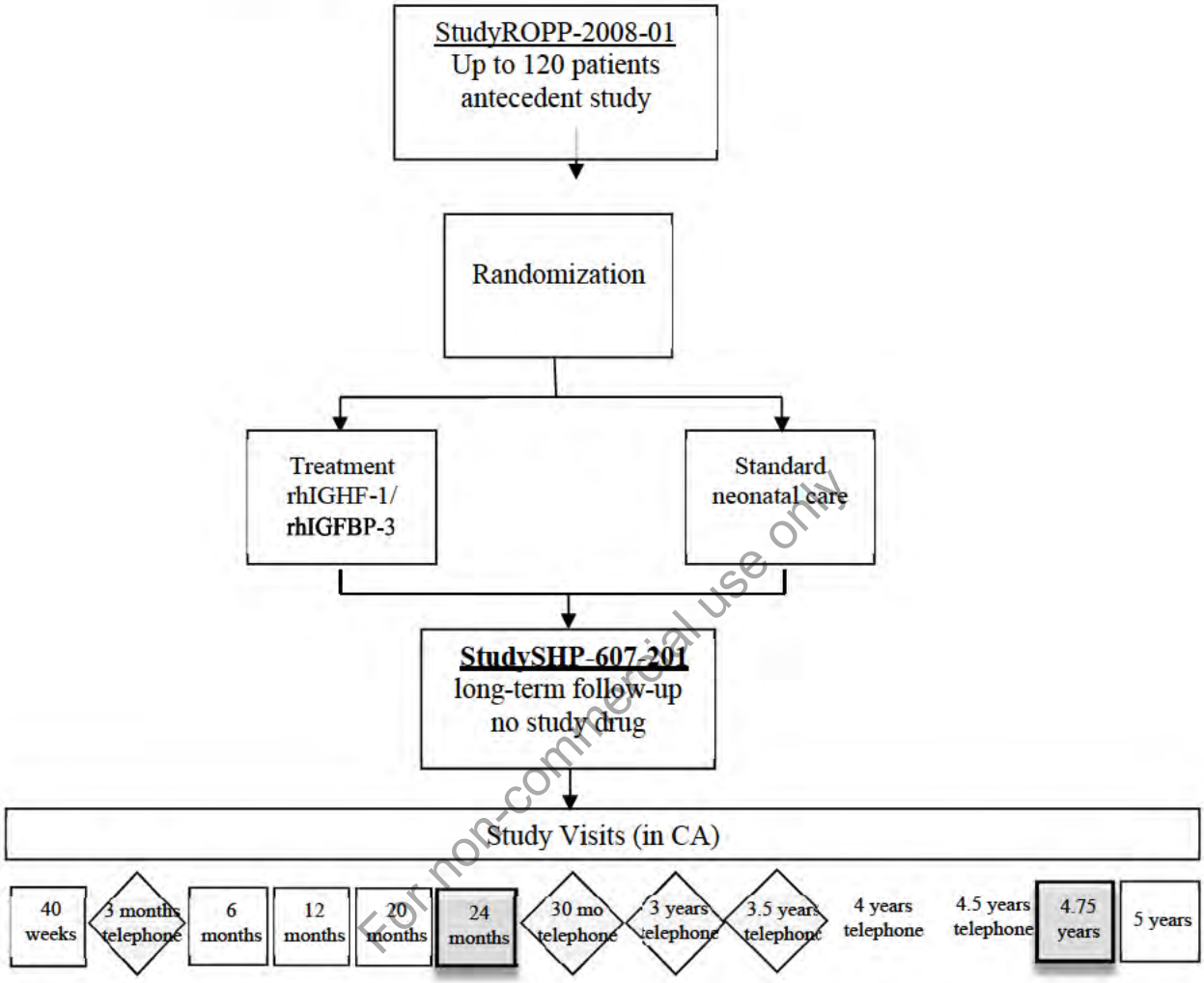
Time points for assessments have been chosen based on standard premature infant follow-up periods and represent important developmental ages for premature infant follow-up. Both telephone and clinical site visits are included to help maintain contact with subjects throughout the 5-year duration of the study.

Subjects will be evaluated at appropriate follow-up site locations with expertise in the assessment of the developmental outcomes of premature infants. Pediatric ophthalmology expertise will also be required.

See Appendix 1 for the Study Schedule of Events table.

The overall study design is outlined in Figure 4-1.

Figure 4-1 Overview of Study Design, Study SHP-607-201



Abbreviations: CA = corrected age

Note: Visits conducted by telephone are indicated with a diamond shape. Visits conducted at the study site are indicated with rectangles. Visit windows are provided in the Schedule of Events (Appendix 1).

4.2 Rationale for Study Design

The only approved therapies for ROP are ablative (cryotherapy or laser therapy). To date, there are no commercially available preventative treatments for ROP.

Although treatment with rhIGF-1/rhIGFBP-3 in ROPP-2008-01 (Section D) after premature birth is limited to less than 2 months of therapy, it remains important to assess the long-term outcomes of treatment on both efficacy and safety. Thus, this long-term follow-up study to Study ROPP-2008 01 (Section D) has been designed to assess long-term efficacy and safety outcomes following short-term exposure to rhIGF-1/rhIGFBP-3.

Insulin-like growth factor-1 (IGF-1) mediates its primary actions by binding to its specific receptor, the insulin-like growth factor 1 receptor (IGF-1R), which is present on many cell types in many tissues. Binding to its receptor initiates intracellular signaling including via the AKT signaling pathway. This pathway is involved in stimulation of cell division, growth and differentiation and inhibits programmed cell death. Specifically regarding premature infants, IGF-1 is an important mediator of fetal growth and has been shown to play a role in early postnatal growth following pre-term delivery.[9,10]

Insulin-like growth factor-1 (IGF-1) has also been shown to play a role in pulmonary development[11] and neural development.[12,13] Given the potential role for IGF-1 in the development of multiple systems, this study has been designed to evaluate the long-term effects of rhIGF-1/rhIGFBP-3, both from a safety and efficacy perspective, on the development of the premature infant.

4.3 Study Duration

Duration for an individual subject's participation in the study will vary depending upon age at enrollment, but subjects will not be followed beyond age 5.5 years CA.

5 STUDY POPULATION SELECTION

5.1 Study Population

Subjects randomized in Study ROPP-2008-01, Section D are eligible to enroll in this study; completion of Study ROPP-2008-01 Section D is not required. Subjects in Study ROPP-2008-01 are premature infants (gestational age of 23 weeks + 0 days to 27 weeks + 6 days) who are randomized to receive either treatment with rhIGF-1/rhIGFBP-3 or standard neonatal care. Up to 120 subjects are planned to be randomized in Study ROPP-2008-01 Section D.

5.2 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study.

1. Subject was randomized in Study ROPP-2008-01, Section D
2. Subject's parent or legally authorized representative(s) must provide written informed consent prior to performing any study-related activities. Study-related activities are any procedures that would not have been performed during normal management of the subject.

5.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study.

1. Any other condition or therapy that, in the Investigator's opinion, may pose a risk to the subject or interfere with the subject's ability to be compliant with this protocol or interfere with the interpretation of results
2. The subject or subject's parent or legally authorized representative(s) is unable to comply with the protocol as determined by the Investigator

6 STUDY TREATMENT

6.1 Description of Treatment

No investigational product will be administered in this study.

6.2 Treatments Administered

Not applicable.

6.3 Selection and Timing of Dose for Each Subject

Not applicable.

6.4 Method of Assigning Subjects to Treatment Groups

Not applicable.

6.5 Masking

Not applicable.

6.6 Medications

Any medications administered to the subjects will be collected from the time of informed consent through the 5-year CA visit (or until the subject withdraws or is discontinued). Any investigational product received by subjects will be recorded separately as part of an assessment of subjects' participation in other clinical studies (Section 7.11.1).

6.7 Restrictions

6.7.1 Prior Therapy

There are no restrictions related to prior therapy.

6.7.2 Other Restrictions

There are no restrictions related to fluid or food intake, or subject activity.

6.7.3 Treatment Compliance

Not applicable.

6.7.4 Packaging and Labeling

Not applicable.

6.8 Storage and Accountability

Not applicable

7 STUDY PROCEDURES

Detailed descriptions of subject procedures and evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of the study (see Schedule of Events in Appendix 1).

All data collected are to be recorded on the subject's appropriate eCRF.

Details for study procedures are described in the Operations Manual for this study.

7.1 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).

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 11.4. Documentation and filing of informed consent documents should be completed according to Section 11.4.

7.2 Study Entrance Criteria and Eligibility

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 informed consent is not obtained at or before the 3-month visit in Study ROPP-2008-01 for inclusion in this study (SHP607-201), the subject may still be enrolled until they turn 2 years CA +3 months. Subjects are no longer eligible to participate in this study after they turn 2 years CA +3 months.

7.3 Study Enrollment

Subjects will be considered enrolled in the study once written informed consent has been obtained from the subject's parent(s) or legally authorized representative(s).

7.4 Demographics

Subject demographic information including gender, date of birth, and race will be recorded.

7.5 Growth Parameters: Length (and Height), Weight, and Head Circumference

7.5.1 Length and Height

Body length (supine measurement) will be collected when subjects are 24-months CA or younger. 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 when subjects are older than 24-months CA. 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).

7.5.2 Body Weight

Body weight will be collected. Calibrated scales should be utilized for body weight measures (type of scale will depend upon subject's age). Care should be taken to remove any extraneous clothing prior to measures and shoes should be removed.

The measure should be recorded to the nearest 0.1 kg.

7.5.3 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.

7.6 Efficacy Assessments

7.6.1 Visual Assessments

After corrective lens determination has occurred (Section 7.6.1.2), all visual assessments should be conducted with best-corrected vision, ie, with corrective lenses in place (if required); this applies to 24-month and 5-year visits.

7.6.1.1 Visual Acuity

Visual acuity is a measure of how well a subject sees at different distances. It will be assessed by the methods summarized in Table 7-1; the method employed will be selected based on the subject's age (CA) at the time of the study visit. Visual acuity measurements will be measured and recorded for the left (OS), right (OD) eye, and both eyes (OU).

At ages 6 months and 12 months CA, visual acuity will be assessed with Teller acuity cards. At ages 24 months and 5 years CA an attempt should be made to assess visual acuity by the LEA Symbols Test and LEA Symbols Chart, respectively. If during this attempt, the examiner determines that it will not be possible to perform an accurate assessment with the relevant LEA tool, visual acuity should be assessed with the Teller acuity cards.

The visual acuity assessments should be performed by an optometrist or ophthalmologist trained in pediatrics.

Table 7-1 Summary of Visual Acuity Assessments

Visual Acuity Assessment Tool	Description	Unit of Measure	Applicable Age/Study Visit (CA)
Teller acuity cards	Resolution acuity – discrimination of a grating optotype from a background with the same mean luminance	cycles per degree	6 months 12 months
LEA Symbols Test	Recognition acuity - tests recognition of 4 optotypes	Snellen fraction (eg, 20/20)	24 months[a]
LEA Symbols (ETDRS-style) chart	Distance visual acuity test	Snellen fraction (eg, 20/20)	5 years[a]

Abbreviations: CA = corrected age; ETDRS = Early Treatment of Diabetic Retinopathy Study

[a] At ages 24 months and 5 years CA an attempt should be made to assess visual acuity by the LEA Symbols Test and LEA Symbols Chart, respectively. If during this attempt, the examiner determines that it will not be possible to perform an accurate assessment with the relevant LEA tool, visual acuity should be assessed with the Teller acuity cards.

7.6.1.2 Corrective Lens Determination

An assessment to determine if the subject requires vision correction with corrective lenses will be performed. This is being performed to ensure the accuracy of subjects' subsequent visual acuity assessments (at the 24-month and 5-year visits). The corrective lens determination will be performed according to the guidelines published by the American Academy of Ophthalmology (AAO).[14]

This assessment should be performed by an optometrist or ophthalmologist trained in pediatrics.

7.6.1.3 Ocular Alignment and Oculomotor Examination (Motility)

Ocular alignment will be assessed in primary gaze by comparing the position of the corneal light reflection in OS and OD (corneal light reflection assessment). Presence or absence of strabismus will be recorded in primary gaze and in as many of the 9 positions of gaze as feasible with the cover test assessment of refixation movement. Extraocular muscle over-action or deficiency will be recorded. The assessment will be performed according to the AAO guidelines.[14]

Presence or absence of nystagmus as observed during the ocular alignment assessments will also be recorded.

The assessment will be performed by a pediatric ophthalmologist or an ophthalmologist trained in the care of pediatric subjects with a history of premature birth. Degree of adherence to the AAO guidelines will be at the discretion of the examining physician in consideration of the need for patient cooperation.

Ocular motility refers to eye movements, which are governed by the 6 extraocular muscles in each eye. It will be assessed by examiner observation of the subject's ability to abduct, adduct, supra, and inferoduct each eye (to assess for strabismus). Any of the observed misalignment (strabismus classifications) will be recorded:

- esotropia
- exotropia
- hypertropia
- hypotropia

The frequency (constant or intermittent) with which any misalignment occurs and whether the turning eye is always the same eye or if it alternates between OS and OD, will be recorded. Extraocular muscle over-action or deficiency will be recorded.

This assessment should be performed by an optometrist or ophthalmologist trained in pediatrics.

7.6.1.4 Refraction with Cycloplegia

Refraction is a measure of the lens power required for a focused image on the retina. Refraction with cycloplegia will be measured and recorded in diopters for each eye individually (OS and OD).

Cycloplegia may be induced according to site standard practice.

This assessment should be performed by an optometrist or ophthalmologist trained in pediatrics.

7.6.1.5 Stereoacuity

Stereoacuity is a measure of depth perception and will be assessed using the Lang Stereotest and performed by certified personnel. The presence or absence of stereopsis will be recorded.

7.6.1.6 [redacted]

[redacted]

7.6.2 Hearing Assessment History

Results of previously completed hearing assessments will be recorded at the 6-month CA and 5-year CA visits; hearing tests are not being performed as part of this study.

7.6.3 Behavioral Assessments

7.6.3.1 Bayley Scales of Infant and Toddler Development, Third Edition

The BSID-III will be used to assess cognitive, motor, and language skills, and is applicable to children aged 1 to 42 months.

The BSID-III is an assessment tool designed to measure a young child's skills in the 3 core areas of development: cognitive, language, and motor. There are 5 subscales, the cognitive subscale stands alone while 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 examiner's manual.

The BSID-III 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.

7.6.3.2 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.[19] It is applicable to preschoolers and young children aged 2 years + 6 months to 7 years + 7 months, and is a direct assessment of a child's cognitive skills.

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[20] 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. Scores to be recorded are detailed in the Study Operations Manual.

7.6.3.3 Child Behavior Checklist (CBCL)

The CBCL (1 ½ to 5) is a parent-reported outcome measure used to assess behavioral, emotional, and social functioning of toddlers and preschool children aged 18 to 60 months.[21] It is composed of 99 items that are rated on a Likert scale and includes the following 7 syndrome scales arranged under 2 domains (ie, Internalizing and Externalizing Problems):[22]

- Internalizing Problems
- Emotionally Reactive
- Anxious/Depressed
- Somatic Complaints
- Withdrawn
- Sleep Problems
- Attention Problems
- Aggressive Behavior

The questionnaire is widely used and has been employed to assess long-term behavioral outcomes in children born prematurely, aged similarly to the subjects expected in this study population.[22-24] It is associated with well-established normative data;[25] norms may be selected to aid in interpretation of the scale scores.

The CBCL (1 ½ to 5) is a questionnaire that will be administered to 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.

7.6.3.4 Vineland Adaptive Behavior Scales, Second Edition

The VABS-II Expanded Interview Form will be used to measure the personal and social skills of subjects serially over time; these scales are organized within a 3-domain structure: Communication, Daily Living, and Socialization. In addition, the VABS-II offers a Motor Skills Domain and an optional Maladaptive Behavior Index. The VABS-II Expanded Interview Form assesses what a subject actually does, rather than what he or she is able to do.

The VABS-II Expanded Interview Form will be administered to 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.

7.6.3.5 Attention-Deficit/Hyperactivity Disorder Rating Scale

The ADHD-RS was developed to measure the behaviors of children with ADHD. The ADHD-RS consists of 18 items designed to reflect current symptomatology of ADHD based on DSM-IV 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,[26] will be completed by the subject's parent(s) or legally authorized representative(s). Scores to be recorded are detailed in the Study Operations Manual.

7.6.3.6 Social Communication Questionnaire – Lifetime Form

The SCQ is a brief instrument that helps evaluate communication skills and social functioning in children[27] that can be used for screening for autism or autism spectrum disorders in the general population.[28]

The SCQ will be completed by the subject's parent(s) or legally authorized representative(s). 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.

7.6.4 Cerebral Palsy Assessment

Comprehensive neurological examination for the diagnosis of cerebral palsy (CP) will be conducted. The Amiel-Tison neurological examination framework[29] will be utilized for this assessment and conducted by trained medical professionals.

7.6.5 Pulmonary Morbidity Assessment

Pulmonary morbidity will be assessed with questions related to family history and smoking status as well as diagnosis of select pulmonary symptoms, conditions and related hospitalizations. The assessment will be administered to the subject's parent(s) or legally authorized representative(s). Assessments will be performed as outlined in the Schedule of Events (see Appendix 1). Questionnaires that will be used for these assessments at clinical site visits are provided in the Study Operations Manual for the 6-month,12-month 24-month, and 5-year CA visits. The questionnaire that will be used for these assessments during phone interviews at the 30-month, 3-year, 3.5-year, 4-year, and 4.5-year CA visits is provided in the Study Operations Manual.

7.6.6 Optional Cerebral Magnetic Resonance Imaging

Participation in the MRI assessment is optional and has no impact on participating in the main study. If consented to, magnetic resonance imaging (MRI) of the brain will be performed.

The MRI may be performed with or without sedation. If the scan is performed without sedation and the first attempt is unsuccessful, a second attempt should be made. 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.

7.6.7 Survival Assessment

Survival status will be assessed and recorded.

7.6.8 Health Economic Outcome Research Assessments

7.6.8.1 Health Related Quality of Life

Health-related quality of life (HRQoL) is an important outcome towards improving the health care of pediatric patients as it is that part of a person's overall quality of life that is determined primarily by their health status and which can be influenced by clinical interventions. It is an important concept, which is also used in determining the value of health care services in this population.[30,31] It is a multidimensional construct whose content is guided by the World Health Organization;[32] minimally it includes physical, psychological (including emotional and cognitive), and social health dimensions.

In this study, HRQoL will be assessed via the validated Pediatric Quality of Life Inventory (PedsQL™) Scales appropriate for the child's age of development.[33-35] The development of the PedsQL was based on the delineations of the World Health Organization (WHO) and is a modular approach to assessing HRQoL in the pediatric population. Initially, the PedsQL Generic Scales were developed and continue to be used in children aged 2 to 18 years. More recently Infant Scales have been developed that apply to ages 1 to 24 months.[34]

The following scales will be used in this study:

- Infant Scale for ages 1-12 months (36 Items)
- Infant Scale for ages 13–24 months (45 Items)
- Toddler Scale for 2-4 years of age (21 Items)
- Young Child Scale for 5-7 years of age (23 Items)

The PedsQL will be administered to the subject's parent and may be conducted via telephone by clinical site staff. The scale(s) to be administered at each visit will be specified in the Study Operations Manual.

7.6.9 Health Care Resource Use

To understand the value of the investigational product administered in Study ROPP-2008-01 (Section D), the resource use associated with inpatient visits, outpatient visits, and medical and pharmacy utilization in this study will be recorded.

This assessment may be conducted via telephone by clinical site staff.

7.6.9.1 Health Status Classification System-Preschool

Health status (eg, health utility) will be measured by the Health Status Classification System-Preschool (HSCS-PS), which is a validated instrument adapted for use via parent proxy within the pediatric population age 2.5 to 5 (adapted from the validated Health Utilities Index Mark 2 and 3 [HUI 2/3]).[36] Validity of the HSCS-PS concepts has not been established for ages younger than 2.5 years.

The HSCS-PS was developed to provide a consistent measure of health status in preschool-aged children who had been born prematurely.[36] The system is applicable to children with special needs as may be included in this study; validation cohorts for the system included children with very low birth weight (VLBW), which is congruent with this study population.

The instrument is composed of 12 dimensions (Vision, Hearing, Speech, Mobility, Dexterity, Self-care, Emotion, Learn/remember, Think/problem solve, Pain, General Health, and Behavior) intended to provide a comprehensive assessment of a child's health status as it pertains to health-related quality of life. The individual domains of the instrument will be scored as a mean score, representing the overall state for each concept individually. The global score will be recorded as well as the scores for each of the dimensions.

The HSCS-PS is a questionnaire that will be administered to the subject's parent(s) or legally authorized representative(s) and may be conducted via telephone by clinical site staff.

7.7 Safety Assessments

7.7.1 Abdominal ultrasound

An abdominal ultrasound will be performed to assess the size of the spleen and kidneys. The spleen will be measured in the coronal longitudinal plane and the longest longitudinal length will be measured for each kidney (left and right).[37] Ultrasound results will be assessed by a central reader.

Organ size will be interpreted in the context of reference values established for children.[37,38]

7.7.2 Echocardiogram

Echocardiographic examination (conventional M-mode recording of the left ventricle [LV] parasternal long axis view) will be performed for the evaluation of cardiac size, assessed by measuring the following:

- interventricular septal thickness (during end diastole)
- LV posterior wall thickness
- LV intracavity volume (both in end diastole and end systole)

Echocardiogram results will be assessed by a central reader.

7.7.3 Physical Examination

Physical examinations will include a review of the subject's general appearance, neurological examination, as well as a tonsillar examination (Table 7-2). Any abnormal change in findings will be recorded as an AE.

Table 7-2 Assessments for Physical Examinations

Assessment	Assessment
General appearance	Endocrine
Head and neck	Cardiovascular
Eyes	Abdomen
Ears	Genitourinary
Nose	Skin
Throat	Musculoskeletal
Chest and lungs	Neurological
Tonsils	

7.7.4 Blood Pressure, Heart Rate, and Respiratory Rate

Blood pressure, heart rate, and respiratory will be measured at the 5-year CA visit.

7.8 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 7.11.1).

7.9 Adverse Events Assessments

7.9.1 Definitions of Adverse Events, Serious Adverse Events, and Suspected Unexpected Serious Adverse Reactions

7.9.1.1 Adverse Event

An AE is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered investigational product-related. This includes an exacerbation of a pre-existing condition.

Adverse events include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study
- Intercurrent illnesses
- Drug interactions
- Events related to or possibly related to concomitant medications
- Abnormal laboratory values (this includes significant shifts from baseline within the range of normal that the Investigator considers to be clinically important)
- Clinically significant abnormalities in physical examination, vital signs, and weight

In this long-term outcome study in follow-up to Study ROPP-2008-01 (Section D), no investigational product is being administered. However, the relationship to the investigational product (rhIGF-1/rhIGFBP-3) as administered in Study ROPP-2008-01 (Section D) will be assessed.

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

- those considered related to investigational product (rhIGF-1/rhIGFBP-3 as administered in Study ROPP -2008-01, Section D)
- those considered related to procedures performed in this study (Study SHP-607-201)
- specified targeted medical events (Section 7.9.1.3) regardless of causality

Throughout the study, the Investigator must record AEs on the AE electronic case report form (eCRF), regardless of the severity. The Investigator should treat subjects with AEs appropriately and observe them at suitable intervals until the events stabilize or resolve. Adverse events may be discovered through observation or examination of the subject, questioning of the subject, complaint by the subject, or by abnormal clinical laboratory values.

In addition, AEs may also include laboratory values that become significantly out of range. In the event of an out-of-range value, the laboratory test should be repeated until it returns to normal or can be explained and the subject's safety is not at risk.

Additional illnesses present at the time when informed consent is given are regarded as AEs and will be documented on the appropriate pages of the eCRF. Illnesses first occurring or detected during the study, and worsening of a concomitant illness during the study, are to be regarded as AEs and must be documented as such in the eCRF.

7.9.1.2 Serious Adverse Event

An SAE is any AE that results in any of the following outcomes:

- Death
- Is life-threatening
- Requires hospitalization
- Requires prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect

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 one of the outcomes listed in this definition.

A life-threatening AE is defined as an AE that placed the subject, in the view of the initial reporter, at immediate risk of death from the AE as it occurred (ie, it does not include an AE that, had it occurred in a more severe form, might have caused death).

For the purposes of this study only SAE listed in the following will be collected:

- fatal SAEs regardless of causality
- SAEs related to ROP
- SAEs related to congenital malformations not identified at birth which may impact neurocognitive development

7.9.1.3 Suspected Unexpected Serious Adverse Reaction

Suspected unexpected serious adverse reactions (SUSAR) are suspected adverse reactions related to an investigational product (investigational products and comparators [if applicable]), which occur in the concerned study, and that are both serious and unexpected according to the current Investigator's Brochure.

7.9.1.4 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, as appropriate, regardless of relationship to investigational product (rhIGF-1/rhIGFBP-3 as administered in Study ROPP-2008-01, Section D):

- intracranial hypertension
- any abnormality of glucose metabolism (eg, hypoglycemia, hyperglycemia, and diabetes)
- tonsillar hypertrophy (based on tonsil exam [part of the physical exam])
- increased kidney size
- increased cardiac size
- increased spleen size

7.9.2 Classification of Adverse Events and Serious Adverse Events

The severity of AEs will be assessed by the Investigator based on the definition indicated in Table 7-3. The severity of all AEs/SAEs should be recorded on the appropriate eCRF page to a severity of mild, moderate, or severe.

Table 7-3 Adverse Event Severity

Severity	Definition
Mild	No limitation of usual activities.
Moderate	Some limitation of usual activities.
Severe	Inability to carry out usual activities.

7.9.3 Clarification between Serious and Severe

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) and causality serve as a guide for defining regulatory reporting obligations.

7.9.4 Relatedness of Adverse Events and Serious Adverse Events

Relationship of an AE or SAE to investigational product (rhIGF-1/rhIGFBP-3 as administered in Study ROPP-2008-01, Section D) is to be determined by the Investigator based on the following definitions (See Table 7-4).

Table 7-4 Adverse Event Relatedness

Relationship to Product	Definition
Not Related	Unrelated to investigational product
Possibly Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, but which could also be explained by concurrent disease or other drugs or chemicals.
Probably Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on de-challenge. The association of the clinical event or laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds.
Definitely related	The event follows a reasonable temporal sequence from administration of the investigational product, follows a known or suspected response pattern to the investigational product, is confirmed by improvement upon stopping the investigational product (de-challenge), and reappears upon repeated exposure (re-challenge). Note that this is not to be construed as requiring re-exposure of the subject to investigational product; however, the determination of definitely related can only be used when recurrence of event is observed.

7.9.5 Procedures for Recording and Reporting Adverse Events

7.9.5.1 Adverse Event Monitoring and Period of Observation

Adverse events will be monitored throughout the study.

For the purposes of this study, the period of observation begins from the time at which the subject's parent(s) or legally authorized representative(s) gives informed consent until the subject's final evaluation of the study. When possible, subject's parents or legally authorized representative(s) should be consented at the end of study visit for the ROPP-2008-01. However, if this is not possible, subject's parents or legally authorized representative(s) will be asked to provide consent for any Serious Adverse Events that the subject experiences between ROPP-2008-01 end-of-study visit and the start of the SHP-607-201, to be reported by the Investigator. For safety purposes, the final evaluation will be defined as the last study visit when the subject is 5 years-old in CA.

If the Investigator considers it necessary to report an AE in a study subject after the end of the safety observation period, he or she should contact the Sponsor to determine how the AE should be documented and reported.

7.9.5.2 Reporting Serious Adverse Events

Any SAE meeting the reporting criteria for this study should be recorded by the clinical site on an SAE form. The SAE must be completely described on the subject's eCRF, including the judgment of the Investigator as to the relationship of the SAE to the investigational product. The Investigator will promptly supply all information identified and requested by the Sponsor (or contract research organization [CRO]) regarding the SAE.

The Investigator must report the SAE to the Shire Pharmacovigilance and Risk Management Department AND to the local Shire Medical Monitor on an SAE form. This form must be completed and FAXED or EMAILED within 24 hours of the Investigator's learning of the event to:

Shire Pharmacovigilance and Risk Management Department:

International FAX: [redacted] **(UK) OR United States FAX:** [redacted]

Email: [redacted]

AND

Shire Medical Monitor: [redacted]**, MD, MPH** **E-mail:** [redacted]

Any follow-up information must also be completed on an SAE form and faxed or emailed to the same numbers or emails listed above.

In the event of a severe and unexpected, fatal, or life-threatening SAE, the clinical site must contact the Shire Medical Monitor by telephone as soon as possible and within 24 hours of awareness; this is in addition to completing and transmitting the SAE form as stated above. The following provides contact information for the Shire Medical Monitor.

If an SAE is assessed as severe and unexpected, or life-threatening, contact:
[redacted] MD, MPH [redacted] Shire 300 Shire Way Lexington, MA 02421 USA Telephone: [redacted] Mobile: [redacted] (24-hr access) E-mail: [redacted] Fax: [redacted] (North America)

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

The Sponsor and the CRO are responsible for notifying the relevant regulatory authorities/US central IRBs/European Union (EU) central ECs of related, unexpected SAEs.

For some European regulatory authorities, these reports are submitted directly to Eudravigilance. In case of deaths or life-threatening SUSARs, these must be reported to the relevant regulatory authorities before 7 days have elapsed from that the initial SAE report has reached the Sponsor or its representatives. A full report has to be submitted within another 8 days. For other SUSARs the timelines for reporting are 15 days.

In addition, the CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the rhIGF-1/rhIGFBP-3 program at Shire.

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.

7.10 Removal of Subjects from the Trial

A subject's participation in the study may be discontinued at any time at the discretion of the Investigator. The following may be justifiable reasons for the Investigator to remove a subject from the study:

- Non-compliance, including failure to appear at one or more study visits
- The subject was erroneously included in the study
- The subject develops an exclusion criterion
- The study is terminated by the Sponsor

The subject, the subject's parent(s), or the subject's legally authorized representative acting on behalf of the subject is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment.

If a subject or the subject's parent(s) or the subject's legally authorized representative(s) acting on behalf of the subject, discontinues participation in the study, or the subject is discontinued by the Investigator, reasonable efforts will be made to follow the subject through the end of study assessments. The reason for refusal will be documented on the eCRF. Any AEs experienced up to the point of discontinuation must be documented on the AE eCRF. If AEs are present when the subject withdraws from the study, the subject will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal will be followed until resolution.

7.11 Other Study Procedures

7.11.1 Participation in Other Clinical Studies

Following enrollment, subjects in this study will not be restricted from enrolling in another clinical study that involves 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 being evaluated in the study, and the subject's treatment assignment in the study (if possible).

7.12 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. These are the pulmonary morbidity assessment and the cerebral palsy assessment. In these cases, the tools are either based on validated tools or the current state of knowledge in the literature. For example, the cerebral palsy assessment is based on the Amiel-Tison neurological examination framework[29] and the pulmonary assessment is based on published research in a similar pediatric population[39,40].

8 STUDY ACTIVITIES

The timing of the visits in this study is based on subjects' corrected age (CA).

8.1 Initial Study Visit (40 weeks CA [term equivalent])

The Initial Visit will occur at 40 weeks CA (ie, term equivalent) or upon discontinuation from Study ROPP-2008-01, Section D or any time up to the visit at 3 months CA.

For subjects enrolled between the ages of 9 months CA and 2 years +3 months CA, missed procedures such as neurocognitive assessments, abdominal ultrasounds, and echocardiograms are not required.

At the Initial Visit, informed consent will be obtained followed by an assessment of study eligibility criteria and collection of demographic data.

The following AE data, collected as part of Study ROPP-2008-01 (Section D) will be recorded:

- Ongoing targeted medical events regardless of causality
- Ongoing study drug-related AEs, including SAEs

SAEs, as outlined in Section 7.9.1.1 and Section 7.9.1.2, that the subject experiences between the ROPP-2008-01 end-of-study visit and the time of informed consent for the SHIP-607-201 study will be reported by the Investigator, pending permission for subject's parent or legally authorized representative(s), as documented on the informed consent form.

8.2 Study Visits

Study visits for follow-up outcome assessments will take place at the following time points in CA:

- 3 months (±2 weeks) – conducted by telephone
- 6 months (±1 month) – clinical site visit
- 12 months (±3 months) – clinical site visit
- 20 months (-1 months) – clinical site visit
- 24 months (±3 months) – clinical site visit
- 30 months (±3 months) – conducted by telephone
- 3 years (±3 months) – conducted by telephone
- 3.5 years (±3 months) – conducted by telephone
- 4 years (±3 month) – conducted by telephone
- 4.5 years (±3 month) – conducted by telephone
- 4.75 years (-1 months) – clinical site visit
- 5 years (+6 months) – clinical site visit

In addition, there will be 2 visits that must occur at least 1 month prior to the 24-month and 5-year CA study visits to assess the need for corrective lenses. The timing of these 2 visits (20 months [-1 month] and 4.75 years [-1 month]) was set to ensure that any prescribed corrective lenses would be worn for at least 1 month prior to the visual assessments at the 24-month and 5-year study visits CA.

The activities at the study visits are described in Sections 8.2.1 and 8.2.2.

8.2.1 Outcome Assessment Visits Conducted by Telephone

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

- HRQoL (3-month, 3-year, and 4-year visits)
- HCRU (3-month, 3-year, and 4-year visits)
- HSCS-PS (3-year and 4-year visits)
- Pulmonary morbidity assessment (30-month, 3-year, 3.5-year, 4-year, and 4.5-year visits)
- Medications (3-month, 30 months, 3-year, 3.5 year, 4-year and 4.5 year visits)
- Survival assessment (3-month, 30 month, 3-year, 3.5 year, 4-year and 4.5 year visits)
- Assessment of participation in other clinical studies (3-month, 30 months, 3-year, 3.5 year, 4-year and 4.5 year visits)
- Adverse events, including targeted medical events (3-month, 30 month, 3-year, 3.5 year, 4-year and 4.5 year visits)

8.2.2 Clinical Site Visits

8.2.2.1 Outcome Assessment Site Visits

The following clinical site visits (in CA) to capture follow-up outcome data will occur at the clinical site:

- 6 months (±1 month)
- 12 months (±3 months)
- 20 months (-1 month)
- 24 months (±3 months)
- 4.75 years (-1 months)
- 5 years (+6 months)

The following assessments will be performed at the 6-month visit:

- Visual acuity
- Refraction with cycloplegia
- Length
- Weight
- Head circumference
- VABS-II
- Physical examination (including tonsil examination)
- Hearing Assessment History (Historical hearing test data may be recorded at any time prior to the 6-month visit)
- Pulmonary morbidity assessment
- Survival assessment
- HRQoL (may be performed by telephone if there are time constraints during this clinical site visit)
- HCRU (may be performed by telephone if there are time constraints during this clinical site visit)
- Abdominal ultrasound
- Echocardiogram
- Assessment of participation in other clinical studies
- Medications
- Adverse events (including targeted medical events)

The following assessments will be performed at the 12-month visit:

- Visual acuity
- Corrective lens determination (including refraction with cycloplegia)
- Ocular alignment and motility
- Length
- Weight
- Head circumference
- BSID-III
- VABS-II
- Physical examination (including tonsil examination)
- Pulmonary morbidity assessment

- Survival assessment
- HRQoL (may be performed by telephone if there are time constraints during this clinical site visit)
- HCRU (may be performed by telephone if there are time constraints during this clinical site visit)
- Assessment of participation in other clinical studies
- Medications
- Adverse events (including targeted medical events)

The following assessments will be performed at the 20-month visit:

- Visual acuity
- Corrective lens determination (including refraction with cycloplegia)
- Assessment of participation in other clinical studies

The following assessments will be performed at the 24-month visit:

- Visual acuity
- Ocular alignment and motility
- Length
- Weight
- Head circumference
- BSID-III
- CBCL
- VABS-II
- Physical examination (including tonsil examination)
- Cerebral Palsy assessment
- Pulmonary morbidity assessment
- Survival assessment
- HRQoL (may be performed by telephone if there are time constraints during this clinical site visit)
- HCRU (may be performed by telephone if there are time constraints during this clinical site visit)
- HSCS-PS (may be performed by telephone if there are time constraints during this clinical site visit)

- Assessment of participation in other clinical studies
- Medications
- Adverse events (including targeted medical events)

The following assessments will be performed at 4.75-year visit:

- Visual acuity
- Corrective lens determination (including refraction with cycloplegia)

The following assessments will be performed at the 5-year visit:

- Visual acuity
- Ocular alignment and motility
- Stereoacuity
- Height
- Weight
- WPPSI
- CBCL
- VABS-II
- ADHD-RS
- SCQ
- Physical examination (including tonsil examination)
- Blood pressure, heart rate, and respiratory rate
- Pulmonary morbidity assessment
- Hearing assessment history
- Survival assessment
- [redacted]
- Cerebral MRI
- HRQoL (may be performed by telephone if there are time constraints during this clinical site visit)
- HCRU (may be performed by telephone if there are time constraints during this clinical site visit)
- HSCS-PS (may be performed by telephone if there are time constraints during this clinical site visit)
- Assessment of participation in other clinical studies

- Medications
- Adverse events (including targeted medical events)

8.2.2.2 Visits Dedicated to Corrective Lens Determination

The following clinical site visits are dedicated solely to corrective lens determination in preparation for the outcome assessment visits at 24-months and 5-years CA:

- 20 months (-1 month)
- 4.75 years (-1 month)

At these visits, the following will be performed:

- Visual acuity
- Corrective lens determination (includes refraction with cycloplegia)

The 20-month visit and the 4.75-year (4 years, 9 months) visit must occur at least 1 month prior to the 24-month and 5-year visits, respectively. Any prescribed corrective lenses must be worn for at least 1 month prior to the 24 month and 5 year assessments.

8.3 Assessments upon Discontinuation

If a subject discontinues prior to the 5-year CA visit, every attempt will be made to complete the assessments scheduled for the subject's next visit.

9 QUALITY CONTROL AND ASSURANCE

Training will occur at an Investigator meeting or at the site initiation visit or both, and instruction manuals will be provided to aid consistency in data collection and reporting across sites.

Clinical sites will be monitored by the Sponsor or its designee to ensure the accuracy of data against source documents. The required data will be captured in a validated clinical data management system that is compliant with the FDA 21 Code of Federal Regulations (CFR) Part 11 Guidance. The clinical trial database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be trained and given restricted access, based on their role(s) in the study, through a password-protected environment.

Data entered in the system will be reviewed manually for validity and completeness against the source documents by a clinical monitor from the Sponsor or its designee. If necessary, the study site will be contacted for corrections or clarifications; all missing data will be accounted for.

Serious adverse event information captured in the clinical trial database will be reconciled with the information captured in the Pharmacovigilance and Risk Management database.

10 STATISTICAL ANALYSES

10.1 General Methodology

Details regarding the statistical methods and definitions will be provided in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to database lock. All statistical analyses will be performed by the Biometrics department at Shire. Statistical analyses will be performed using Version 9.1 or higher of SAS® (SAS Institute, Cary, NC 27513).

Continuous variables will be summarized using descriptive statistics including the number of observations, 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 2 possible treatment assignments in the antecedent study, ROPP-2008-01, Section D (rhIGF-1/rhIGFBP-3 or standard neonatal care).

For analysis purposes, baseline is defined as the first assessment either in the antecedent study (ROPP-2008-01) or in this study (SHP-607-201). As necessary, relevant data from Study ROPP-2008-01 may be extracted and summarized with the data from this study (SHP-607-201). For consented patients, additional biomarker analysis may be performed on prior collected blood samples from Study ROPP-2008-01.

10.2 Determination of Sample Size

No formal sample size calculation was performed for this study because this is a follow-up study to Section D of Study ROPP-2008-01. Any subjects enrolled in Study ROPP-2008-01 are eligible to enroll in this study. There are up to 120 subjects who will be eligible to enroll in this long-term developmental outcome study.

10.3 Method of Assigning Study Subjects to Treatment Groups

Not applicable.

10.4 Population Description

10.4.1 Analysis Populations

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

Safety Population- the Safety Population will consist of the subjects in the Enrolled Population who have safety follow-up data in this long-term outcome study.

10.4.2 Subject Disposition

Subjects who complete the study and subjects who prematurely discontinue from the study will be summarized by treatment group using descriptive statistics. In addition, for subjects who prematurely discontinue from the study, the reasons for discontinuation will be summarized by treatment group.

10.4.3 Protocol Violations and Deviations

Protocol violations and deviations will be listed. Details of the criteria for deviations and violations will be provided in the SAP.

10.4.4 Demographics and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group for the Enrolled Population.

Demographics and baseline characteristics will be examined to assess the comparability of the treatment groups. Continuous variables such as age (including corrected age), weight, and length/height will be summarized using number of observations, mean, standard deviation, median, minimum and maximum values. Categorical variables, like gender and race, will be summarized using number of observations and percentages.

Medical history, including maternal and perinatal history, (as obtained from the antecedent study, ROPP-2008-01) will be summarized by treatment group using the number of observations and percentages of subjects reporting each category.

10.5 Efficacy Analysis

All efficacy analyses will be performed using the Enrolled Population.

10.5.1 Primary Efficacy Analysis

The primary efficacy endpoints consist of the following:

- Visual Acuity: Visual acuity will be categorized as the following:
  - normal (measurable acuity ≥20/40),
  - below normal (20/200≤ measurable acuity <20/40),
  - poor (measurable acuity ≤20/200)
  - blind/low vision (only the ability to detect the 2.2 cm wide stripes on the low-vision Teller acuity card and at any location in the visual field).

  The number and proportion of patients within each category listed above will be summarized by treatment group and visit. In addition, acuity results in the normal and below normal categories will be classified as favorable outcomes, and acuity results in the poor and blind/low-vision categories will be classified as unfavorable outcomes. Tabular summaries by treatment group and visit will include the frequency and the percentage for each visual acuity category.

In addition, shift tables of favorable outcomes from baseline (first assessment during this study) to each of the subsequent assessments, including the last assessment, will be presented by treatment group.

- Ocular Alignment and Oculomotor Exam (Motility): Findings from the ocular motility assessment will be either presence or absence of strabismus (esotropia, exotropia, hypertropia, or hypotropia). Tabular summaries by treatment group and visit will include the frequency and the percentage in each category. In addition, shift tables from baseline (first assessment during this study) to the last assessment will be provided by treatment group.
- Nystagmus: Presence or absence of nystagmus will be summarized by treatment group and visit
- Refraction with Cycloplegia: Findings from the refraction with cycloplegia will be summarized by treatment group and visit
- Stereoacuity: Presence or absence of stereopsis will be summarized by treatment group and visit

10.5.2 Secondary Efficacy Analysis

- Growth Parameters (body weight, body length [and height], and head circumference): A standard Z-score, utilizing WHO child growth standards, will be calculated for each assessment by adjusting age- and sex- matched means and standard deviations (norm). The descriptive statistics of the Z-score for each of these parameters will be summarized at each assessment and the corresponding change from baseline. When appropriate, a 95% CI for the corresponding mean change within each group and the difference in the mean change between the 2 treatment groups and the corresponding 95% CI will be presented as appropriate. If the parametric assumption for the distribution of the above endpoints cannot be justified, a non-parametric approach will be utilized to estimate the treatment difference (ie, median difference or Hodges-Lehmann estimator and the corresponding confidence intervals)
- BSID-III and WPPSI: The raw score, age equivalent scores, and standard scores for each domain within each questionnaire will be summarized by treatment group and visit using descriptive statistics.
- ADHD-RS: ADHD-RS total score and subscales (Hyperactivity/Impulsivity and Inattentiveness) will be summarized by treatment group and visit using descriptive statistics.
- SCQ: The SCQ subscales (communication and social) will be summarized by treatment group and visit using descriptive statistics
- VABS-II: The raw score, age equivalent scores, and standard scores for each domain of the scale will be summarized by treatment group and visit using descriptive statistics.
- CBCL: The raw score and change from baseline for each domain of the scale will be summarized by treatment group and visit using descriptive statistics.

- Pulmonary morbidity assessment: The binary response of each question will be by treatment group and visit using descriptive statistics.
- Survival: For subjects who have an event (ie, death), the event time will be calculated as the length of time from the subject's date of birth to death during the study due to any cause. Subjects who do not have an event (ie, death) during the study will be censored at the end of the study. The survival endpoint will be analyzed by treatment group using Kaplan-Meier methods.

10.5.3 Subset Analyses

Subgroup analyses may be explored based on factors that may have influence on the efficacy or safety endpoints. Subgroup analyses will be specified in the SAP.

10.5.4 Exploratory Analyses

[redacted]

10.6 Health Economics and Outcomes Research Analyses

For PedsQL, descriptive statistics will be provided for summary scores by treatment group 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 and at each time point.

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.

10.7 Analysis of Safety

Safety summaries will be based on all assessments post-baseline. The safety data will be assessed by AE monitoring, change in cardiac size, and kidney and spleen size over time.

Adverse events will be summarized by system organ class and preferred term for each treatment group and overall, the number and percentage of subjects having any AE, having an AE in each body system and having each individual AE. In addition, those events which resulted in death, or were otherwise classified as serious will be presented in a separate listing. In addition, the summary of AEs will be presented by severity and relationship to trial medication.

The change in cardiac size, and size of kidney and spleen will be assessed at the 6-month CA visit via echocardiogram and abdominal ultrasound, respectively. These data will be analyzed as a binary response (ie, normal/abnormal) and summarized using frequency count. The number and proportion of patients with each category (ie, normal/abnormal) for each of these safety endpoints will be summarized by treatment group.

In addition, the 2-sided 95% CI for the proportion of patients with a normal status for each of the endpoints will be estimated by treatment group.

Physical examinations findings will be summarized descriptively.

10.8 Statistical/Analytical Issues

10.8.1 Adjustment for Covariates

If any baseline data are imbalanced and are considered to be clinically relevant, between-group comparisons for efficacy outcomes will be adjusted for covariates and detailed in the SAP.

10.8.2 Handling of Dropouts or Missing Data

Handling of missing data rules will be described in the SAP.

10.8.3 Interim Analyses and Data Monitoring

An interim analysis will be performed after all data from all enrolled subjects in this study have either completed 2-year follow-up (24-month visit) assessments or have prematurely withdrawn from the study (before completing 2 years of follow-up) has been entered into the database, queried and discrepancies resolved. A full 2-year study report based on these data, including efficacy and safety endpoint analyses, will be completed.

Additionally, descriptive analyses of the data at other time points before study completion may be performed for safety monitoring, regulatory reporting or general planning purposes.

10.8.4 Multiple Comparisons/Multiplicity

Not applicable.

10.8.5 Sensitivity Analyses

Sensitivity analyses for the efficacy outcomes will be detailed in the SAP, as necessary.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

Before initiation of the study, the Investigators must provide the Sponsor with a completed Form FDA 1572 and Investigator Agreement. Curriculum vitae must be provided for the Investigators and sub-investigators listed on Form FDA 1572 or Investigator Agreement.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, and their study related duties and functions. The Investigator must maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study related duties.

11.2 Institutional Review Board or Independent Ethics Committee Approval

Before initiation of the study, the Investigator must provide the Sponsor with a copy of the written IRB/IEC/REB approval of the protocol and the informed consent form. This approval must refer to the informed consent form and to the study title, study number, and version and date of issue of the study protocol, as given by the Sponsor on the cover page of the protocol.

Status reports must be submitted to the IRB/IEC/REB at least once per year. The IRB/IEC/REB must be notified of completion of the study. Within 3 months of study completion or termination, a final report must be provided to the IRB/IECREB. A copy of these reports will be sent to the study clinical monitor. The Investigators must maintain an accurate and complete record of all submissions made to the IRB/IEC, including a list of all reports and documents submitted. AEs which are reported to the US (FDA or other Regulatory agencies (Safety Reports) must be submitted promptly to the IRB/IEC/REB.

11.3 Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigators abide by good clinical practice (GCP) as described in the 21 CFR Parts 50, 56, and 312 and the International Conference on Harmonization (ICH) GCP Guidelines Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

11.4 Subject Information and Consent

Before enrolling in the clinical study, the subject or the subject's parent(s) or legally authorized representative(s) must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her.

An informed consent form (assent form if applicable) that includes information about the study will be prepared and given to the subject or the subject's parent(s) or legally authorized representative(s). This document will contain all FDA and ICH-required elements.

The informed consent (or assent) form must be in a language understandable to the subject or the subject's parent(s) or legally authorized representative(s) and must specify who informed the subject, the subject's parent(s), or the subject's legally authorized representative(s).

After reading the informed consent document, the subject or the subject's parent(s) or legally authorized representative(s) must give consent in writing. Consent must be confirmed at the time of consent by the personally dated signature of the subject, the subject's parent(s) or the subject's legally authorized representative(s) and by the personally dated signature of the person conducting the informed consent discussions.

If the subject or the subject's parent(s) or legally authorized representative(s) is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the subject or by a local legally recognized alternative (eg, the subject's thumbprint or mark) or by the personally dated signature of the subject's parent(s) or the subject's legally authorized representative. The witness and the person conducting the informed consent discussions must also sign and personally date the informed consent document. It should also be recorded and dated in the source document that consent was given.

A copy of the signed and dated consent document(s) must be given to the subject or the subject's parent(s) or legal representative(s). The original signed and dated consent document will be retained by the Investigator.

The Investigator will not undertake any measures specifically required solely for the clinical study until valid consent has been obtained.

A model of the informed consent form to be used in this study will be provided to the sites separately from this protocol.

11.5 Subject Confidentiality

Subject names will not be supplied to the Sponsor. Only the subject number - will be recorded in the eCRF, and if the subject name appears on any other document, it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be told that representatives of the Sponsor, a designated CRO, the IRB/IEC/REB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. The Investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

11.6 Study Monitoring

Monitoring procedures that comply with current Good Clinical Practice (GCP) guidelines will be followed. Review of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by the Sponsor or its designee. Monitoring will be performed by a representative of the Sponsor (Clinical Study Monitor) who will review the eCRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and communications (letter, telephone, and facsimile).

11.7 Case Report Forms and Study Records

11.7.1 Case Report Forms

Electronic case report forms (eCRFs) are provided for each subject. All forms must be filled out by authorized study personnel. All corrections to the original eCRF entry must indicate the reason for change. The Investigator is required to sign the eCRF after all data have been captured for each subject. If corrections are made after review and signature by the Investigator, he or she must be made aware of the changes, and his or her awareness documented by resigning the eCRF.

11.7.2 Critical Documents

Before the Sponsor initiates the trial (ie, obtains informed consent from the first subject), it is the responsibility of the Investigator to ensure that the following documents are available to Sponsor or their designee:

- Completed FDA Form 1572 (Statement of Investigator), signed, dated, and accurate
- Curricula vitae of Investigator and sub-investigator(s) (current, dated and signed within 12 months of study initiation)
- Copy of Investigator and sub-investigator(s) current medical license (indicating license number and expiration date)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/IEC/REB clearly identifying the documents reviewed by name, number and date of approval or re approval: protocol, any amendments, Subject Information/Informed Consent Form, and any other written information to be provided regarding subject recruitment procedures
- Copy of IRB/IEC/REB approved Subject Information/Informed Consent Form/any other written information/advertisement (with IRB approval stamp and date of approval)

- Current list of IRB/IEC/REB Committee members/constitution (dated within 12 months prior to study initiation)
- Financial Disclosure Form signed by Investigator and sub-investigator(s)
- Current laboratory reference ranges (if applicable)
- Certification/QA scheme/other documentation (if applicable)

Regulatory approval and notification as required must also be available; these are the responsibility of Shire.

11.8 Data Monitoring Committee

Given that any long-term safety signal observed in this study could impact the safety profile of rhIGF-1/rhIGFBP-3 as administered in premature neonates being enrolled in the antecedent study (ROPP-2008-01, Section D), the Data Monitoring Committee (DMC) for Study ROPP-2008-01 will review safety data from this long-term outcome study.

11.9 Protocol Violations/Deviations

The Investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the IRB/IEC/REB and the appropriate regulatory authorities, where applicable, have given approval/favorable opinion. Modifications to the protocol will not be made without agreement of the Sponsor. Changes to the protocol will require written IRB/IEC/REB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB/IEC/REB may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC/REB. The Sponsor will submit all protocol modifications to the regulatory authorities, where applicable, in accordance with the governing regulations.

A record of subjects screened, but not entered into the study, is also to be maintained. No protocol exemption will be granted for this study.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Sponsor or its designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will need to be reviewed by the medical monitor and may also be required to be submitted to the IRB/IEC/REB.

Protocol modifications will only be initiated by the Sponsor and must be approved by the IRB/IEC/REB and submitted to the FDA or other applicable international regulatory authority before initiation, if applicable.

11.10 Premature Closure of the Study

If the Sponsor, Investigator, or regulatory authorities discover conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable subject risk, the study may be terminated after appropriate consultation between the Sponsor and the Investigator(s). In addition, a decision on the part of the Sponsor to suspend or discontinue development of the investigational product may be made at any time. Conditions that may warrant termination of the study or site include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study
- Failure of the Investigator to comply with pertinent global regulations
- Submission of knowingly false information from the study site to the Sponsor or other pertinent regulatory authorities
- Insufficient adherence by the Investigator to protocol requirements

11.11 Access to Source Documentation

Regulatory authorities, the IRB/IEC/REB, or the Sponsor may request access to all source documents, eCRFs, and other study documentation for onsite audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Monitoring and auditing procedures that comply with current GCP guidelines will be followed. On-site review of the eCRFs for completeness and clarity, crosschecking with source documents, and clarification of administrative matters may be performed.

11.12 Data Generation and Analysis

The clinical database will be developed and maintained by a contract research organization or an electronic data capture technology provider as designated by the Sponsor. The Sponsor or its designee will be responsible for performing study data management activities.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medication will be coded using WHO-Drug Dictionary (WHO-DD). Central reads will be employed as described in the study manual to aid in consistent measurement of abdominal ultrasound and echocardiogram parameters.

11.13 Retention of Data

Essential documents should be retained until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The Sponsor will notify the Investigator if these documents must be retained for a longer period of time. It is the responsibility of the Sponsor to inform the Investigator or institution as to when these documents no longer need to be retained.

11.14 Financial Disclosure

The Investigator should disclose any financial interests in the Sponsor as described in 21 CFR Part 54 prior to beginning this study. The appropriate form will be provided to the Investigator by the Sponsor, which will be signed and dated by the Investigator, prior to the start of the study.

11.15 Publication and Disclosure Policy

All information concerning the study material, such as patent applications, manufacturing processes, basic scientific data, and formulation information supplied by the Sponsor and not previously published are considered confidential and will remain the sole property of the Sponsor. The Investigator agrees to use this information only in accomplishing this study and will not use it for other purposes.

It is understood by the Investigator that the information developed in the clinical study may be disclosed as required to the authorized regulatory authorities and governmental agencies. In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the Sponsor with complete test results and all data developed in the study in a timely manner.

The Investigator and any other study personnel associated with this study will not publish the results of the study, in whole or in part, at any time, unless they have consulted with the Sponsor, provided the Sponsor a copy of the draft document intended for publication, and obtained the Sponsor's written consent for such publication. All information obtained during the conduct of this study will be regarded as confidential.

12 LIST OF REFERENCES

1. Maida JM, Mathers K, Alley CL. Pediatric ophthalmology in the developing world. Current opinion in ophthalmology 2008;19:403-8.
2. O'Connor AR, Stephenson TJ, Johnson A, et al. Visual function in low birthweight children. The British journal of ophthalmology 2004;88:1149-53.
3. Keith CG, Kitchen WH. Ocular morbidity in infants of very low birth weight. The British journal of ophthalmology 1983;67:302-5.
4. Laws D, Shaw DE, Robinson J, Jones HS, Ng YK, Fielder AR. Retinopathy of prematurity: a prospective study. Review at six months. Eye 1992;6:477-83.
5. O'Connor AR, Stephenson T, Johnson A, et al. Long-term ophthalmic outcome of low birth weight children with and without retinopathy of prematurity. Pediatr 2002;109:12-8.
6. Schaffer DB, Quinn GE, Johnson L. Sequelae of arrested mild retinopathy of prematurity. Archives of ophthalmology 1984;102:373-6.
7. Cats BP, Tan KE. Prematures with and without regressed retinopathy of prematurity: comparison of long-term (6-10 years) ophthalmological morbidity. Journal of pediatric ophthalmology and strabismus 1989;26:271-5.
8. Chard T. Insulin-like growth factors and their binding proteins in normal and abnormal human fetal growth. Growth Regul 1994;4:91-100.
9. Hansen-Pupp I, Lofqvist C, Polberger S, et al. Influence of insulin-like growth factor I and nutrition during phases of postnatal growth in very preterm infants. Pediatr Res 2011;69:448-53.
10. Ohkawa N, Shoji H, Kitamura T, et al. IGF-I, leptin and active ghrelin levels in very low birth weight infants during the first 8 weeks of life. Acta Paediatr 2010;99:37-41.
11. Lofqvist C, Hellgren G, Niklasson A, Engstrom E, Ley D, Hansen-Pupp I. Low postnatal serum IGF-I levels are associated with bronchopulmonary dysplasia (BPD). Acta Paediatr 2012;101:1211-6.
12. Ishii DN, Glazner GW, Whalen LR. Regulation of peripheral nerve regeneration by insulin-like growth factors. Annals of the New York Academy of Sciences 1993;692:172-82.
13. Lewis ME, Neff NT, Contreras PC, et al. Insulin-like growth factor-I: potential for treatment of motor neuronal disorders. Experimental neurology 1993;124:73-88.
14. Pediatric Ophthalmology/Strabismus Preferred Practice Pattern Development Process and Participants. Pediatric Eye Evaluations: American Academy of OphthalmologyPediatric Ophthalmology/Strabismus Preferred Practice Pattern Panel; 2012.

[redacted]

[redacted]

19. Wechsler D. Wechsler preschool and primary scale of intelligence 4th ed. Bloomington, MN: Pearson; 2012.
20. Wechsler D. Technical and Interpretive Manual Supplement: Special Group Validity Studies With Other Measures2012.
21. Achenbach T, Rescorla L. Manual for the ASEBA preschool forms and profiles. Burlington, VT: University of Vermont; 2000.
22. Vinall J, Miller SP, Synnes AR, Grunau RE. Parent behaviors moderate the relationship between neonatal pain and internalizing behaviors at 18 months corrected age in children born very prematurely. Pain 2013;154:1831-9.
23. Scott MN, Taylor HG, Fristad MA, et al. Behavior disorders in extremely preterm/extremely low birth weight children in kindergarten. J Dev Behav Pediatr 2012;33:202-13.
24. Wu YC, Leng CH, Hsieh WS, et al. A randomized controlled trial of clinic-based and home-based interventions in comparison with usual care for preterm infants: Effects and mediators. Res Dev Disabil 2014;35:2384-93.
25. Ebesutani C, Bernstein A, Nakamura BJ, Chorpita BF, Higa-McMillan CK, Weisz JR. Concurrent Validity of the Child Behavior Checklist DSM-Oriented Scales: Correspondence with DSM Diagnoses and Comparison to Syndrome Scales. Journal of psychopathology and behavioral assessment 2010;32:373-84.
26. DuPaul G, Power T, Anastopoulos A, Reed R. The ADHD rating scale IV: checklists, norms and clinical interpretation. New York: Guilford Press; 1998.
27. Rutter M, Bailey A, Lord C. Manual for the Social Communication Questionnaire2003.
28. Chandler S, Charman T, Baird G, et al. Validation of the social communication questionnaire in a population cohort of children with autism spectrum disorders. Journal of the American Academy of Child and Adolescent Psychiatry 2007;46:1324-32.
29. Gosselin J, Amiel-Tison C. Neurological Assessment from Birth to 6 Years. 2nd ed. Montreal: CHU Sainte-Justine; 2011.
30. Matza LS, Swensen AR, Flood EM, Secnik K, Leidy NK. Assessment of health-related quality of life in children: a review of conceptual, methodological, and regulatory issues. Value Health 2004;7:79-92.
31. Varni JW, Burwinkle TM, Lane MM. Health-related quality of life measurement in pediatric clinical practice: an appraisal and precept for future research and application. Health Qual Life Outcomes 2005;3:34.

32. Constitution of the World Health Organization: basic document. Geneva, Switzerland: World Health Organization; 1948.

33. Varni JW, Limbers CA. The pediatric quality of life inventory: measuring pediatric health-related quality of life from the perspective of children and their parents. Pediatr Clin North Am 2009;56:843-63.

34. Varni JW, Limbers CA, Neighbors K, et al. The PedsQL Infant Scales: feasibility, internal consistency reliability, and validity in healthy and ill infants. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2011;20:45-55.

35. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Medical care 2001;39:800-12.

36. Saigal S, Rosenbaum P, Stoskopf B, et al. Development, reliability and validity of a new measure of overall health for pre-school children. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2005;14:243-57.

37. Rosenbaum DM, Korngold E, Teele RL. Sonographic assessment of renal length in normal children. Am J Roentgenol 1984;142:467-9.

38. Rosenberg HK, Markowitz RI, Kolberg H, Park C, Hubbard A, Bellah RD. Normal splenic size in infants and children: sonographic measurements. Am J Roentgenol 1991;157:119-21.

39. Stevens TP, Finer NN, Carlo WA, et al. Respiratory Outcomes of the Surfactant Positive Pressure and Oximetry Randomized Trial (SUPPORT). J Pediatr 2014;165:240-9.e4.

40. Zivanovic S, Peacock J, Alcazar-Paris M, et al. Late outcomes of a randomized trial of high-frequency oscillation in neonates. N Engl J Med 2014;370:1121-30.

Appendix 1 Study Schedule of Events

Procedures	Initial Study Visit[e]	Months (CA)						Years (CA)					
	40 weeks (CA)/term equivalent	3[f] ± 2 wks	6 ± 1 mth	12 ± 3 mths	20 -1 mth[g]	24 ± 3 mth	30[f] ± 3 mth	3[f] ± 3 mths	3.5[f] ± 3 mth	4[f] ± 3 mths	4.5[f] ± 3 mth	4.75 -1 mth[g]	5 + 6 mths
Informed Consent	•												
Eligibility Criteria	•												
Demographics	•												
Visual acuity[a]			•	•	•	•						•	•
Corrective lens determination[h]				•	•[g]							•[g]	
Ocular alignment and motility				•		•							•
Refraction with cycloplegia[h]			•										
Stereoacuity													•
Length			•	•		•							
Height													•
Weight			•	•		•							•
Head Circumference			•	•		•							
BSID-III				•		•							
WPPSI													•
CBCL						•							•
VABS-II			•	•		•							•
ADHD-RS													•
SCQ													•
Physical Examination including tonsil examination			•	•		•							•
Blood Pressure, Heart Rate, and Respiratory Rate													•
Cerebral Palsy Assessment						•							
Hearing Assessment History[b]			•										•
Pulmonary Morbidity Assessment 1			•	•									
Pulmonary Morbidity Assessment 2 (clinical site visit)						•							•
Pulmonary Morbidity Assessment (phone interview)							•	•	•	•	•		

Procedures	Initial Study Visit[e]	Months (CA)						Years (CA)					
	40 weeks (CA)/term equivalent	3[f] ± 2 wks	6 ± 1 mth	12 ± 3 mths	20 -1 mth[g]	24 ± 3 mth	30[f] ± 3 mth	3[f] ± 3 mths	3.5[f] ± 3 mth	4[f] ± 3 mths	4.5[f] ± 3 mth	4.75 -1 mth[g]	5 + 6 mths
Survival assessment		•	•	•		•	•	•	•	•	•		•
[redacted]	[redacted]												
Cerebral MRI													•
HRQoL[c]		•	•[i]	•[i]		•[i]		•		•			•[i]
HCRU		•	•[i]	•[i]		•[i]		•		•			•[i]
HSCS-PS						•[i]		•		•			•[i]
Abdominal Ultrasound			•										
Echocardiogram			•										
Assessment of Participation in Other Clinical Studies		•	•	•		•	•	•	•	•	•		•
Medications		•	•	•		•	•	•	•	•	•		•
Adverse events[d]	•[j]	•	•	•		•	•	•	•	•	•		•

Abbreviations: ADHD-RS = Attention-Deficit/Hyperactivity Disorder Rating Scale; BSID-III = Bayley Scales of Infant and Toddler Development-Third Edition, CBCL = Child Behavior Checklist; CA = corrected age; HCRU = health care resource use; HRQoL = health-related quality of life; HSCS-PS = Health Status Classification System; mth(s) = months; [redacted]; PedsQL = Pediatric Quality of Life Inventory; SCQ = Social Communication Questionnaire; VABS-II = Vineland Adaptive Behavior Scales, Second Edition; wks = weeks; WPPSI = Wechsler Preschool and Primary Scale of Intelligence

[a] The tools used to assess visual acuity will change as the subject ages during their participation in the study. The tools that will be used in this study and are summarized by applicable study visit in Table A1.

[b] Historical hearing test data may be recorded at any time during the study prior to the 6-month visit.

[c] HRQoL will be assessed via the validated PedsQL™ scales appropriate for the child's age of development as specified in the Study Operations Manual.

[d] Adverse event collection will include an assessment of the specified targeted medical events.

[e] The Initial Visit may be performed prior to 40 weeks CA for any subject who discontinued from Study ROPP-2008-01 and, for all subjects, any time after 40 weeks CA, up to the study visit to occur at 3 months CA.

[f] Visits at 3 months, 30 months, 3 years, 3.5 years, 4 years, and 4.5 years CA will be conducted by telephone.

[g] The 20-month visit and the 4.75-year (4 years, 9 months) visit must occur at least 1 month prior to the 24-month and 5-year visits, respectively. Any prescribed corrective lenses must be worn for at least 1 month prior to the 24-month and 5-year assessments.

[h] Refraction with cycloplegia will be performed as part of the corrective lens determination procedure.

Procedures	Initial Study Visit[e]	Months (CA)						Years (CA)					
	40 weeks (CA)/term equivalent	3[f] ± 2 wks	6 ± 1 mth	12 ± 3 mths	20 -1 mth[g]	24 ± 3 mth	30[f] ± 3 mth	3[f] ± 3 mths	3.5[f] ± 3 mth	4[f] ± 3 mths	4.5[f] ± 3 mth	4.75 -1 mth[g]	5 + 6 mths

[i] The HRQoL, HCRU, and HSCS-PS assessments for the 6-month, 12-month, 24-month and 5-year visits may be performed through clinical site staff if there are time constraints during the on-site visit. At the 3-month, 3-year, and 4-year visits, these assessments will be performed through clinical site staff and may be performed at any time within the visit window.

[j] The following, collected as part of the ROPP-2008-01 study, will be used as part of this study (SHP-607-201): any ongoing targeted medical events regardless of causality and any ongoing study drug-related AEs, including SAEs.

Table A1 Summary of Visual Acuity Assessments

Visual Acuity Assessment Tool	Description	Unit of Measure	Applicable Age/Study Visit (CA)
Teller acuity cards	Resolution acuity – discrimination of a grating optotype from a background with the same mean luminance	cycles per degree	6 months 12 months
LEA Symbols Test	Recognition acuity - tests recognition of 4 optotypes	Snellen fraction (eg, 20/20)	24 months[a]
LEA Symbols (ETDRS-style) chart	Distance visual acuity test	Snellen fraction (eg, 20/20)	5 years[a]

Abbreviations: CA = corrected age; ETDRS = Early Treatment of Diabetic Retinopathy Study

[a] At ages 24 months and 5 years CA an attempt should be made to assess visual acuity by the LEA Symbols Test and LEA Symbols Chart, respectively. If during this attempt, the examiner determines that it will not be possible to perform an accurate assessment with the relevant LEA tool, visual acuity should be assessed with the Teller acuity cards.

Appendix 2 Summary of Changes

Description of Change	Section(s) Affected
Added hearing assessment history to the 6-month CA visit.	Section 7.6.2
Added language explaining that cerebral magnetic resonance imagining (MRI) procedures are optional. Language was also added explaining that the nature, scope, risks, benefits, and potential sedation associated with cerebral MRI will be explained to the subject and subject's parent(s) or legally authorized representative(s).	Section 7.6.6
Added cerebral MRI to the 5-year CA visit.	Section 7.6.6 Section 8.2.2.1 Appendix 1
Added medications, survival assessment, assessment of participation in other clinical studies and adverse events, including targeted medical events to the 30 months, 3.5 years, 4.5 years CA visits conducted by telephone.	Section 8.2.1 Appendix 1
Clarified that age equivalent scores and standard scores will be summarized for Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III), Wechsler Preschool and Primary Scale of Intelligence (WPPSI), and Vineland Adaptive Behavior Scales, Second Edition (VABS-II).	Section 10.5.2
Removed the pulmonary morbidity assessments from the appendices as they will be provided in the Study Operations Manual.	Section 7.6.5 (formerly) Appendix 2, (formerly) Appendix 3, (formerly) Appendix 4
Administrative errors were corrected throughout the protocol.	All sections

Appendix 3 Protocol Signature Page

Study Title:	Long-term Outcome of Children Enrolled in Study ROPP-2008-01 Previously Treated with rhIGF-1/rhIGFBP-3 for the Prevention of Retinopathy of Prematurity (ROP) or Who Received Standard Neonatal Care
Study Number:	SHP-607-201
Final Date:	11 May 2017
Version	Amendment 3

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signatory:

Investigator

_____
Signature **Date**

_____
Printed Name

I have read and approve the protocol described above.

Signatory:

Shire Medical Monitor

[redacted] 11 May 2017
Signature **Date**

[redacted] MD, MPH
Printed Name

Clinical Trial Protocol: SHP-607-201

Study Title:	Long-term Outcome of Children Enrolled in Study ROPP-2008-01 Previously Treated with rhIGF-1/rhIGFBP-3 for the Prevention of Retinopathy of Prematurity (ROP) or Who Received Standard Neonatal Care
Study Number:	SHP-607-201
Study Phase:	II
Product Name:	Mecasermin rinfabate (rhIGF-1/rhIGFBP-3)
IND Number:	121698
EUDRACT Number	2014-003556-31
Indication:	Retinopathy of Prematurity
Investigators:	Multicenter
Sponsor:	Premacure AB, A Member of the Shire Group of Companies
Sponsor Contact:	300 Shire Way Lexington, MA 02421 USA [redacted]
Medical Monitor:	[redacted], MD, MPH [redacted]

	Date
Original Protocol:	27 August 2014
Amendment 1	19 February 2016
Amendment 2	21 February 2017
Amendment 3	11 May 2017
Amendment 4	09 April 2018

Confidentiality Statement

SYNOPSIS

Sponsor:

Premacure AB, A Member of the Shire Group of Companies

Name of Finished Product:

Mecasermin rinfabate (rhIGF-1/rhIGFBP-3)

Study Title:

Long-term Outcome of Children Enrolled in Study ROPP-2008-01 Previously Treated with rhIGF-1/rhIGFBP-3 for the Prevention of Retinopathy of Prematurity (ROP) or Who Received Standard Neonatal Care

Study Number:

SHP-607-201

Study Phase: II

Investigational Product, Dose, and Mode of Administration:
Not applicable.

Primary Objectives

The primary objectives of this study are:

- To evaluate the long-term efficacy outcomes following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D) as assessed by ROP associated visual outcomes
- To evaluate the long-term safety outcomes following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D)

Secondary Objectives

The secondary objectives of this study are to evaluate the effect following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D) on:

- Growth parameters
- Cognitive development
- Physical development
- Child behavior
- Pulmonary morbidity
- Survival
- Health-related quality of life (HRQoL)
- Health utility
- Health care resource use (HCRU)

Exploratory Objectives

[redacted]

- [redacted]

- [redacted]

Study Endpoints

The primary efficacy endpoints of this study are:

- Visual acuity as assessed by an age appropriate method
- Ocular alignment and ocular motor examination in primary gaze and in as many of 9 positions of gaze as possible as assessed by corneal light reflex and by the cover test
- Assessment of nystagmus by observation
- Refraction as assessed by retinoscopy with cycloplegia
- Stereoacuity as assessed with the Lang Stereotest

The secondary efficacy endpoints of this study are:

- Growth parameters including body weight, body length (or height), and head circumference
- Cognitive development as assessed by the following standardized, age-appropriate tools:
    - Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)
    - Wechsler Preschool and Primary Scale of Intelligence (WPPSI)
- Physical development as assessed by the following standardized, age appropriate tools:
    - Physical exam
    - Neurological examination for assessment of cerebral palsy
    - Hearing assessment
    - Blood pressure, heart rate, and respiratory rate
- Child behavior as assessed by the following:
    - Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
    - Child Behavior Checklist (CBCL; 1 ½ to 5)
    - Attention Deficit/Hyperactivity Disorder Rating Scale (ADHD RS) for the assessment of symptoms of attention deficit/hyperactivity disorder (ADHD)
    - Social Communication Questionnaire (SCQ) for screening of Autism Spectrum Disorder (ASD)
- Pulmonary morbidity data (eg, hospitalizations, emergency room [ER] visits, pulmonary medications)
- Survival as assessed by death during the study due to any cause

The exploratory efficacy endpoints of this study are:

- [redacted]
- [redacted]

The health economic outcome research endpoints of this study are:

- Health-related quality of life (HRQoL) 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, respectively)

- Health status (eg, health utility) will be measured by the Health Status Classification System-Preschool (HSCS-PS) and the Health Utilities Index Mark 2 (HUI2) and Mark 3 (HUI3)
- Resource use associated with inpatient visits, outpatient visits, medical utilization and pharmacy utilization will be assessed

The safety endpoints of this study are:

- Physical examination including tonsil examination
- Adverse events (AEs), as follows:
    - those considered related to rhIGF-1/rhIGFBP-3 (as administered in Study ROPP-2008-01, Section D)
    - those considered related to procedures performed in this study (Study SHP-607-201)
    - specified targeted medical events regardless of causality
    - fatal SAEs regardless of causality
- Cardiac size as assessed by echocardiogram
- Kidney and spleen size and any other gross abnormalities as assessed by abdominal ultrasound

Study Population:

Subjects randomized in Study ROPP-2008-01, Section D are eligible to enroll in this study; completion of Study ROPP-2008-01 Section D is not required. Subjects in Study ROPP-2008-01 are premature infants (gestational age of 23 weeks + 0 days to 27 weeks + 6 days) who are randomized to receive either treatment with rhIGF-1/rhIGFBP-3 or standard neonatal care. Up to 120 subjects are planned to be randomized into Study ROPP-2008-01 Section D.

Study Design:

This is a Phase II, multicenter, long-term developmental outcome study enrolling subjects who were randomized in Section D of Study ROPP-2008-01. Enrolled subjects in this study will be followed through age 5 years corrected age (CA). This study will enroll both subjects who were in the treated (received rhIGF-1/rhIGFBP-3) and control (received standard neonatal care) groups of Study ROPP-2008-01 (Section D) to enable assessment of rhIGF-1/rhIGFBP-3 long-term efficacy and safety outcomes versus standard neonatal care. No investigational product will be administered in this study.

Study Duration:

Duration for an individual subject's participation in the study will vary depending upon age at enrollment, but subjects will not be followed beyond age 5.5 years corrected age (CA).

Study Inclusion and Exclusion Criteria:

Subjects randomized in Study ROPP-2008-01, Section D are eligible to enroll in this study. Subjects will not be excluded from participating in other clinical studies.

Efficacy Assessments:

Efficacy will be assessed by visual outcomes, growth parameters, cognitive development, physical development, child behavior, pulmonary morbidity, and survival.

Safety Assessments:

Safety will be assessed by physical examination (including tonsil examination), AEs (as specified), echocardiogram, and abdominal ultrasound.

Statistical Methods

Details regarding the statistical methods and definitions will be provided in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to database lock. All statistical analyses will be performed by the sponsor or CRO after the database is locked. Statistical analyses will be performed using Version 9.1 or higher of SAS® (SAS Institute, Cary, NC 27513).

Continuous variables will be summarized using descriptive statistics including the number of observations, 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 2 possible treatment assignments in the antecedent study, ROPP-2008-01, Section D (rhIGF-1/rhIGFBP-3 or standard neonatal care).

For analysis purposes, baseline is defined as the first assessment either in the antecedent study (ROPP-2008-01) or in this study (SHP-607-201). As necessary, relevant data from Study ROPP-2008-01 may be summarized with the data from this study (SHP-607-201).

Date of Original Protocol: 27 August 2014

Date of Amendment 1: 19 February 2016

Date of Amendment 2: 21 February 2017

Date of Amendment 3: 11 May 2017

Date of Amendment 4: 09 April 2018

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AAO	American Academy of Ophthalmology
ADHD	attention-deficit hyperactivity disorder
ADHD-RS	Attention-Deficit/Hyperactivity Disorder Rating Scale
AE	adverse event
ASD	Autism Spectrum Disorder
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
CBCL	Child Behavior Checklist (1 ½ to 5)
CFR	Code of Federal Regulations
CA	corrected age
CI	confidence interval
CRF	case report form (electronic)
CRO	contract research organization
DMC	data monitoring committee
eCRF	electronic case report form
EOS	end of study
ETDRS	Early Treatment of Diabetic Retinopathy Study
ER	emergency room
EU	European Union
FDA	Food and Drug Administration
FEV1	forced expiratory volume over 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
GH	growth hormone
HRQoL	health-related quality of life
HSCS-PS	Health Status Classification System-Preschool
HUI	Health Utilities Index
HUI2/3	Health Utilities Index Mark 2 and Mark 3
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IGF	insulin-like growth factor
IGFBP-3	insulin-like growth factor binding protein-3
IND	Investigational New Drug application
IRB	institutional review board
LV	left ventricle

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
OD	right eye
OS	left eye
OU	both eyes
PedsQL	Pediatric Quality of Life Inventory
REB	research ethics board
ROP	retinopathy of prematurity
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System©
SCQ	Social Communication Questionnaire
SD	standard deviation
SOE	schedule of events
SUSAR	suspected unexpected serious adverse reaction
UK	United Kingdom
US	United States
VABS-II	Vineland Adaptive Behavior Scales, Second Edition
VLBW	very low birth weight
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

1 INTRODUCTION

Retinopathy of prematurity (ROP) is a rare disorder of the developing retinal blood vessels and retinal neurons of the preterm infant and is one of the leading causes of preventable blindness in children.[1]

Visual acuity is decreased in infants with a history of ROP.[2] In addition to acuity, other aspects of eye health are also significantly impacted by ROP. Strabismus and myopia are clearly increased in patients with a history of ROP.[3-6] Additionally, more than half of patients at 6-10 years of age with a history of Stage 1 and Stage 2 ROP were reported to have ongoing visual issues.[7]

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. During fetal life, IGF-1 is available through placental absorption and ingestion from amniotic fluid.[8] Deprivation of such factors is likely to cause inhibition or improper stimulation of important pathways, which in the eye may cause abnormal retinal vascular development, the hallmark of ROP.

The finding in both a mouse model of ROP and preterm infants that development of ROP is associated with low levels of IGF-1 after premature birth, indicates a possible role for replacement of IGF-1 to levels found in utero as a strategy to potentially decrease abnormal retinal vascularization and abnormal retinal neural development, and ultimately, ROP.

Mecasermin rinfabate (rhIGF-1/rhIGFBP-3) is the human recombinant form of the naturally occurring protein complex of IGF-1 and insulin-like growth factor binding protein-3 (IGFBP-3). rhIGF-1/rhIGFBP-3 was developed to enhance the systemic exposure of administered rhIGF-1 and to improve the safety profile of rhIGF-1 therapy. rhIGF-1/rhIGFBP-3 was approved by the Food and Drug Administration (FDA) in 2005 for the treatment of growth failure in children with severe primary IGF-1 deficiency or with growth hormone (GH) gene deletions who have developed neutralizing antibodies to GH.

The pharmacokinetics and safety of rhIGF-1/rhIGFBP-3 have been evaluated in a Phase I study (ROPP-2005-01) and pharmacokinetics, safety, and efficacy were evaluated in the Phase II study (ROPP-2008-01). Section D of the ROPP-2008-01 study was conducted to assess pharmacokinetics, safety, and efficacy of rhIGF-1/rhIGFBP-3 for the prevention of ROP in premature infants (up to a corrected age [CA] of 40 weeks [± 4 days]). Subjects in Study ROPP-2008-01 were randomly assigned to receive rhIGF-1/rhIGFBP-3 or standard neonatal care. The target dose of rhIGF-1/rhIGFBP-3 for Study Section D was 250 µg/kg/24 hours to be administered via continuous infusion starting on Study Day 0 (day of birth) and continuing through postmenstrual age (gestational age + time elapsed from birth) 29 weeks + 6 days.

Although the rhIGF-1/rhIGFBP-3 therapy in Section D of the Phase II study (Study ROPP-2008-01) represented a short-term exposure (<2 months for each subject), rhIGF-1/rhIGFBP-3 may have long-lasting effects on visual outcomes as well as other potential outcomes related to complications of prematurity such as neurodevelopment, pulmonary function, and growth. In addition, it is critical to understand any long term safety effects from short term exposure to rhIGF-1/rhIGFBP-3.

The long-term outcomes assessed in this study will require utilization of different assessment tools than were utilized in the Phase II study, ROPP-2008-01 Section D, given the changes in physical and cognitive development that will occur in the subjects as they age during their participation in this study.

Please refer to the current edition of the Investigator's Brochure for further information concerning the safety and clinical development of rhIGF-1/rhIGFBP-3.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are:

- To evaluate the long-term efficacy outcomes following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D) as assessed by ROP-associated visual outcomes
- To evaluate the long-term safety outcomes following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D)

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate the effect following short-term exposure to rhIGF-1/rhIGFBP-3 versus standard neonatal care in Study ROPP-2008-01 (Section D) on:

- Growth parameters
- Cognitive development
- Physical development
- Child behavior
- Pulmonary morbidity
- Survival
- Health-related quality of life (HRQoL)
- Health utility
- Health care resource use (HCRU)

2.3 Exploratory Objectives

[redacted]

- [redacted]
- [redacted]

3 STUDY ENDPOINTS

3.1 Efficacy Endpoints

3.1.1 Primary Efficacy Endpoints

- Visual acuity as assessed by an age-appropriate method
- Ocular alignment and ocular motor examination in primary gaze and in as many of 9 positions of gaze as possible as assessed by corneal light reflex and by the cover test
- Assessment of nystagmus by observation
- Refraction as assessed by retinoscopy with cycloplegia
- Stereoacuity as assessed with the Lang Stereotest

3.1.2 Secondary Efficacy Endpoints

- Growth parameters including body weight, body length (or height), and head circumference
- Cognitive development as assessed by the following standardized, age-appropriate tools:
    - Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)
    - Wechsler Preschool and Primary Scale of Intelligence (WPPSI)
- Physical development as assessed by standardized, age appropriate tools including physical examination, neurological examination for assessment of cerebral palsy, and hearing assessment
- Child behavior as assessed by the following:
    - Vineland Adaptive Behavior Scales, Second Edition (VABS-II)
    - Child Behavior Checklist (CBCL; 1 ½ to 5)
    - Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS) for the assessment of symptoms of attention-deficit/hyperactivity disorder (ADHD)
    - Social Communication Questionnaire (SCQ) for screening of Autism Spectrum Disorder (ASD)
- Pulmonary morbidity data (eg, hospitalizations, emergency room [ER] visits, pulmonary medications)
- Survival as assessed by death during the study due to any cause

3.1.3 Exploratory Efficacy Endpoints

- [redacted]
- [redacted]

3.2 Health Economic Outcome Research Endpoints

- Health Related Quality of Life (HRQoL) 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, respectively)
- Health status (eg, health utility) will be measured by the Health Status Classification System-Preschool (HSCS-PS) and the Health Utilities Index Mark 2 (HUI2) and Mark 3 (HUI3).
- Resource use associated with inpatient visits, outpatient visits, medical utilization and pharmacy utilization will be assessed

3.3 Safety Endpoints

- Physical examination including tonsil examination
- Adverse events (AEs), as follows:
    - those considered related to rhIGF-1/rhIGFBP-3 (as administered in Study ROPP-2008-01, Section D)
    - those considered related to procedures performed in this study (SHP-607-201)
    - specified targeted medical events regardless of causality
    - fatal serious adverse events (SAEs) regardless of causality
- Cardiac size as assessed by echocardiogram
- Kidney and spleen size and any other gross abnormalities as assessed by abdominal ultrasound

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase II, multicenter, long-term developmental outcome study enrolling subjects who were randomized in Section D of Study ROPP-2008-01 to receive either rhIGF-1/rhIGFBP-3 (treated) or standard neonatal care (control). Enrolled subjects in this study will be followed through age 5 years CA. This study will enroll both subjects who were in the treated (received rhIGF-1/rhIGFBP-3) and control (received standard neonatal care) groups of Study ROPP-2008-01 (Section D) to enable assessment of rhIGF-1/rhIGFBP-3 long-term efficacy and safety outcomes versus standard neonatal care. No investigational product will be administered in this study.

In this study, the Initial Visit will occur at 40 weeks CA (ie, term equivalent) or upon discontinuation from Study ROPP-2008-01, or may occur any time until 2 years CA +3 months. Subjects are no longer eligible to participate in this study after they turn 2 years CA +3 months. Subjects in Study ROPP-2008-01 are premature infants enrolling at gestational age of 23 weeks +0 days to 27 weeks +6 days.

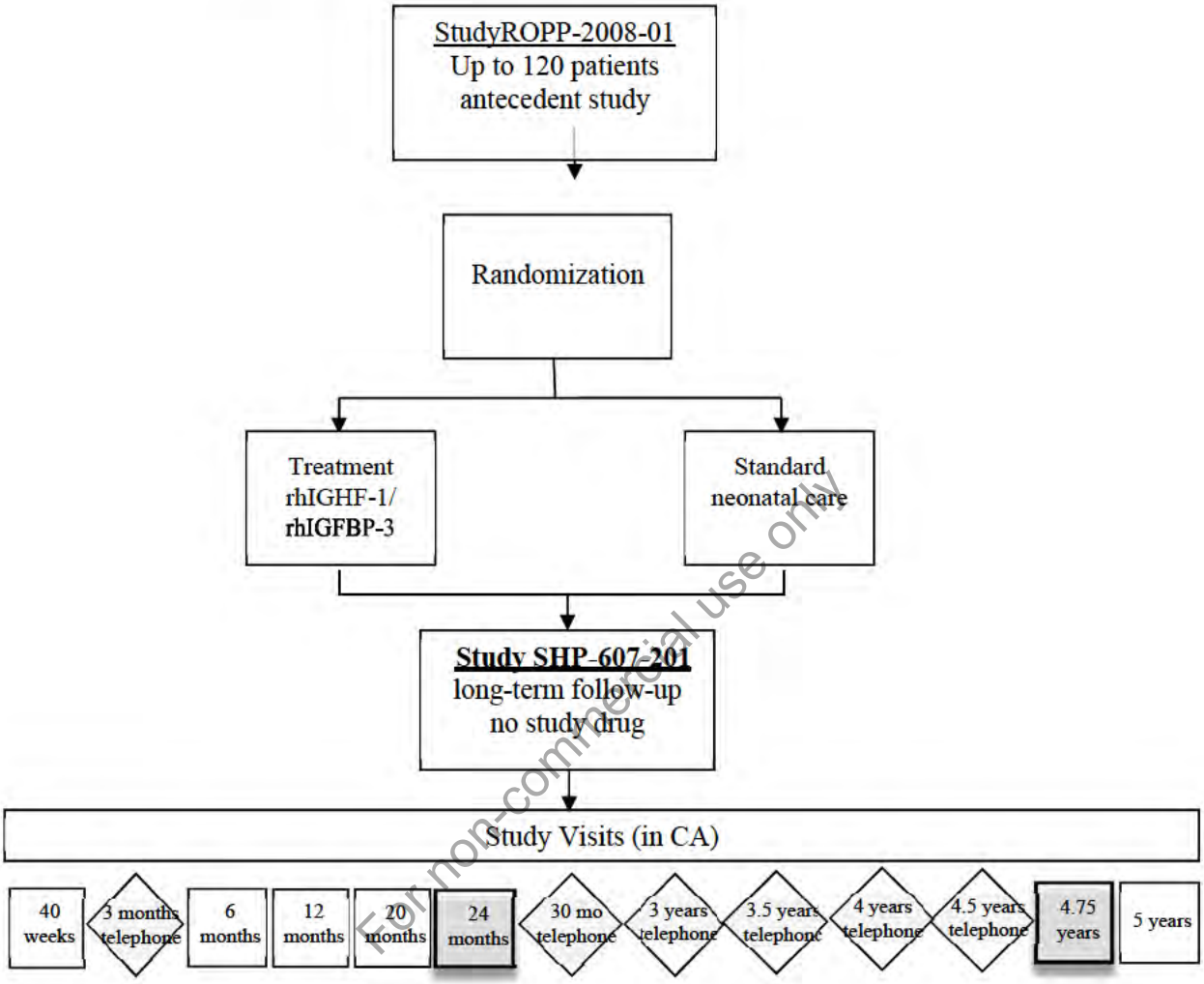
Time points for assessments have been chosen based on standard premature infant follow-up periods and represent important developmental ages for premature infant follow-up. Both telephone and clinical site visits are included to help maintain contact with subjects throughout the 5-year duration of the study.

Subjects will be evaluated at appropriate follow-up site locations with expertise in the assessment of the developmental outcomes of premature infants. Pediatric ophthalmology expertise will also be required.

See Appendix 1 for the Study Schedule of Events table.

The overall study design is outlined in Figure 4-1.

Figure 4-1 Overview of Study Design, Study SHP-607-201



Abbreviations: CA = corrected age

Note: Visits conducted by telephone are indicated with a diamond shape. Visits conducted at the study site are indicated with rectangles. Visit windows are provided in the Schedule of Events (Appendix 1).

4.2 Rationale for Study Design

The only approved therapies for ROP are ablative (cryotherapy or laser therapy). To date, there are no commercially available preventative treatments for ROP.

Although treatment with rhIGF-1/rhIGFBP-3 in ROPP-2008-01 (Section D) after premature birth is limited to less than 2 months of therapy, it remains important to assess the long-term outcomes of treatment on both efficacy and safety. Thus, this long-term follow-up study to Study ROPP-2008 01 (Section D) has been designed to assess long-term efficacy and safety outcomes following short-term exposure to rhIGF-1/rhIGFBP-3.

Insulin-like growth factor-1 (IGF-1) mediates its primary actions by binding to its specific receptor, the insulin-like growth factor 1 receptor (IGF-1R), which is present on many cell types in many tissues. Binding to its receptor initiates intracellular signaling including via the AKT signaling pathway. This pathway is involved in stimulation of cell division, growth and differentiation and inhibits programmed cell death. Specifically regarding premature infants, IGF-1 is an important mediator of fetal growth and has been shown to play a role in early postnatal growth following pre-term delivery.[9,10]

Insulin-like growth factor-1 (IGF-1) has also been shown to play a role in pulmonary development[11] and neural development.[12,13] Given the potential role for IGF-1 in the development of multiple systems, this study has been designed to evaluate the long-term effects of rhIGF-1/rhIGFBP-3, both from a safety and efficacy perspective, on the development of the premature infant.

4.3 Study Duration

Duration for an individual subject's participation in the study will vary depending upon age at enrollment, but subjects will not be followed beyond age 5.5 years CA.

5 STUDY POPULATION SELECTION

5.1 Study Population

Subjects randomized in Study ROPP-2008-01, Section D are eligible to enroll in this study; completion of Study ROPP-2008-01 Section D is not required. Subjects in Study ROPP-2008-01 are premature infants (gestational age of 23 weeks +0 days to 27 weeks +6 days) who are randomized to receive either treatment with rhIGF-1/rhIGFBP-3 or standard neonatal care. A total of 121 subjects were randomized in Study ROPP-2008-01 Section D.

5.2 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study.

1. Subject was randomized in Study ROPP-2008-01, Section D
2. Subject's parent or legally authorized representative(s) must provide written informed consent prior to performing any study-related activities. Study-related activities are any procedures that would not have been performed during normal management of the subject.

5.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study.

1. Any other condition or therapy that, in the Investigator's opinion, may pose a risk to the subject or interfere with the subject's ability to be compliant with this protocol or interfere with the interpretation of results
2. The subject or subject's parent or legally authorized representative(s) is unable to comply with the protocol as determined by the Investigator

6 STUDY TREATMENT

6.1 Description of Treatment

No investigational product will be administered in this study.

6.2 Treatments Administered

Not applicable.

6.3 Selection and Timing of Dose for Each Subject

Not applicable.

6.4 Method of Assigning Subjects to Treatment Groups

Not applicable.

6.5 Masking

Not applicable.

6.6 Medications

Any medications administered to the subjects will be collected from the time of informed consent through the 5-year CA visit (or until the subject withdraws or is discontinued). Any investigational product received by subjects will be recorded separately as part of an assessment of subjects' participation in other clinical studies (Section 7.11.1).

6.7 Restrictions

6.7.1 Prior Therapy

There are no restrictions related to prior therapy.

6.7.2 Other Restrictions

There are no restrictions related to fluid or food intake, or subject activity.

6.7.3 Treatment Compliance

Not applicable.

6.7.4 Packaging and Labeling

Not applicable.

6.8 Storage and Accountability

Not applicable

7 STUDY PROCEDURES

Detailed descriptions of subject procedures and evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of the study (see Schedule of Events in Appendix 1).

All data collected are to be recorded on the subject's appropriate eCRF.

Details for study procedures are described in the Operations Manual for this study.

7.1 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).

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 11.4. Documentation and filing of informed consent documents should be completed according to Section 11.4.

7.2 Study Entrance Criteria and Eligibility

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 does not occur at or before 40 weeks CA, the subject may still be enrolled until 2 years CA +3 months. Subjects are no longer eligible to participate in this study after they turn 2 years CA +3 months.

7.3 Study Enrollment

Subjects will be considered enrolled in the study once written informed consent has been obtained from the subject's parent(s) or legally authorized representative(s).

7.4 Demographics

Subject demographic information including gender, date of birth, and race will be recorded.

7.5 Growth Parameters: Length (and Height), Weight, and Head Circumference

7.5.1 Length and Height

Body length (supine measurement) will be collected when subjects are 24-months CA or younger. 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 when subjects are older than 24-months CA. 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).

7.5.2 Body Weight

Body weight will be collected. Calibrated scales should be utilized for body weight measures (type of scale will depend upon subject's age). Care should be taken to remove any extraneous clothing prior to measures and shoes should be removed.

The measure should be recorded to the nearest 0.1 kg.

7.5.3 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.

7.6 Efficacy Assessments

7.6.1 Visual Assessments

After corrective lens determination has occurred (Section 7.6.1.2), all visual assessments should be conducted with best-corrected vision, ie, with corrective lenses in place (if required); this applies to 24-month and 5-year visits.

7.6.1.1 Visual Acuity

Visual acuity is a measure of how well a subject sees at different distances. It will be assessed by the methods summarized in Table 7-1; the method employed will be selected based on the subject's age (CA) at the time of the study visit. Visual acuity measurements will be measured and recorded for the left (OS), right (OD) eye, and both eyes (OU).

At ages 6 months and 12 months CA, visual acuity will be assessed with Teller acuity cards. At ages 24 months and 5 years CA an attempt should be made to assess visual acuity by the LEA

Symbols Test and LEA Symbols Chart, respectively. If during this attempt, the examiner determines that it will not be possible to perform an accurate assessment with the relevant LEA tool, visual acuity should be assessed with the Teller acuity cards.

The visual acuity assessments should be performed by an optometrist or ophthalmologist trained in pediatrics.

Table 7-1 Summary of Visual Acuity Assessments

Visual Acuity Assessment Tool	Description	Unit of Measure	Applicable Age/Study Visit (CA)
Teller acuity cards	Resolution acuity – discrimination of a grating optotype from a background with the same mean luminance	cycles per degree	6 months 12 months
LEA Symbols Test	Recognition acuity - tests recognition of 4 optotypes	Snellen fraction (eg, 20/20)	24 months[a]
LEA Symbols (ETDRS-style) chart	Distance visual acuity test	Snellen fraction (eg, 20/20)	5 years[a]

Abbreviations: CA = corrected age; ETDRS = Early Treatment of Diabetic Retinopathy Study

[a] At ages 24 months and 5 years CA an attempt should be made to assess visual acuity by the LEA Symbols Test and LEA Symbols Chart, respectively. If during this attempt, the examiner determines that it will not be possible to perform an accurate assessment with the relevant LEA tool, visual acuity should be assessed with the Teller acuity cards.

7.6.1.2 Corrective Lens Determination

An assessment to determine if the subject requires vision correction with corrective lenses will be performed. This is being performed to ensure the accuracy of subjects' subsequent visual acuity assessments (at the 24-month and 5-year visits). The corrective lens determination will be performed according to the guidelines published by the American Academy of Ophthalmology (AAO).[14]

This assessment should be performed by an optometrist or ophthalmologist trained in pediatrics.

7.6.1.3 Ocular Alignment and Oculomotor Examination (Motility)

Ocular alignment will be assessed in primary gaze by comparing the position of the corneal light reflection in OS and OD (corneal light reflection assessment). Presence or absence of strabismus will be recorded in primary gaze and in as many of the 9 positions of gaze as feasible with the cover test assessment of refixation movement. Extraocular muscle over-action or deficiency will be recorded. The assessment will be performed according to the AAO guidelines.[14]

Presence or absence of nystagmus as observed during the ocular alignment assessments will also be recorded.

The assessment will be performed by a pediatric ophthalmologist or an ophthalmologist trained in the care of pediatric subjects with a history of premature birth. Degree of adherence to the AAO guidelines will be at the discretion of the examining physician in consideration of the need for patient cooperation.

Ocular motility refers to eye movements, which are governed by the 6 extraocular muscles in each eye. It will be assessed by examiner observation of the subject's ability to abduct, adduct, supra, and inferoduct each eye (to assess for strabismus). Any observed misalignment (strabismus classifications) will be recorded:

- esotropia
- exotropia
- hypertropia
- hypotropia

The frequency (constant or intermittent) with which any misalignment occurs and whether the turning eye is always the same eye or if it alternates between OS and OD, will be recorded. Extraocular muscle over-action or deficiency will be recorded.

This assessment should be performed by an optometrist or ophthalmologist trained in pediatrics.

7.6.1.4 Refraction with Cycloplegia

Refraction is a measure of the lens power required for a focused image on the retina. Refraction with cycloplegia will be measured and recorded in diopters for each eye individually (OS and OD).

Cycloplegia may be induced according to site standard practice.

This assessment should be performed by an optometrist or ophthalmologist trained in pediatrics.

7.6.1.5 Stereoacuity

Stereoacuity is a measure of depth perception and will be assessed using the Lang Stereotest and performed by certified personnel. The presence or absence of stereopsis will be recorded.

7.6.2 Hearing Assessment History

Results of previously completed hearing assessments will be recorded at the 6-month CA and 5-year CA visits; hearing tests are not being performed as part of this study.

7.6.3 Behavioral Assessments

7.6.3.1 Bayley Scales of Infant and Toddler Development, Third Edition

The BSID-III will be used to assess cognitive, motor, and language skills, and is applicable to children aged 1-42 months.

The BSID-III is an assessment tool designed to measure a young child's skills in the 3 core areas of development: cognitive, language, and motor. There are 5 subscales, the cognitive subscale stands alone while 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 examiner's manual.

The BSID-III 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.

7.6.3.2 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.[15] It is applicable to preschoolers and young children aged 2 years +6 months to 7 years +7 months, and is a direct assessment of a child's cognitive skills.

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[16] 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. Scores to be recorded are detailed in the Study Operations Manual.

7.6.3.3 Child Behavior Checklist (CBCL)

The CBCL (1 ½ to 5) is a parent-reported outcome measure used to assess behavioral, emotional, and social functioning of toddlers and preschool children aged 18-60 months.[17] It is composed of 99 items that are rated on a Likert scale and includes the following 7 syndrome scales arranged under 2 domains (ie, Internalizing and Externalizing Problems):[18]

- Internalizing Problems
- Emotionally Reactive

- Anxious/Depressed
- Somatic Complaints
- Withdrawn
- Sleep Problems
- Attention Problems
- Aggressive Behavior

The questionnaire is widely used and has been employed to assess long-term behavioral outcomes in children born prematurely, aged similarly to the subjects expected in this study population.[18-20] It is associated with well-established normative data;[21] norms may be selected to aid in interpretation of the scale scores.

The CBCL (1 ½ to 5) is a questionnaire that will be administered to 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.

7.6.3.4 Vineland Adaptive Behavior Scales, Second Edition

The VABS-II Expanded Interview Form will be used to measure the personal and social skills of subjects serially over time; these scales are organized within a 3-domain structure: Communication, Daily Living, and Socialization. In addition, the VABS-II offers a Motor Skills Domain and an optional Maladaptive Behavior Index. The VABS-II Expanded Interview Form assesses what a subject actually does, rather than what he or she is able to do.

The VABS-II Expanded Interview Form will be administered to 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.

7.6.3.5 Attention-Deficit/Hyperactivity Disorder Rating Scale

The ADHD-RS was developed to measure the behaviors of children with ADHD. The ADHD-RS consists of 18 items designed to reflect current symptomatology of ADHD based on DSM-IV 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,[22] will be completed by the subject's parent(s) or legally authorized representative(s). Scores to be recorded are detailed in the Study Operations Manual.

7.6.3.6 Social Communication Questionnaire – Lifetime Form

The SCQ is a brief instrument that helps evaluate communication skills and social functioning in children[23] that can be used for screening for autism or autism spectrum disorders in the general population.[24]

The SCQ will be completed by the subject's parent(s) or legally authorized representative(s). 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.

7.6.4 Cerebral Palsy Assessment

Comprehensive neurological examination for the diagnosis of cerebral palsy (CP) will be conducted. The Amiel-Tison neurological examination framework[25] will be utilized for this assessment and conducted by trained medical professionals.

7.6.5 Pulmonary Morbidity Assessment

Pulmonary morbidity will be assessed with questions related to family history and smoking status as well as diagnosis of select pulmonary symptoms, conditions and related hospitalizations. The assessment will be administered to the subject's parent(s) or legally authorized representative(s). Assessments will be performed as outlined in the Schedule of Events (see Appendix 1). Questionnaires that will be used for these assessments at clinical site visits are provided in the Study Operations Manual for the 6-month, 12-month, 24-month, and 5-year CA visits. The questionnaire that will be used for these assessments during phone interviews at the 30-month, 3-year, 3.5-year, 4-year, and 4.5-year CA visits is provided in the Study Operations Manual.

7.6.6 [redacted]

[redacted]

7.6.7 [redacted]

[redacted]

7.6.8 Survival Assessment

Survival status will be assessed and recorded.

7.6.9 Health Economic Outcome Research Assessments

7.6.9.1 Health Related Quality of Life

Health-related quality of life (HRQoL) is an important outcome towards improving the health care of pediatric patients as it is that part of a person's overall quality of life that is determined primarily by their health status and which can be influenced by clinical interventions. It is an important concept, which is also used in determining the value of health care services in this population.[26,27] It is a multidimensional construct whose content is guided by the World Health Organization;[28] minimally it includes physical, psychological (including emotional and cognitive), and social health dimensions.

In this study, HRQoL will be assessed via the validated Pediatric Quality of Life Inventory (PedsQL™) Scales appropriate for the child's age of development.[29-31] The development of the PedsQL was based on the delineations of the World Health Organization (WHO) and is a modular approach to assessing HRQoL in the pediatric population. Initially, the PedsQL Generic Scales were developed and continue to be used in children aged 2-18 years. More recently Infant Scales have been developed that apply to ages 1-24 months.[30]

The following scales will be used in this study:

- Infant Scale for ages 1-12 months (36 Items)
- Infant Scale for ages 13–24 months (45 Items)
- Toddler Scale for 2-4 years of age (21 Items)
- Young Child Scale for 5-7 years of age (23 Items)

The PedsQL will be administered to the subject's parent and may be conducted via telephone by clinical site staff. The scale(s) to be administered at each visit will be specified in the Study Operations Manual.

7.6.10 Health Care Resource Use

To understand the value of the investigational product administered in Study ROPP-2008-01 (Section D), the resource use associated with inpatient visits, outpatient visits, and medical and pharmacy utilization in this study will be recorded.

This assessment may be conducted via telephone by clinical site staff.

7.6.10.1 Health Utility

Health Status Classification System-Preschool

Health status (eg, health utility) will be measured by the Health Status Classification System-Preschool (HSCS-PS), which is a validated instrument adapted for use via parent proxy within the pediatric population age 2.5-5 (adapted from the validated Health Utilities Index Mark 2 and 3 [HUI2/3]).[32] Validity of the HSCS-PS concepts has not been established for ages younger than 2.5 years.

The HSCS-PS was developed to provide a consistent measure of health status in preschool-aged children who had been born prematurely.[32] The system is applicable to children with special needs as may be included in this study; validation cohorts for the system included children with very low birth weight (VLBW), which is congruent with this study population.

The instrument is composed of 12 dimensions (Vision, Hearing, Speech, Mobility, Dexterity, Self-care, Emotion, Learn/remember, Think/problem solve, Pain, General Health, and Behavior) intended to provide a comprehensive assessment of a child's health status as it pertains to health-related quality of life. The individual domains of the instrument will be scored as a mean score, representing the overall state for each concept individually. The global score will be recorded as well as the scores for each of the dimensions.

The HSCS-PS is a questionnaire that will be administered to the subject's parent(s) or legally authorized representative(s) and may be conducted via telephone by clinical site staff.

Health Utilities Index

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.[33] 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 Events.

7.7 Safety Assessments

7.7.1 Abdominal ultrasound

An abdominal ultrasound will be performed to assess the size of the spleen and kidneys. The spleen will be measured in the coronal longitudinal plane and the longest longitudinal length will be measured for each kidney (left and right).[35] Ultrasound results will be assessed by a central reader.

Organ size will be interpreted in the context of reference values established for children.[34,35]

7.7.2 Echocardiogram

Echocardiographic examination (conventional M-mode recording of the left ventricle [LV] parasternal long axis view) will be performed for the evaluation of cardiac size, assessed by measuring the following:

- interventricular septal thickness (during end diastole)
- LV posterior wall thickness
- LV intracavity volume (both in end diastole and end systole)

Echocardiogram results will be assessed by a central reader.

7.7.3 Physical Examination

Physical examinations will include a review of the subject's general appearance, neurological examination, as well as a tonsillar examination (Table 7-2). Adverse events will be collected as described in Section 7.9.1.1.

Table 7-2 Assessments for Physical Examinations

Assessment	Assessment
General appearance	Endocrine
Head and neck	Cardiovascular
Eyes	Abdomen
Ears	Genitourinary
Nose	Skin
Throat	Musculoskeletal
Chest and lungs	Neurological
Tonsils	

7.7.4 Blood Pressure, Heart Rate, and Respiratory Rate

Blood pressure, heart rate, and respiratory will be measured at the 5-year CA visit.

7.8 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 7.11.1).

7.9 Adverse Events Assessments

7.9.1 Definitions of Adverse Events, Serious Adverse Events, and Suspected Unexpected Serious Adverse Reactions

7.9.1.1 Adverse Event

An AE is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered investigational product-related. This includes an exacerbation of a pre-existing condition.

Adverse events include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study
- Intercurrent illnesses
- Drug interactions
- Events related to or possibly related to concomitant medications
- Abnormal laboratory values (this includes significant shifts from baseline within the range of normal that the Investigator considers to be clinically important)
- Clinically significant abnormalities in physical examination, vital signs, and weight

In this long-term outcome study in follow-up to Study ROPP-2008-01 (Section D), no investigational product is being administered. However, the relationship to the investigational product (rhIGF-1/rhIGFBP-3) as administered in Study ROPP-2008-01 (Section D) will be assessed.

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

- Those considered related to investigational product (rhIGF-1/rhIGFBP-3 as administered in Study ROPP -2008-01, Section D)
- Those considered related to procedures performed in this study (Study SHP-607-201)
- AEs related to ROP
- AEs related to congenital malformations not identified at birth which may impact neurocognitive development
- Additional illnesses present at the time when informed consent is given are to be regarded as AEs
- Specified targeted medical events (Section 7.9.1.4) regardless of causality

Throughout the study, the Investigator must record these AEs or any AEs resulting in death in the eCRF, regardless of the severity or causality. The Investigator should treat subjects with AEs appropriately and observe them at suitable intervals until the events stabilize or resolve. Adverse events may be discovered through observation or examination of the subject, questioning of the subject, complaint by the subject, or by abnormal clinical laboratory values.

7.9.1.2 Serious Adverse Event

An SAE is any AE that results in any of the following outcomes:

- Death
- Is life-threatening
- Requires hospitalization
- Requires prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect

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 one of the outcomes listed in this definition.

A life-threatening AE is defined as an AE that placed the subject, in the view of the initial reporter, at immediate risk of death from the AE as it occurred (ie, it does not include an AE that, had it occurred in a more severe form, might have caused death).

For the purposes of this study only the SAEs listed below will be collected:

- Fatal SAEs regardless of causality
- SAEs considered related to investigational product (rhIGF-1/rhIGFBP-3 as administered in Study ROPP-2008-01, Section D)
- SAEs considered related to procedures performed in this study (Study SHP-607-201)
- SAEs related to ROP
- SAEs related to congenital malformations not identified at birth which may impact neurocognitive development
- SAEs related to additional illnesses present at the time when informed consent is given
- Specified targeted medical events (Section 7.9.1.4) regardless of causality

7.9.1.3 Suspected Unexpected Serious Adverse Reaction

Suspected unexpected serious adverse reactions (SUSAR) are suspected adverse reactions related to an investigational product (investigational products and comparators [if applicable]), which occur in the concerned study, and that are both serious and unexpected according to the current Investigator's Brochure.

7.9.1.4 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, as appropriate, regardless of relationship to investigational product (rhIGF-1/rhIGFBP-3 as administered in Study ROPP-2008-01, Section D):

- intracranial hypertension
- any abnormality of glucose metabolism (eg, hypoglycemia, hyperglycemia, and diabetes)
- tonsillar hypertrophy (based on tonsil exam [part of the physical exam])
- increased kidney size
- increased cardiac size
- increased spleen size

7.9.2 Classification of Adverse Events and Serious Adverse Events

The severity of AEs will be assessed by the Investigator based on the definition indicated in Table 7-3. The severity of all AEs/SAEs should be recorded on the appropriate eCRF page to a severity of mild, moderate, or severe.

Table 7-3 Adverse Event Severity

Severity	Definition
Mild	No limitation of usual activities.
Moderate	Some limitation of usual activities.
Severe	Inability to carry out usual activities.

7.9.3 Clarification between Serious and Severe

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) and causality serve as a guide for defining regulatory reporting obligations.

7.9.4 Relatedness of Adverse Events and Serious Adverse Events

Relationship of an AE or SAE to investigational product (rhIGF-1/rhIGFBP-3 as administered in Study ROPP-2008-01, Section D) is to be determined by the Investigator based on the following definitions (See Table 7-4).

Table 7-4 Adverse Event Relatedness

Relationship to Product	Definition
Not Related	Unrelated to investigational product
Possibly Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, but which could also be explained by concurrent disease or other drugs or chemicals.
Probably Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on de-challenge. The association of the clinical event or laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds.
Definitely related	The event follows a reasonable temporal sequence from administration of the investigational product, follows a known or suspected response pattern to the investigational product, is confirmed by improvement upon stopping the investigational product (dechallenge), and reappears upon repeated exposure (rechallenge). Note that this is not to be construed as requiring re-exposure of the subject to investigational product; however, the determination of definitely related can only be used when recurrence of event is observed.

7.9.5 Procedures for Recording and Reporting Adverse Events

7.9.5.1 Adverse Event Monitoring and Period of Observation

Adverse events will be monitored throughout the study.

For the purposes of this study, the period of observation begins from the time at which the subject's parent(s) or legally authorized representative(s) gives informed consent until the subject's final evaluation of the study. When possible, subject's parents or legally authorized representative(s) should be consented at the end of study visit for the ROPP-2008-01. However, if this is not possible, subject's parents or legally authorized representative(s) will be asked to provide consent for any Serious Adverse Events that the subject experiences between ROPP-2008-01 end-of-study visit and the start of the SHP-607-201, to be reported by the Investigator. For safety purposes, the final evaluation will be defined as the last study visit when the subject is 5 years-old in CA.

If the Investigator considers it necessary to report an AE in a study subject after the end of the safety observation period, he or she should contact the Sponsor to determine how the AE should be documented and reported.

7.9.5.2 Reporting Serious Adverse Events

Any SAE meeting the reporting criteria for this study should be recorded by the clinical site on an SAE form. The SAE must be completely described on the subject's eCRF, including the judgment of the Investigator as to the relationship of the SAE to the investigational product. The Investigator will promptly supply all information identified and requested by the Sponsor (or contract research organization [CRO]) regarding the SAE.

The Investigator must report the SAE to the Shire Global Drug Safety Department AND to the local Shire Medical Monitor on an SAE form. This form must be completed and FAXED or EMAILED within 24 hours of the Investigator's learning of the event to:

Shire Global Drug Safety Department:

International FAX: [redacted] **OR United States FAX:** [redacted]

Email: [redacted]

AND

Shire Medical Monitor: [redacted], **MD, MPH**
E-mail: [redacted]

Any follow-up information must also be completed on an SAE form and faxed or emailed to the same numbers or emails listed above.

In the event of a severe and unexpected, fatal, or life-threatening SAE, the clinical site must contact the Shire Medical Monitor by telephone as soon as possible and within 24 hours of awareness; this is in addition to completing and transmitting the SAE form as stated above. The following provides contact information for the Shire Medical Monitor.

If an SAE is assessed as severe and unexpected, or life-threatening, contact:
[redacted], MD, MPH [redacted] Shire 650 East Kendall Street Cambridge, MA 02142 USA Telephone: [redacted] Mobile: [redacted] (24-hr access) E-mail: [redacted]

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

The Sponsor and the CRO are responsible for notifying the relevant regulatory authorities/US central IRBs/European Union (EU) central ECs of related, unexpected SAEs.

For some European regulatory authorities, these reports are submitted directly to Eudravigilance. In case of deaths or life-threatening SUSARs, these must be reported to the relevant regulatory authorities before 7 days have elapsed from that the initial SAE report has reached the Sponsor or its representatives. A full report has to be submitted within another 8 days. For other SUSARs the timelines for reporting are 15 days.

In addition, the CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the rhIGF-1/rhIGFBP-3 program at Shire.

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.

7.10 Removal of Subjects from the Trial

A subject's participation in the study may be discontinued at any time at the discretion of the Investigator. The following may be justifiable reasons for the Investigator to remove a subject from the study:

- Noncompliance, including failure to appear at one or more study visits
- The subject was erroneously included in the study
- The subject develops an exclusion criterion
- The study is terminated by the Sponsor

The subject, the subject's parent(s), or the subject's legally authorized representative acting on behalf of the subject is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment.

If a subject or the subject's parent(s) or the subject's legally authorized representative(s) acting on behalf of the subject, discontinues participation in the study, or the subject is discontinued by the Investigator, reasonable efforts will be made to follow the subject through the end of study assessments. The reason for refusal will be documented on the eCRF. Any AEs experienced up to the point of discontinuation must be documented on the AE eCRF. If AEs are present when the subject withdraws from the study, the subject will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal will be followed until resolution.

7.11 Other Study Procedures

7.11.1 Participation in Other Clinical Studies

Following enrollment, subjects in this study will not be restricted from enrolling in another clinical study that involves 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 being evaluated in the study, and the subject's treatment assignment in the study (if possible).

7.12 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. These are the pulmonary morbidity assessment and the cerebral palsy assessment. In these cases, the tools are either based on validated tools or the current state of knowledge in the literature. For example, the cerebral palsy assessment is based on the Amiel-Tison neurological examination framework[25] and the pulmonary assessment is based on published research in a similar pediatric population.[36,37]

8 STUDY ACTIVITIES

The timing of the visits in this study is based on subjects' corrected age (CA).

8.1 Initial Study Visit (40 weeks CA [term equivalent])

The Initial Visit will occur at 40 weeks CA (ie, term equivalent) or upon discontinuation from Study ROPP-2008-01, Section D or any time up to the visit at 3 months CA.

For subjects enrolled between the ages of 9 months CA and 2 years +3 months CA, missed procedures such as neurocognitive assessments, abdominal ultrasounds, and echocardiograms are not required.

At the Initial Visit, informed consent will be obtained followed by an assessment of study eligibility criteria and collection of demographic data.

The following AE data, collected as part of Study ROPP-2008-01 (Section D) will be recorded:

- Ongoing targeted medical events regardless of causality
- Ongoing study drug-related AEs, including SAEs

Serious adverse events, as outlined in Section 7.9.1.1 and Section 7.9.1.2, that the subject experiences between the ROPP-2008-01 end-of-study visit and the time of informed consent for Study SHP-607-201 will be reported by the Investigator, pending permission for subject's parent or legally authorized representative(s), as documented on the informed consent form.

8.2 Study Visits

Study visits for follow-up outcome assessments will take place at the following time points in CA:

- 3 months (±2 weeks) – conducted by telephone
- 6 months (±1 month) – clinical site visit
- 12 months (±3 months) – clinical site visit
- 20 months (-1 months) – clinical site visit
- 24 months (±3 months) – clinical site visit
- 30 months (±3 months) – conducted by telephone
- 3 years (±3 months) – conducted by telephone
- 3.5 years (±3 months) – conducted by telephone
- 4 years (±3 month) – conducted by telephone
- 4.5 years (±3 month) – conducted by telephone

- 4.75 years (-1 months) – clinical site visit
- 5 years (+6 months) – clinical site visit

Multiple visits and/or phone contacts are allowed to complete all assessments, if needed. In addition, there will be 2 visits that must occur at least 1 month prior to the 24-month and 5-year CA study visits to assess the need for corrective lenses. The timing of these 2 visits (20 months [-1 month] and 4.75 years [-1 month]) was set to ensure that any prescribed corrective lenses would be worn for at least 1 month prior to the visual assessments at the 24-month and 5-year study visits CA.

The activities at the study visits are described in Sections 8.2.1 and 8.2.2.

8.2.1 Outcome Assessment Visits Conducted by Telephone

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

- HRQoL (3-month, 3-year, and 4-year visits)
- HCRU (3-month, 3-year, and 4-year visits)
- HSCS-PS (3-year and 4-year visits)
- Pulmonary morbidity assessment (30-month, 3-year, 3.5-year, 4-year, and 4.5-year visits)
- Medications (3-month, 30 months, 3-year, 3.5 year, 4-year and 4.5 year visits)
- Survival assessment (3-month, 30 month, 3-year, 3.5 year, 4-year and 4.5 year visits)
- Assessment of participation in other clinical studies (3-month, 30 months, 3-year, 3.5 year, 4-year and 4.5 year visits)
- Adverse events, including targeted medical events (3-month, 30 month, 3-year, 3.5 year, 4-year and 4.5 year visits)

8.2.2 Clinical Site Visits

8.2.2.1 Outcome Assessment Site Visits

The following clinical site visits (in CA) to capture follow-up outcome data will occur at the clinical site:

- 6 months (±1 month)
- 12 months (±3 months)
- 20 months (-1 month)
- 24 months (±3 months)

- 4.75 years (-1 months)
- 5 years (+6 months)

The following assessments will be performed at the 6-month visit:

- Visual acuity
- Refraction with cycloplegia
- Length
- Weight
- Head circumference
- VABS-II
- Physical examination (including tonsil examination)
- Hearing Assessment History (Historical hearing test data may be recorded at any time prior to the 6-month visit)
- Pulmonary morbidity assessment
- Survival assessment
- HRQoL (may be performed by telephone if there are time constraints during this clinical site visit)
- HCRU (may be performed by telephone if there are time constraints during this clinical site visit)
- Abdominal ultrasound
- Echocardiogram
- Assessment of participation in other clinical studies
- Medications
- Adverse events (including targeted medical events)

The following assessments will be performed at the 12-month visit:

- Visual acuity
- Corrective lens determination (including refraction with cycloplegia)
- Ocular alignment and motility
- Length
- Weight
- Head circumference
- BSID-III

- VABS-II
- Physical examination (including tonsil examination)
- Pulmonary morbidity assessment
- Survival assessment
- HRQoL (may be performed by telephone if there are time constraints during this clinical site visit)
- HCRU (may be performed by telephone if there are time constraints during this clinical site visit)
- Assessment of participation in other clinical studies
- Medications
- Adverse events (including targeted medical events)

The following assessments will be performed at the 20-month visit:

- Visual acuity
- Corrective lens determination (including refraction with cycloplegia)
- Assessment of participation in other clinical studies

The following assessments will be performed at the 24-month visit:

- Visual acuity
- Ocular alignment and motility
- Length
- Weight
- Head circumference
- BSID-III
- CBCL
- VABS-II
- Physical examination (including tonsil examination)
- Cerebral Palsy assessment
- Pulmonary morbidity assessment
- Survival assessment
- HRQoL (may be performed by telephone if there are time constraints during this clinical site visit)
- HCRU (may be performed by telephone if there are time constraints during this clinical site visit)

- HSCS-PS (may be performed by telephone if there are time constraints during this clinical site visit)
- Assessment of participation in other clinical studies
- Medications
- Adverse events (including targeted medical events)

The following assessments will be performed at 4.75-year visit:

- Visual acuity
- Corrective lens determination (including refraction with cycloplegia)

The following assessments will be performed at the 5-year visit:

- Visual acuity
- Ocular alignment and motility
- Stereoacuity
- Height
- Weight
- WPPSI
- CBCL
- VABS-II
- ADHD-RS
- SCQ
- Physical examination (including tonsil examination)
- Blood pressure, heart rate, and respiratory rate
- Pulmonary morbidity assessment
- Hearing assessment history
- Survival assessment
- [redacted]
- [redacted]
- HRQoL (may be performed by telephone if there are time constraints during this clinical site visit)
- HCRU (may be performed by telephone if there are time constraints during this clinical site visit)
- HSCS-PS (may be performed by telephone if there are time constraints during this clinical site visit)

- HUI2/3 (may be performed by telephone if there are time constraints during this clinical site visit)
- Assessment of participation in other clinical studies
- Medications
- Adverse events (including targeted medical events)

8.2.2.2 Visits Dedicated to Corrective Lens Determination

The following clinical site visits are dedicated solely to corrective lens determination in preparation for the outcome assessment visits at 24-months and 5-years CA:

- 20 months (-1 month)
- 4.75 years (-1 month)

At these visits, the following will be performed:

- Visual acuity
- Corrective lens determination (includes refraction with cycloplegia)

The 20-month visit and the 4.75-year (4 years, 9 months) visit must occur at least 1 month prior to the 24-month and 5-year visits, respectively. Any prescribed corrective lenses must be worn for at least 1 month prior to the 24 month and 5 year assessments.

8.3 Assessments upon Discontinuation

If a subject discontinues prior to the 5-year CA visit, every attempt will be made to complete the assessments scheduled for the subject's next visit.

9 QUALITY CONTROL AND ASSURANCE

Training will occur at an Investigator meeting or at the site initiation visit or both, and instruction manuals will be provided to aid consistency in data collection and reporting across sites.

Clinical sites will be monitored by the Sponsor or its designee to ensure the accuracy of data against source documents. The required data will be captured in a validated clinical data management system that is compliant with the FDA 21 Code of Federal Regulations (CFR) Part 11 Guidance. The clinical trial database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be trained and given restricted access, based on their role(s) in the study, through a password-protected environment.

Data entered in the system will be reviewed manually for validity and completeness against the source documents by a clinical monitor from the Sponsor or its designee. If necessary, the study site will be contacted for corrections or clarifications; all missing data will be accounted for.

Serious adverse event information captured in the clinical trial database will be reconciled with the information captured in the Global Drug Safety database.

10 STATISTICAL ANALYSES

10.1 General Methodology

Details regarding the statistical methods and definitions will be provided in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to database lock. All statistical analyses will be performed by the Biometrics department at Shire. Statistical analyses will be performed using Version 9.1 or higher of SAS® (SAS Institute, Cary, NC 27513).

Continuous variables will be summarized using descriptive statistics including the number of observations, 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 2 possible treatment assignments in the antecedent study, ROPP-2008-01, Section D (rhIGF-1/rhIGFBP-3 or standard neonatal care).

For analysis purposes, baseline is defined as the first assessment either in the antecedent study (ROPP-2008-01) or in this study (SHP-607-201). As necessary, relevant data from Study ROPP-2008-01 may be extracted and summarized with the data from this study (SHP-607-201). For consented patients, additional biomarker analysis may be performed on prior collected blood samples from Study ROPP-2008-01.

10.2 Determination of Sample Size

No formal sample size calculation was performed for this study because this is a follow-up study to Section D of Study ROPP-2008-01. Any subjects enrolled in Study ROPP-2008-01 are eligible to enroll in this study. There are up to 120 subjects who will be eligible to enroll in this long-term developmental outcome study.

10.3 Method of Assigning Study Subjects to Treatment Groups

Not applicable.

10.4 Population Description

10.4.1 Analysis Populations

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

Safety Population- the Safety Population will consist of the subjects in the Enrolled Population who have safety follow-up data in this long-term outcome study.

10.4.2 Subject Disposition

Subjects who complete the study and subjects who prematurely discontinue from the study will be summarized by treatment group using descriptive statistics. In addition, for subjects who prematurely discontinue from the study, the reasons for discontinuation will be summarized by treatment group.

10.4.3 Protocol Violations and Deviations

Protocol violations and deviations will be listed. Details of the criteria for deviations and violations will be provided in the SAP.

10.4.4 Demographics and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group for the Enrolled Population.

Demographics and baseline characteristics will be examined to assess the comparability of the treatment groups. Continuous variables such as age (including corrected age), weight, and length/height will be summarized using number of observations, mean, standard deviation, median, minimum and maximum values. Categorical variables, like gender and race, will be summarized using number of observations and percentages.

Medical history, including maternal and perinatal history, (as obtained from the antecedent study, ROPP-2008-01) will be summarized by treatment group using the number of observations and percentages of subjects reporting each category.

10.5 Efficacy Analysis

All efficacy analyses will be performed using the Enrolled Population.

10.5.1 Primary Efficacy Analysis

The primary efficacy endpoints consist of the following:

- Visual Acuity: Visual acuity will be categorized as the following:
  - normal (measurable acuity ≥20/40),
  - below normal (20/200≤ measurable acuity <20/40),
  - poor (measurable acuity ≤20/200)
  - blind/low vision (only the ability to detect the 2.2 cm wide stripes on the low-vision Teller acuity card and at any location in the visual field).

  The number and proportion of patients within each category listed above will be summarized by treatment group and visit. In addition, acuity results in the normal and below normal categories will be classified as favorable outcomes, and acuity results in the poor and blind/low-vision categories will be classified as unfavorable outcomes. Tabular summaries by treatment group and visit will include the frequency and the percentage for each visual acuity category.

In addition, shift tables of favorable outcomes from baseline (first assessment during this study) to each of the subsequent assessments, including the last assessment, will be presented by treatment group.

- Ocular Alignment and Oculomotor Exam (Motility): Findings from the ocular motility assessment will be either presence or absence of strabismus (esotropia, exotropia, hypertropia, or hypotropia). Tabular summaries by treatment group and visit will include the frequency and the percentage in each category. In addition, shift tables from baseline (first assessment during this study) to the last assessment will be provided by treatment group.
- Nystagmus: Presence or absence of nystagmus will be summarized by treatment group and visit
- Refraction with Cycloplegia: Findings from the refraction with cycloplegia will be summarized by treatment group and visit
- Stereoacuity: Presence or absence of stereopsis will be summarized by treatment group and visit

10.5.2 Secondary Efficacy Analysis

- Growth Parameters (body weight, body length [and height], and head circumference): A standard Z-score, utilizing WHO child growth standards, will be calculated for each assessment by adjusting age- and sex- matched means and standard deviations (norm). The descriptive statistics of the Z-score for each of these parameters will be summarized at each assessment and the corresponding change from baseline. When appropriate, a 95% CI for the corresponding mean change within each group and the difference in the mean change between the 2 treatment groups and the corresponding 95% CI will be presented as appropriate. If the parametric assumption for the distribution of the above endpoints cannot be justified, a non-parametric approach will be utilized to estimate the treatment difference (ie, median difference or Hodges-Lehmann estimator and the corresponding confidence intervals)
- BSID-III and WPPSI: The raw score, age equivalent scores, and standard scores for each domain within each questionnaire will be summarized by treatment group and visit using descriptive statistics.
- ADHD-RS: ADHD-RS total score and subscales (Hyperactivity/Impulsivity and Inattentiveness) will be summarized by treatment group and visit using descriptive statistics.
- SCQ: The SCQ subscales (communication and social) will be summarized by treatment group and visit using descriptive statistics
- VABS-II: The raw score, age equivalent scores, and standard scores for each domain of the scale will be summarized by treatment group and visit using descriptive statistics.
- CBCL: The raw score and change from baseline for each domain of the scale will be summarized by treatment group and visit using descriptive statistics.

- Pulmonary morbidity assessment: The binary response of each question will be by treatment group and visit using descriptive statistics.
- Survival: For subjects who have an event (ie, death), the event time will be calculated as the length of time from the subject's date of birth to death during the study due to any cause. Subjects who do not have an event (ie, death) during the study will be censored at the end of the study. The survival endpoint will be analyzed by treatment group using Kaplan-Meier methods.

10.5.3 Subset Analyses

Subgroup analyses may be explored based on factors that may have influence on the efficacy or safety endpoints. Subgroup analyses will be specified in the SAP.

10.5.4 Exploratory Analyses

[redacted]

- [redacted]
- [redacted]

10.6 Health Economics and Outcomes Research Analyses

For PedsQL, descriptive statistics will be provided for summary scores by treatment group and at each time point.

The HSCS-PS instrument is composed of 12 dimensions (Vision, Hearing, Speech, Mobility, Dexterity, Self-care, Emotion, Learn/remember, Think/problem solve, Pain, General Health, and Behavior) intended to provide a comprehensive assessment of a child's health status as it pertains to health-related quality of life. The individual domains of the instrument will be scored as a mean score, representing the overall state for each concept individually. The global score will be recorded as well as the scores for each of the dimensions. Summary statistics will be provided by treatment group 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 1-5 (higher numbers indicating a more severe level). Summary statistics will be provided by treatment group and at each time point.

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.

10.7 Analysis of Safety

Safety summaries will be based on all assessments post-baseline. The safety data will be assessed by AE monitoring, change in cardiac size, and kidney and spleen size over time.

Adverse events will be summarized by MedDRA system organ class (SOC) and preferred term for each treatment group and overall, the number and percentage of subjects having any AE, having an AE in each SOC and having each individual AE. In addition, those events which resulted in death, or were otherwise classified as serious will be presented in a separate listing. In addition, the summary of AEs will be presented by severity and relationship to trial medication.

The change in cardiac size and size of kidney and spleen will be assessed at the 6-month CA visit via echocardiogram and abdominal ultrasound, respectively. These data will be analyzed as a binary response (ie, normal/abnormal) and summarized using frequency count. The number and proportion of patients with each category (ie, normal/abnormal) for each of these safety endpoints will be summarized by treatment group.
In addition, the 2-sided 95% CI for the proportion of patients with a normal status for each of the endpoints will be estimated by treatment group.

Physical examinations findings will be summarized descriptively.

10.8 Statistical/Analytical Issues

10.8.1 Adjustment for Covariates

If any baseline data are imbalanced and are considered to be clinically relevant, between-group comparisons for efficacy outcomes will be adjusted for covariates and detailed in the SAP.

10.8.2 Handling of Dropouts or Missing Data

Handling of missing data rules will be described in the SAP.

10.8.3 Interim Analyses and Data Monitoring

No interim analysis is planned. However, a snapshot of the data will be reviewed after all data from all enrolled subjects in this study (after either completed 2-year follow-up [24-month visit] assessments or have prematurely withdrawn from the study [before completing 2 years of follow up]) has been entered into the database, queried, and discrepancies resolved. A selective descriptive analysis of the data for this interim review may be performed and used to understand the progress of the study, completion of the data, safety monitoring, regulatory communication, or general planning purposes.

10.8.4 Multiple Comparisons/Multiplicity

Not applicable.

10.8.5 Sensitivity Analyses

Sensitivity analyses for the efficacy outcomes will be detailed in the SAP, as necessary.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

Before initiation of the study, the Investigators must provide the Sponsor with a completed Form FDA 1572 and Investigator Agreement. Curriculum vitae must be provided for the Investigators and subinvestigators listed on Form FDA 1572 or Investigator Agreement.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, and their study related duties and functions. The Investigator must maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study related duties.

11.2 Institutional Review Board or Independent Ethics Committee Approval

Before initiation of the study, the Investigator must provide the Sponsor with a copy of the written IRB/IEC/REB approval of the protocol and the informed consent form. This approval must refer to the informed consent form and to the study title, study number, and version and date of issue of the study protocol, as given by the Sponsor on the cover page of the protocol.

Status reports must be submitted to the IRB/IEC/REB at least once per year. The IRB/IEC/REB must be notified of completion of the study. Within 3 months of study completion or termination, a final report must be provided to the IRB/IEC/REB. A copy of these reports will be sent to the study clinical monitor. The Investigators must maintain an accurate and complete record of all submissions made to the IRB/IEC, including a list of all reports and documents submitted. AEs which are reported to the US (FDA or other Regulatory agencies (Safety Reports) must be submitted promptly to the IRB/IEC/REB.

11.3 Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigators abide by good clinical practice (GCP) as described in the 21 CFR Parts 50, 56, and 312 and the International Conference on Harmonization (ICH) GCP Guidelines Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

11.4 Subject Information and Consent

Before enrolling in the clinical study, the subject or the subject's parent(s) or legally authorized representative(s) must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her.

An informed consent form (assent form if applicable) that includes information about the study will be prepared and given to the subject or the subject's parent(s) or legally authorized representative(s). This document will contain all FDA and ICH-required elements.

The informed consent (or assent) form must be in a language understandable to the subject or the subject's parent(s) or legally authorized representative(s) and must specify who informed the subject, the subject's parent(s), or the subject's legally authorized representative(s).

After reading the informed consent document, the subject or the subject's parent(s) or legally authorized representative(s) must give consent in writing. Consent must be confirmed at the time of consent by the personally dated signature of the subject, the subject's parent(s) or the subject's legally authorized representative(s) and by the personally dated signature of the person conducting the informed consent discussions.

If the subject or the subject's parent(s) or legally authorized representative(s) is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the subject or by a local legally recognized alternative (eg, the subject's thumbprint or mark) or by the personally dated signature of the subject's parent(s) or the subject's legally authorized representative. The witness and the person conducting the informed consent discussions must also sign and personally date the informed consent document. It should also be recorded and dated in the source document that consent was given.

A copy of the signed and dated consent document(s) must be given to the subject or the subject's parent(s) or legal representative(s). The original signed and dated consent document will be retained by the Investigator.

The Investigator will not undertake any measures specifically required solely for the clinical study until valid consent has been obtained.

A model of the informed consent form to be used in this study will be provided to the sites separately from this protocol.

11.5 Subject Confidentiality

Subject names will not be supplied to the Sponsor. Only the subject number - will be recorded in the eCRF, and if the subject name appears on any other document, it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be told that representatives of the Sponsor, a designated CRO, the IRB/IEC/REB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. The Investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

11.6 Study Monitoring

Monitoring procedures that comply with current Good Clinical Practice (GCP) guidelines will be followed. Review of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by the Sponsor or its designee. Monitoring will be performed by a representative of the Sponsor (Clinical Study Monitor) who will review the eCRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and communications (letter, telephone, and facsimile).

11.7 Case Report Forms and Study Records

11.7.1 Case Report Forms

Electronic case report forms (eCRFs) are provided for each subject. All forms must be filled out by authorized study personnel. All corrections to the original eCRF entry must indicate the reason for change. The Investigator is required to sign the eCRF after all data have been captured for each subject. If corrections are made after review and signature by the Investigator, he or she must be made aware of the changes, and his or her awareness documented by resigning the eCRF.

11.7.2 Critical Documents

Before the Sponsor initiates the trial (ie, obtains informed consent from the first subject), it is the responsibility of the Investigator to ensure that the following documents are available to Sponsor or their designee:

- Completed FDA Form 1572 (Statement of Investigator), signed, dated, and accurate
- Curricula vitae of Investigator and subinvestigator(s) (current, dated and signed within 12 months of study initiation)
- Copy of Investigator and subinvestigator(s) current medical license (indicating license number and expiration date)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/IEC/REB clearly identifying the documents reviewed by name, number and date of approval or re approval: protocol, any amendments, Subject Information/Informed Consent Form, and any other written information to be provided regarding subject recruitment procedures
- Copy of IRB/IEC/REB approved Subject Information/Informed Consent Form/any other written information/advertisement (with IRB approval stamp and date of approval)
- Current list of IRB/IEC/REB Committee members/constitution (dated within 12 months prior to study initiation)

- Financial Disclosure Form signed by Investigator and sub-investigator(s)
- Current laboratory reference ranges (if applicable)
- Certification/QA scheme/other documentation (if applicable)

Regulatory approval and notification as required must also be available; these are the responsibility of Shire.

11.8 Data Monitoring Committee

Given that any long-term safety signal observed in this study could impact the safety profile of rhIGF-1/rhIGFBP-3 as administered in premature neonates being enrolled in the antecedent study (ROPP-2008-01, Section D), the Data Monitoring Committee (DMC) for Study ROPP-2008-01 will review safety data from this long-term outcome study.

11.9 Protocol Violations/Deviations

The Investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the IRB/IEC/REB and the appropriate regulatory authorities, where applicable, have given approval/favorable opinion. Modifications to the protocol will not be made without agreement of the Sponsor. Changes to the protocol will require written IRB/IEC/REB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB/IEC/REB may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC/REB. The Sponsor will submit all protocol modifications to the regulatory authorities, where applicable, in accordance with the governing regulations.

A record of subjects screened, but not entered into the study, is also to be maintained. No protocol exemption will be granted for this study.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Sponsor or its designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will need to be reviewed by the medical monitor and may also be required to be submitted to the IRB/IEC/REB.

Protocol modifications will only be initiated by the Sponsor and must be approved by the IRB/IEC/REB and submitted to the FDA or other applicable international regulatory authority before initiation, if applicable.

11.10 Premature Closure of the Study

If the Sponsor, Investigator, or regulatory authorities discover conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable subject risk, the study may be terminated after appropriate consultation between the Sponsor and the Investigator(s). In addition, a decision on the part of the Sponsor to suspend or discontinue

development of the investigational product may be made at any time. Conditions that may warrant termination of the study or site include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study
- Failure of the Investigator to comply with pertinent global regulations
- Submission of knowingly false information from the study site to the Sponsor or other pertinent regulatory authorities
- Insufficient adherence by the Investigator to protocol requirements

11.11 Access to Source Documentation

Regulatory authorities, the IRB/IEC/REB, or the Sponsor may request access to all source documents, eCRFs, and other study documentation for onsite audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Monitoring and auditing procedures that comply with current GCP guidelines will be followed. On-site review of the eCRFs for completeness and clarity, crosschecking with source documents, and clarification of administrative matters may be performed.

11.12 Data Generation and Analysis

The clinical database will be developed and maintained by a contract research organization or an electronic data capture technology provider as designated by the Sponsor. The Sponsor or its designee will be responsible for performing study data management activities.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medication will be coded using WHO-Drug Dictionary (WHO-DD). Central reads will be employed as described in the study manual to aid in consistent measurement of abdominal ultrasound and echocardiogram parameters.

11.13 Retention of Data

Essential documents should be retained until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The Sponsor will notify the Investigator if these documents must be retained for a longer period of time. It is the responsibility of the Sponsor to inform the Investigator or institution as to when these documents no longer need to be retained.

11.14 Financial Disclosure

The Investigator should disclose any financial interests in the Sponsor as described in 21 CFR Part 54 prior to beginning this study. The appropriate form will be provided to the Investigator by the Sponsor, which will be signed and dated by the Investigator, prior to the start of the study.

11.15 Publication and Disclosure Policy

All information concerning the study material, such as patent applications, manufacturing processes, basic scientific data, and formulation information supplied by the Sponsor and not previously published are considered confidential and will remain the sole property of the Sponsor. The Investigator agrees to use this information only in accomplishing this study and will not use it for other purposes.

It is understood by the Investigator that the information developed in the clinical study may be disclosed as required to the authorized regulatory authorities and governmental agencies. In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the Sponsor with complete test results and all data developed in the study in a timely manner.

The Investigator and any other study personnel associated with this study will not publish the results of the study, in whole or in part, at any time, unless they have consulted with the Sponsor, provided the Sponsor a copy of the draft document intended for publication, and obtained the Sponsor's written consent for such publication. All information obtained during the conduct of this study will be regarded as confidential.

12 LIST OF REFERENCES

1. Maida JM, Mathers K, Alley CL. Pediatric ophthalmology in the developing world. Current opinion in ophthalmology 2008;19:403-8.
2. O'Connor AR, Stephenson TJ, Johnson A, et al. Visual function in low birthweight children. The British journal of ophthalmology 2004;88:1149-53.
3. Keith CG, Kitchen WH. Ocular morbidity in infants of very low birth weight. The British journal of ophthalmology 1983;67:302-5.
4. Laws D, Shaw DE, Robinson J, Jones HS, Ng YK, Fielder AR. Retinopathy of prematurity: a prospective study. Review at six months. Eye 1992;6:477-83.
5. O'Connor AR, Stephenson T, Johnson A, et al. Long-term ophthalmic outcome of low birth weight children with and without retinopathy of prematurity. Pediatr 2002;109:12-8.
6. Schaffer DB, Quinn GE, Johnson L. Sequelae of arrested mild retinopathy of prematurity. Archives of ophthalmology 1984;102:373-6.
7. Cats BP, Tan KE. Prematures with and without regressed retinopathy of prematurity: comparison of long-term (6-10 years) ophthalmological morbidity. Journal of pediatric ophthalmology and strabismus 1989;26:271-5.
8. Chard T. Insulin-like growth factors and their binding proteins in normal and abnormal human fetal growth. Growth Regul 1994;4:91-100.
9. Hansen-Pupp I, Lofqvist C, Polberger S, et al. Influence of insulin-like growth factor I and nutrition during phases of postnatal growth in very preterm infants. Pediatr Res 2011;69:448-53.
10. Ohkawa N, Shoji H, Kitamura T, et al. IGF-I, leptin and active ghrelin levels in very low birth weight infants during the first 8 weeks of life. Acta Paediatr 2010;99:37-41.
11. Lofqvist C, Hellgren G, Niklasson A, Engstrom E, Ley D, Hansen-Pupp I. Low postnatal serum IGF-I levels are associated with bronchopulmonary dysplasia (BPD). Acta Paediatr 2012;101:1211-6.
12. Ishii DN, Glazner GW, Whalen LR. Regulation of peripheral nerve regeneration by insulin-like growth factors. Annals of the New York Academy of Sciences 1993;692:172-82.
13. Lewis ME, Neff NT, Contreras PC, et al. Insulin-like growth factor-I: potential for treatment of motor neuronal disorders. Experimental neurology 1993;124:73-88.
14. Pediatric Ophthalmology/Strabismus Preferred Practice Pattern Development Process and Participants. Pediatric Eye Evaluations: American Academy of OphthalmologyPediatric Ophthalmology/Strabismus Preferred Practice Pattern Panel; 2012.
15. Wechsler D. Wechsler preschool and primary scale of intelligence 4th ed. Bloomington, MN: Pearson; 2012.
16. Wechsler D. Technical and Interpretive Manual Supplement: Special Group Validity Studies With Other Measures 2012.

17. Achenbach T, Rescorla L. Manual for the ASEBA preschool forms and profiles. Burlington, VT: University of Vermont; 2000.
18. Vinall J, Miller SP, Synnes AR, Grunau RE. Parent behaviors moderate the relationship between neonatal pain and internalizing behaviors at 18 months corrected age in children born very prematurely. Pain 2013;154:1831-9.
19. Scott MN, Taylor HG, Fristad MA, et al. Behavior disorders in extremely preterm/extremely low birth weight children in kindergarten. J Dev Behav Pediatr 2012;33:202-13.
20. Wu YC, Leng CH, Hsieh WS, et al. A randomized controlled trial of clinic-based and home-based interventions in comparison with usual care for preterm infants: Effects and mediators. Res Dev Disabil 2014;35:2384-93.
21. Ebesutani C, Bernstein A, Nakamura BJ, Chorpita BF, Higa-McMillan CK, Weisz JR. Concurrent Validity of the Child Behavior Checklist DSM-Oriented Scales: Correspondence with DSM Diagnoses and Comparison to Syndrome Scales. Journal of psychopathology and behavioral assessment 2010;32:373-84.
22. DuPaul G, Power T, Anastopoulos A, Reed R. The ADHD rating scale IV: checklists, norms and clinical interpretation. New York: Guilford Press; 1998.
23. Rutter M, Bailey A, Lord C. Manual for the Social Communication Questionnaire2003.
24. Chandler S, Charman T, Baird G, et al. Validation of the social communication questionnaire in a population cohort of children with autism spectrum disorders. Journal of the American Academy of Child and Adolescent Psychiatry 2007;46:1324-32.
25. Gosselin J, Amiel-Tison C. Neurological Assessment from Birth to 6 Years. 2nd ed. Montreal: CHU Sainte-Justine; 2011.
26. Matza LS, Swensen AR, Flood EM, Secnik K, Leidy NK. Assessment of health-related quality of life in children: a review of conceptual, methodological, and regulatory issues. Value Health 2004;7:79-92.
27. Varni JW, Burwinkle TM, Lane MM. Health-related quality of life measurement in pediatric clinical practice: an appraisal and precept for future research and application. Health Qual Life Outcomes 2005;3:34.
28. Constitution of the World Health Organization: basic document. Geneva, Switzerland: World Health Organization; 1948.
29. Varni JW, Limbers CA. The pediatric quality of life inventory: measuring pediatric health-related quality of life from the perspective of children and their parents. Pediatr Clin North Am 2009;56:843-63.
30. Varni JW, Limbers CA, Neighbors K, et al. The PedsQL Infant Scales: feasibility, internal consistency reliability, and validity in healthy and ill infants. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2011;20:45-55.
31. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Medical care 2001;39:800-12.

32. Saigal S, Rosenbaum P, Stoskopf B, et al. Development, reliability and validity of a new measure of overall health for pre-school children. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2005;14:243-57.

33. Horsman J, Furlong W, Feeny D, Torrance G. The Health Utilities Index (HUI®): concepts, measurement properties and applications. Health Qual Life Outcomes. 2003;1:54.

34. Rosenbaum DM, Korngold E, Teele RL. Sonographic assessment of renal length in normal children. Am J Roentgenol 1984;142:467-9.

35. Rosenberg HK, Markowitz RI, Kolberg H, Park C, Hubbard A, Bellah RD. Normal splenic size in infants and children: sonographic measurements. Am J Roentgenol 1991;157:119-21.

36. Stevens TP, Finer NN, Carlo WA, et al. Respiratory Outcomes of the Surfactant Positive Pressure and Oximetry Randomized Trial (SUPPORT). J Pediatr 2014;165:240-9.e4.

37. Zivanovic S, Peacock J, Alcazar-Paris M, et al. Late outcomes of a randomized trial of high-frequency oscillation in neonates. N Engl J Med 2014;370:1121-30.

[redacted]

13 APPENDICES

Appendix 1 Study Schedule of Events

Procedures	Initial Study Visit[e]	Months (CA)[k]						Years (CA)[k]					
	40 weeks (CA)/term equivalent	3[f] ± 2 wks	6 ± 1 mth	12 ± 3 mths	20 -1 mth[g]	24 ± 3 mth	30[f] ± 3 mth	3[f] ± 3 mths	3.5[f] ± 3 mth	4[f] ± 3 mths	4.5[f] ± 3 mth	4.75 -1 mth[g]	5 + 6 mths
Informed Consent	•												
Eligibility Criteria	•												
Demographics	•												
Visual acuity[a]			•	•	•	•						•	•
Corrective lens determination[h]				•	•[g]							•[g]	
Ocular alignment and motility				•		•							•
Refraction with cycloplegia[h]			•										
Stereoacuity													•
Length			•	•		•							
Height													•
Weight			•	•		•							•
Head Circumference			•	•		•							
BSID-III				•		•							
WPPSI													•
CBCL						•							•
VABS-II			•	•		•							•
ADHD-RS													•
SCQ													•
Physical Examination including tonsil examination			•	•		•							•
Blood Pressure, Heart Rate, and Respiratory Rate													•
Cerebral Palsy Assessment						•							
Hearing Assessment History[b]			•										•
Pulmonary Morbidity Assessment 1			•	•									
Pulmonary Morbidity Assessment 2 (clinical site visit)						•							•
Pulmonary Morbidity Assessment (phone interview)							•	•	•	•	•		

Procedures	Initial Study Visit[e]	Months (CA)[k]						Years (CA)[k]					
	40 weeks (CA)/term equivalent	3[f] ± 2 wks	6 ± 1 mth	12 ± 3 mths	20 -1 mth[g]	24 ± 3 mth	30[f] ± 3 mth	3[f] ± 3 mths	3.5[f] ± 3 mth	4[f] ± 3 mths	4.5[f] ± 3 mth	4.75 -1 mth[g]	5 + 6 mths
Survival assessment		•	•	•		•	•	•	•	•	•		•
[redacted]		[redacted]											
[redacted]		[redacted]											
HRQoL[c]		•	•[i]	•[i]		•[i]		•		•			•[i]
HCRU		•	•[i]	•[i]		•[i]		•		•			•[i]
HSCS-PS						•[i]		•		•			•[i]
HUI2/3													•
Abdominal Ultrasound			•										
Echocardiogram			•										
Assessment of Participation in Other Clinical Studies		•	•	•		•	•	•	•	•	•		•
Medications		•	•	•		•	•	•	•	•	•		•
Adverse events[d]	•[j]	•	•	•		•	•	•	•	•	•		•

Abbreviations: ADHD-RS = Attention-Deficit/Hyperactivity Disorder Rating Scale; BSID-III = Bayley Scales of Infant and Toddler Development-Third Edition, CBCL = Child Behavior Checklist; CA = corrected age; HCRU = health care resource use; HRQoL = health-related quality of life; HSCS-PS = Health Status Classification System; HUI2/HUI3=Health Utilities Index Mark 2 and Mark 3; mth(s) = months; PedsQL = Pediatric Quality of Life Inventory; SCQ = Social Communication Questionnaire; VABS-II = Vineland Adaptive Behavior Scales, Second Edition; wks = weeks; WPPSI = Wechsler Preschool and Primary Scale of Intelligence

[a] The tools used to assess visual acuity will change as the subject ages during their participation in the study. The tools that will be used in this study and are summarized by applicable study visit in Table A1.

[b] Historical hearing test data may be recorded at any time during the study prior to the 6-month visit.

[c] HRQoL will be assessed via the validated PedsQL™ scales appropriate for the child's age of development as specified in the Study Operations Manual.

[d] Adverse event collection will include an assessment of the specified targeted medical events.

[e] The Initial Visit may be performed prior to 40 weeks CA for any subject who discontinued from Study ROPP-2008-01 and, for all subjects, any time after 40 weeks CA. If the Initial Visit does not occur at or before 40 weeks CA, the subject may still be enrolled until 2 years CA +3 months. Subjects are no longer eligible to participate in this study after they turn 2 years CA +3 months.

[f] Visits at 3 months, 30 months, 3 years, 3.5 years, 4 years, and 4.5 years CA will be conducted by telephone.

[g] The 20-month visit and the 4.75-year (4 years, 9 months) visit must occur at least 1 month prior to the 24-month and 5-year visits, respectively. Any prescribed corrective lenses must be worn for at least 1 month prior to the 24-month and 5-year assessments.

Procedures	Initial Study Visit[e]	Months (CA)[k]						Years (CA)[k]					
	40 weeks (CA)/term equivalent	3[f] ± 2 wks	6 ± 1 mth	12 ± 3 mths	20 -1 mth[g]	24 ± 3 mth	30[f] ± 3 mth	3[f] ± 3 mths	3.5[f] ± 3 mth	4[f] ± 3 mths	4.5[f] ± 3 mth	4.75 -1 mth[g]	5 + 6 mths

[h] Refraction with cycloplegia will be performed as part of the corrective lens determination procedure.

[i] The HRQoL, HCRU, and HSCS-PS assessments for the 6-month, 12-month, 24-month and 5-year visits may be performed through clinical site staff if there are time constraints during the on-site visit. At the 3-month, 3-year, and 4-year visits, these assessments will be performed through clinical site staff and may be performed at any time within the visit window.

[j] The following, collected as part of the ROPP-2008-01 study, will be used as part of this study (SHP-607-201): any ongoing targeted medical events regardless of causality and any ongoing study drug-related AEs, including SAEs.

[k] Multiple visits and/or phone contacts are allowed to complete all assessments, if needed.

Table A1 Summary of Visual Acuity Assessments

Visual Acuity Assessment Tool	Description	Unit of Measure	Applicable Age/Study Visit (CA)
Teller acuity cards	Resolution acuity – discrimination of a grating optotype from a background with the same mean luminance	cycles per degree	6 months 12 months
LEA Symbols Test	Recognition acuity - tests recognition of 4 optotypes	Snellen fraction (eg, 20/20)	24 months[a]
LEA Symbols (ETDRS-style) chart	Distance visual acuity test	Snellen fraction (eg, 20/20)	5 years[a]

Abbreviations: CA = corrected age; ETDRS = Early Treatment of Diabetic Retinopathy Study

[a] At ages 24 months and 5 years CA an attempt should be made to assess visual acuity by the LEA Symbols Test and LEA Symbols Chart, respectively. If during this attempt, the examiner determines that it will not be possible to perform an accurate assessment with the relevant LEA tool, visual acuity should be assessed with the Teller acuity cards.

Appendix 2 Summary of Changes

Description of Change	Section(s) Affected by
Updated Medical Monitor and Shire Global Drug Safety contact information.	Title Page Section 7.9.5.2
[redacted].	Synopsis Section 2.2 Section 3.1.2 Section 7.6.6 Section 8.2.2.1 Section 10.5.2 Appendix 1
Added assessment of Health Utilities Index Mark 2 and Mark 3 (HUI2/3) to the 5 year CA visit.	Synopsis Section 3.2 Section 7.6.10.1 Section 8.2.2.1 Appendix 1
[redacted]	Synopsis (formerly) Section 2.3 (formerly) Section 3.4 (formerly) Section 7.6.1.6 Section 8.2.2.1 Appendix 1
Updated the status of Section D of Study ROPP-2008-01 since the study has now been completed.	Section 1 Section 5.1
Clarified that if the Initial Visit does not occur at or before 40 weeks CA, the subject may still be enrolled until they turn 2 years CA +3 months.	Section 4.1 Section 7.2 Appendix 1
Removed language stating that any abnormal change in physical examination findings will be recorded as an adverse event (AE).	Section 7.7.3
Clarified that the Investigator must record AEs in the electronic case report form (eCRF), regardless of the severity or causality. Language regarding the AEs that will be collected was clarified and condensed.	Section 7.9.1.1
Clarified language regarding the serious adverse events (SAEs) that will be collected.	Section 7.9.1.2

Description of Change	Section(s) Affected by
Clarified that multiple visits and/or phone contacts are allowed to complete all assessments, if needed.	Section 8.2 Appendix 1
A description of the Health Status Classification System-Preschool (HSCS-PS) statistical analysis was added.	Section 10.6
Removed language stating that a full 2-year clinical study report based on the data at the interim analysis will be completed.	Section 10.8.3
Administrative errors were corrected throughout the protocol.	All sections

Appendix 3 Protocol Signature Page

Study Title:	Long-term Outcome of Children Enrolled in Study ROPP-2008-01 Previously Treated with rhIGF-1/rhIGFBP-3 for the Prevention of Retinopathy of Prematurity (ROP) or Who Received Standard Neonatal Care
Study Number:	SHP-607-201
Final Date:	09 April 2018
Version	Amendment 4

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.
Signatory:

Investigator

_____
Signature **Date**

_____
Printed Name

I have read and approve the protocol described above.
Signatory:

Shire Medical Monitor

[redacted] [redacted]
Signature **Date**

[redacted] MD, MPH
Printed Name