Clinical Research Protocol Approval for Study STP206-002
July 08, 2018

A Phase Ib Randomized, Placebo Controlled Study of the Safety and Efficacy of Once Daily Dosing of STP206 in Premature Very Low Birth Weight and Extremely Low Birth Weight Neonates

NCT01954017

Leadiant Biosciences

Clinical Research Protocol Approval

Protocol Number:	**STP206-002**
Protocol Title:	**A Phase Ib Randomized, Placebo Controlled Study of the Safety and Efficacy of Once Daily Dosing of STP206 in Premature Very Low Birth Weight and Extremely Low Birth Weight Neonates**
Version Number, Amendment Level:	**3.0, Amendment 2**
Date:	**July 08, 2018**

Leadiant Biosciences, Inc. Approvals:

[redacted] July 27, 2018

Director Clinical Affairs, Product Development **Date**

[redacted] July 27, 2018

Vice President, Product Development **Date**

[redacted] 7-27-18

Chief Medical Officer, Vice President **Date**

CLINICAL RESEARCH PROTOCOL

Sponsor: Leadiant Biosciences, Inc.
9841 Washingtonian Blvd.
Suite 500
Gaithersburg, Maryland 20878
(800) 447-0169

IND Number: BB 14,046

Protocol Number: STP206-002

Phase: Ib

Protocol Title: A Phase Ib Randomized, Placebo Controlled Study of the Safety and Efficacy of Once Daily Dosing of STP206 in Premature Very Low Birth Weight and Extremely Low Birth Weight Neonates

Version Number: 3.0

Amendment No.: Amendment 2

Date: July 08, 2018

1. TABLE OF CONTENTS

List of Appendices

List of Tables

List of Figures

2. STUDY SYNOPSIS

		IND No.: BB 14,046
Protocol No.: STP206-002	**Development Phase**: I	**Indication:** Necrotizing Enterocolitis
Protocol Title: A Phase Ib Randomized, Placebo Controlled Study of the Safety and Efficacy of Once Daily Dosing of STP206 in Premature Very Low Birth Weight and Extremely Low Birth Weight Neonates		
Country: USA	**No. of centers:** Up to 20	**Expected Study Duration:** Approximately 55 Months

Purpose:
To examine the safety, tolerability, and preliminary NEC-preventative efficacy of two dose levels of STP206 in premature VLBW and ELBW neonates

Study Objectives:

Primary Objective:

- To assess the safety and tolerability of once-daily dosing of two dose levels of STP206 versus control in four different birth weight strata in premature neonates

Secondary Objective(s):

- Assess the fecal shedding after daily dosing of each component of STP206 throughout the dosing phase
- Describe the incidence of NEC in STP206-treated subjects compared to control subjects
- Describe the incidence of clinical events (sepsis/bacteremia, feeding intolerance, morbidity/complications of prematurity) in STP206-treated subjects compared to control subjects
- Describe the progression of standard neonatal growth parameters in STP206-treated subjects compared to control subjects

Study Endpoints:

Primary Endpoint:

- The incidence and severity of adverse events (AEs), serious adverse events (SAEs), and changes in clinical parameters from baseline in STP206-treated subjects compared to control subjects from baseline through 30 days after the last dose of blinded study treatment

Secondary Endpoints:

- The incidence and the severity of AEs and SAEs in STP206-treated subjects compared to control subjects from baseline through six months after the last dose of blinded study treatment
- The incidence of clinical events (NEC, sepsis/bacteremia, feeding intolerance, death, morbidity/complications of prematurity) in STP206-treated subjects compared to control subjects from baseline through hospital discharge
- The assessment of the fecal shedding of STP206 organisms in STP206-treated subjects compared to its baseline and to control subjects through the last dose of blinded study treatment
- The assessment of the changes in routine clinical parameters in STP206-treated subjects compared to control subjects at baseline through the last dose of blinded study treatment
- The assessment of the progression of standard neonatal growth parameters in STP206 treated subjects compared to control subjects through the 6-month postdosing visit.

Exploratory Endpoints:

- The incidence of suspected NEC (Stage I NEC) in STP206-treated subjects compared to control subjects through hospital discharge
- The incidence of suspected sepsis in STP206-treated subjects compared to control subjects through hospital discharge
- The incidence of antibiotic usage in STP206-treated subjects compared to control subjects through hospital discharge
-

Study Design and Methodology:

		IND No.: BB 14,046
Protocol No.: STP206-002	**Development Phase**: I	**Indication:** Necrotizing Enterocolitis
Protocol Title: A Phase Ib Randomized, Placebo Controlled Study of the Safety and Efficacy of Once Daily Dosing of STP206 in Premature Very Low Birth Weight and Extremely Low Birth Weight Neonates		

Protocol STP206-002 is designed as a multi-center, randomized, double-blind, placebo-controlled dose escalation study of the safety and tolerability of two doses of STP206 versus control in four sequentially decreasing birth weight strata.

Neonates for whom informed consent is obtained and who meet eligibility criteria will be eligible to enroll in this study. All neonates enrolled will receive daily doses of blinded study treatment for between 2 and 11 weeks with the duration of dosing based upon gestational age at birth. All neonates enrolled in the study will be placed under Universal Precautions and all study personnel with subject contact are trained in appropriate NICU infection control practices. While in the NICU, neonates will be evaluated daily for signs/symptoms of NEC, feeding volumes/feeding tolerance, AEs, and concomitant medications. Physical examinations and vital signs will be performed daily during the dosing period and at the end of dosing/NICU discharge. Growth assessments will be performed every other week while in the NICU and at the end of dosing/NICU discharge. Assessments for complications of prematurity, including retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), and bronchopulmonary dysplasia (BPD) will be performed at protocol defined timeframes. Neonates enrolled in the study will have fecal/meconium samples collected daily through 4 days following the start of dosing and weekly thereafter until NICU discharge to determine fecal shedding of [redacted] STP6 and [redacted] STP11. Following completion of blinded study treatment dosing, neonates will be evaluated at 1 week, 4 weeks, 3 months, and 6 months for safety and growth assessments.

Neonates will be stratified into the following four birth weights: 2000-1501g, 1500 to 1000 g, 999 to 750 g and 749 to 500 g. Each birth weight stratum will contain 2 dosing groups – a low dose STP206 group and a high dose STP206 group. Within each birth weight strata/dose level, subjects will be randomized in a 2:1 ratio to the STP206 or control group. Enrollment of neonates into study groups will occur sequentially. Enrollment into the high dose group within a birth weight stratum will not proceed until after the safety data from the low dose group is reviewed by the study independent Data Safety Monitoring Committee (DSMC). Similarly, enrollment into the next lower birth weight stratum will not proceed until the safety data from the high dose group of the prior weight stratum is reviewed by the study independent Data Safety Monitoring Committee (DSMC).

Sample Size:

The study will enroll approximately 100 to 110 neonates.

Subject Selection Criteria:

Inclusion Criteria

1. Neonates with birth weights between 2000-500g
2. Ability to start treatment within four (4) days after birth
3. Gestational age between 23 and 32 weeks at birth
4. Obtaining of informed consent from the subject's appropriate legally authorized representative(s) (e.g., one or both parents, legal guardian), as defined by local law and IRB/IEC requirements, after those individuals have been provided with a full understanding of the study purpose and procedures.
5. Parent(s) who agree to allow the Principal Investigator and his/her staff to follow the procedures and assessments required by the protocol

Exclusion Criteria

1. Infants with, or at high probability for, early onset sepsis (positive blood cultures or the expectation of empirical antimicrobial therapy for ≥5 days)
2. Infants with persistent pulmonary hypertension of the newborn (PPHN)
3. Congenital chromosomal anomalies
4. Congenital or acquired gastrointestinal pathology that preclude feeds within 7 days after birth (e.g. cleft lip is not an exclusion criterion, but a duodenal atresia is)
5. Infants in extremis to whom no further intensive care is offered by attending neonatologist (e.g., infant being provided only hospice/comfort care)

		IND No.: BB 14,046
Protocol No.: STP206-002	**Development Phase**: I	**Indication:** Necrotizing Enterocolitis
Protocol Title: A Phase Ib Randomized, Placebo Controlled Study of the Safety and Efficacy of Once Daily Dosing of STP206 in Premature Very Low Birth Weight and Extremely Low Birth Weight Neonates		

6. Other conditions of the infant, which in the opinion of the attending neonatologist, preclude participation
7. Positive maternal HIV status
8. Participation in another interventional clinical trial
9. Small for gestational age neonates, i.e. neonates that weigh less than the 10th percentile for their gestational age according to the Estimated Fetal Weight Percentile Chart in Appendix D.

Study Duration:
Neonates will be dosed for between 2 and 11 weeks as determined by gestational age at birth, and all neonates will be followed until the 6-month post dosing visit. Thus, the total duration of study participation for each study subject will be between 28 and 39 weeks.

The total duration of the study will be approximately 55 months.

Study Drug, Dose, Route of Administration, and Duration of Treatment:
STP206 will be dosed orally at one of two doses

- STP 206 Low dose**:** approximately 1 billion ($1x10^9$) cfu of [redacted] and approximately 100 million ($1x10^8$) cfu of [redacted] (total of 1.1 billion cfu)
- STP206 High Dose: approximately 9 billion ($9x10^9$) cfu of [redacted] and approximately 900 million ($9x10^8$) cfu of [redacted] (total of 9.9 billion cfu)

Neonates will be dosed for between 2 and 11 weeks with the duration of dosing based upon gestational age at birth. Doses of STP206 are planned to be administered once daily, however, in neonates with dose volume restrictions, doses may be divided into a BID or TID schedule.

Reference Therapy, Dose Route of Administration and Duration of Treatment:
The control treatment will be dosed orally.

- Control: matching volume of water for injection United States Pharmacopeia (USP).

Neonates will be dosed for between 2 and 11 weeks with the duration of dosing based upon gestational age at birth. Doses of the control treatment are planned to be administered once daily; however, in neonates with dose volume restrictions, doses may be divided into a BID or TID schedule.

Criteria for Evaluation:

Safety Variables: Adverse events, SAEs, and changes in clinical (physical examinations, vital signs), growth parameters (head circumference, body length, body weight)

Efficacy Variables: Feeding intolerance, clinical events (NEC, sepsis/bacteremia, feeding intolerance, death, morbidity/complications of prematurity)

Pharmacokinetic Variables: None

Pharmacodynamic Variables: None

Other Variables: Fecal shedding

Statistical Methodology:

Safety Variables:
Adverse events (AEs) will be coded according to MedDRA and will be summarized in frequency tables displaying counts and percentages by body system, preferred term, and treatment group. In addition, AEs will be summarized by relationship to study drug and by severity. All Serious AEs will be summarized in a frequency table.

		IND No.: BB 14,046
Protocol No.: STP206-002	**Development Phase**: I	**Indication:** Necrotizing Enterocolitis
Protocol Title: A Phase Ib Randomized, Placebo Controlled Study of the Safety and Efficacy of Once Daily Dosing of STP206 in Premature Very Low Birth Weight and Extremely Low Birth Weight Neonates		

Efficacy Variables: the incidence of feeding intolerance and clinical events will be compared between treatment groups.

Other Variables:
Fecal shedding [redacted] will be assessed by quantitative and/or qualitative methods and be summarized descriptively by treatment at each time point. Counts will be summarized as a continuous measure and will be summarized descriptively by treatment at each time point. Qualitative responses will be categorized and analyzed by counts and percentages and summarized by treatment at each time point. Change from baseline will also be summarized descriptively by treatment to determine whether fecal shedding values return to baseline levels. Duration of fecal shedding will be summarized descriptively by treatment group.

3. LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
BP	blood pressure
BPD	Bronchopulmo\ ]nary Dysplasia
BUN	blood urea nitrogen
CBC	complete blood count
CBER	Center for Biologics Evaluation and Research
CRADA	Cooperative Research and Development Agreement
CRF	case report form
DCF	data clarification form
DGGE	denaturing gradient gel electrophoresis
DSMC	data safety and monitoring committee
DVRPA	Division of Vaccines and Related Products Applications.
ECG	electrocardiogram
FDA	U.S. Food and Drug Administration
G	gram
GCP	good clinical practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
IEC	independent ethics committee
IND	investigational new drug
INR	international normalized ratio
IP	Investigational Product
IRB	institutional review board
IVH	intraventricular hemorrhage
LBW	low birth weight
LDH	lactate dehydrogenase
LBP	live biotherapeutic
µL	microliter
mg	milligram
mL	milliliter
MIC	minimum inhibitory concentration
MTD	maximally tolerated dose
NICHD	National Institute of Child Health and Human Development

Abbreviation	Term
NICU	neonatal intensive care unit
NIH	National Institutes of Health
PCR	polymerase chain reaction
PDA	patent ductus arteriosus
PK	pharmacokinetic
Po	per os; by mouth; oral
PT	prothrombin time
PTT	partial thromboplastin time
qPCR	quantitative polymerase chain reaction
ROP	retinopathy of prematurity
SAE	serious adverse event
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SPO_2	oxygen saturation by pulse oximeter
TPN	total parenteral nutrition
ULN	upper limit of normal
USP	United States Pharmacopeia

4. GENERAL STUDY INFORMATION

Sponsor Name:	Leadiant Biosciences, Inc.
Sponsor Address:	9841 Washingtonian Blvd. Suite 500 Gaithersburg, Maryland 20878 (800) 447-0169
Sponsors Authorized Representative:	[redacted] Vice President & Chief Medical Officer Leadiant Biosciences, Inc. 9841 Washingtonian Blvd. Suite 500 Gaithersburg, Maryland 20878 Tel: [redacted] Fax: [redacted]
Lead PI/Coordinating Investigator:	[redacted]
Medical Monitor:	[redacted] Vice President & Chief Medical Officer Leadiant Biosciences, Inc. 9841 Washingtonian Blvd. Suite 500 Gaithersburg, Maryland 20878 Tel: [redacted] Fax: [redacted]

The following study information is contained in a study specific reference manual for this study protocol:

- Participating Investigators
- Contract Research Organization(s)
- Central Laboratories
- Data and Safety Monitoring Committee

5. INTRODUCTION

Leadiant Biosciences, Inc. (Leadiant) is developing a probiotic, STP206 Live Biotherapeutic, for prevention of Necrotizing Enterocolitis (NEC) in premature very low birth weight (VLBW) (<1500 g) and extremely low birth weight (ELBW) (<1000 g) neonates.

5.1. Disease Background

NEC is the most common serious acquired disease of the gastrointestinal tract in preterm infants[1], with the majority of NEC occurring in infants with birth weights below 1500 g.[2] NEC is characterized by signs of abdominal distension, intra-abdominal inflammation, and radiologic presence of pneumatosis intestinalis and/or portal venous air or free air indicating perforation.

In 2008, there were approximately 347,209 premature babies weighing less than 2500 g born in the United States, with approximately 61,773 of these babies weighing less than 1500 g at birth.[3] These VLBW babies are at the highest risk for developing NEC. NEC has been reported to occur in approximately 10% of VLBW infants,[2] although the incidence varies among countries and neonatal centers. The mortality rate of VLBW infants with NEC is approximately 20%.[4, 5] In addition to the mortality rates, infants with NEC often require surgical intervention,[1] have an increased rate of total parenteral nutrition (TPN) related complications and require extended hospitalizations.[6] Data from the National Institute of Child Health and Human Development Network (NICHD) suggest an increase in neurodevelopmental impairment rates among infants with NEC and sepsis.[7]

Over the past 30 years, several interventions to decrease the incidence of NEC in VLBW infants have been attempted, including feeding manipulation, prophylactic antibiotics, and immunoglobulins; however, the mortality rate has remained unchanged.

5.2. Description of Investigational Product

STP206 Live Biotherapeutic (LBP) contains [redacted] STP6 [redacted] and [redacted] STP11. The product is manufactured by [redacted] for Leadiant under current good manufacturing practices (cGMP) regulations for pharmaceutical grade biologic drugs.

5.3. Investigational Product Background Information

5.3.1. Non-Clinical Studies

There have been no non-clinical studies of STP206 in models of NEC. [redacted]

A variety of pathophysiological mechanisms have been cited as being of importance for the development of NEC. These include abnormal colonization of the gut with enterobacteriaceae and clostridia, increased mucosal permeability allowing translocation of macromolecules and bacteria, abnormalities in the intestinal immune response, and aberrant gut metabolism.

Non-clinical studies [redacted] have shown these bacteria to have the following beneficial effects with respect to NEC pathophysiology:

- [redacted]

[redacted]

[redacted]

[redacted]

There have been three neonatal animal studies designed to evaluate the role of probiotic supplementation on the development of experimental necrotizing enterocolitis. [redacted]

[redacted]

5.3.2. Clinical Studies

5.3.2.1. Phase 1 Study in Healthy Adult Volunteers

The safety and tolerability of STP206 in healthy adult subjects has been studied in a randomized, double blind, placebo controlled clinical study (Leadiant Protocol STP206-001). In this study, subjects received STP206 as either a single dose or daily doses for seven consecutive days. Each STP206 dose consisted of 100 billion ($1x10^{11}$) CFU of [redacted] (STP6) and 10 billion ($1x10^{10}$) CFU of [redacted]

(STP11). Subjects were monitored for fecal shedding of STP206 organisms for 30 days following completion of dosing and for adverse events (AEs) through 6 months following dosing.

Twenty-four (24) subjects were enrolled in the study. Seventeen (17) subjects received STP206 with nine (9) subjects receiving single dose STP206 and eight (8) subjects receiving daily doses of STP206 for seven consecutive days; seven (7) control subjects received placebo (vehicle).

Thirty (30) AEs were reported by 8 STP206-treated subjects, and 11 of these events, reported by 6 subjects were considered to be related to STP206. Related AEs included nausea, diarrhea, flatulence, stomach cramps, dry mouth, lightheadedness, dizziness, feeling hot and feeling cold. All events were mild or moderate in severity and most were not related to STP206. There were no serious adverse events (SAEs) and none of the events required the discontinuation of STP206 dosing.

[redacted] (STP11) was below quantifiable limits in all fecal samples from all subjects throughout the study. [redacted] (STP6) was detected in four subjects: one subject in Cohort 1 and three subjects in Cohort 2. All four subjects with STP6 detected were STP206-treated subjects. Fecal shedding returned to baseline in all four subjects by the next scheduled assessment.

5.3.2.2. Probiotics for the Prevention of NEC

Prior to the initiation of ongoing study STP206-002, no clinical trials of STP206 for the prevention of NEC in neonates had been conducted.

A review of published clinical trials on the use of probiotics for the prevention of NEC through 2009 revealed six randomized, controlled studies[24-29] and one historical controlled study.[30] [redacted]

Additional details regarding these studies are contained in the STP206 Investigators Brochure.

5.4. Target Population and Study Rationale

The target population for intended clinical use of STP206 is premature VLBW infants (1500 to 1001 g) and ELBW infants (1000 to 500 g) who are at risk of developing NEC. NEC is of multifactorial origin and one of the predisposing factors for NEC is an abnormal pattern of bowel colonization [redacted] Probiotics administered to preterm infants may colonize the bowel with normal flora and thereby counterbalance the increase in those organisms that have been associated with NEC.[28, 30] [redacted] Therefore, the hypothesis is that influencing the intestinal flora by the administration of probiotics can provide a balance between beneficial and pathogenic bacteria, modulate the pro-inflammatory response, and enhance intestinal maturation, thus possibly reducing the incidence of NEC. This hypothesis is supported by the clinical trials (see Section 5.3.2.2 for a summary of studies conducted with probiotics to date). These published clinical studies conducted in neonates [redacted] suggest that supplementation of VLBW infants with STP206 may have clinical use in the prevention of NEC.

5.5. Potential Risks and Benefits

Potential risks associated with the administration of STP206 LBP in humans are not fully known. Based upon the results of the Phase 1 adult study, the nature of the product and published clinical reports, possible AEs include the following:

- Nausea
- Vomiting
- Diarrhea
- Flatulence
- Constipation
- Abdominal Pain
- Epigastric pain
- Dysgeusia
- Dry Mouth
- Dehydration
- Fever
- Chills
- Chills
- Diaphoresis
- Infections, including bacteremia
- Feeling hot or cold
- White blood cell count increased
- Dizziness
- Headache
- Anxiety
- Cough
- Nasal congestion
- Oropharyngeal pain

Refer to the STP206 Investigator's Brochure for additional information.

6. STUDY PURPOSE, OBJECTIVES, AND ENDPOINTS

6.1. Purpose

The purpose of this study is to examine the safety, tolerability, and preliminary NEC-preventative efficacy of two dose levels of STP206 in premature VLBW and ELBW neonates.

6.2. Objectives

6.2.1. Primary Objective

The primary objective of the study is to assess the safety and tolerability of once-daily dosing of two dose levels of STP206 versus control in four different birth weight strata in premature neonates.

6.2.2. Secondary Objectives

The secondary objectives of the study are to:

- Assess the fecal shedding after daily dosing of each component of STP206 throughout the dosing phase
- Describe the incidence of NEC in STP206-treated subjects compared to control subjects
- Describe the incidence of clinical events (sepsis/bacteremia, feeding intolerance, morbidity/complications of prematurity) in STP206-treated subjects compared to control subjects
- Describe the progression of standard neonatal growth parameters in STP206-treated subjects compared to control subjects

6.3. Endpoints

6.3.1. Primary Endpoints

The incidence and severity of AEs, SAEs and changes in clinical parameters in STP206-treated subjects compared to control subjects from baseline through 30 days after the last dose of blinded study treatment.

6.3.2. Secondary Endpoints

The secondary endpoints of the study are:

- The incidence and the severity of AEs and SAEs in STP206-treated subjects compared to control subjects from baseline through six months after the last dose of blinded study treatment
- The incidence of clinical events (NEC, sepsis/bacteremia, feeding intolerance, death, morbidity/complications of prematurity) in STP206-treated subjects compared to control subjects from baseline through hospital discharge
- The assessment of the fecal shedding of STP206 organisms in STP206-treated subjects compared to its baseline and to control subjects through the last dose of blinded study treatment

- The assessment of the changes in routine clinical parameters in STP206-treated subjects compared to control subjects at baseline through the last dose of blinded study treatment
- The assessment of the progression of standard neonatal growth parameters in STP206-treated subjects compared to control subjects through the 6-month postdosing visit.

6.3.2.1. Exploratory Endpoints

Exploratory Endpoints of the study include:

- The incidence of suspected NEC (Stage I NEC) in STP206-treated subjects compared to control subjects through hospital discharge
- The incidence of suspected sepsis in STP206-treated subjects compared to control subjects through hospital discharge
- The incidence of antibiotic usage in STP206-treated subjects compared to control subjects through hospital discharge

7. STUDY DESIGN

7.1. Overview of Study Design

Protocol STP206-002 is designed as a multi-center, randomized, double-blind, placebo-controlled study. This will be a dose escalation study to determine safety and tolerability of two doses of STP206 versus control in four sequentially decreasing birth weight strata.

Neonates for whom informed consent is obtained and who meet eligibility criteria will be eligible to enroll in this study. All neonates enrolled in the study will be randomized and will receive daily doses of blinded study treatment (STP206 or control) for between 2 and 11 weeks with the duration of dosing based upon gestational age at birth. All neonates enrolled in the study will be placed under Universal Precautions and all study personnel with subject contact are trained in appropriate NICU infection control practices.

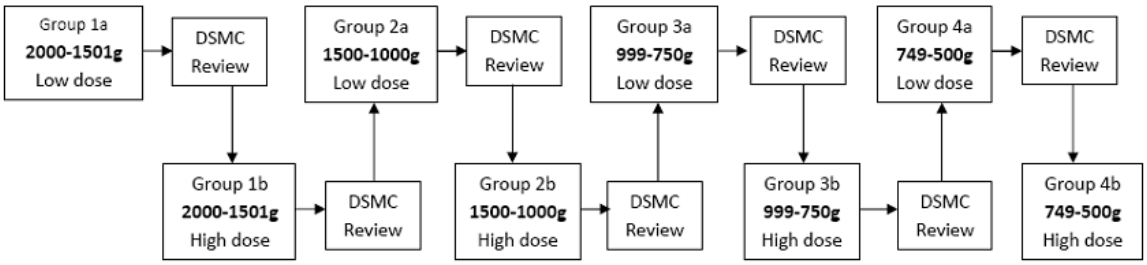
- The doses of STP206 to be administered are:
  - Low dose STP206: approximately 1 billion ($1x10^9$) CFU of [redacted] and approximately 100 million ($1x10^8$) CFU of [redacted] (total of 1.1 billion CFU)
  - High dose STP206: approximately 9 billion ($9x10^9$) CFU of [redacted] and approximately 900 million ($9x10^8$) CFU of [redacted] (total of 9.9 billion CFU)
- Neonates will be stratified into the following four birth weights: 2000-1501 g, 1500 to 1000 g, 999 to 750 g, and 749 to 500 g.
- Within each birth weight strata, subjects will be randomized to the STP206 low dose or control group followed by the STP206 high dose or control group, resulting in the following eight study groups:
  - Study Group 1a – Birth weight 2000 to 1501 g and Low dose STP206 versus control
  - Study Group 1b – Birth weight 2000 to 1501 g and High dose STP206 versus control

- Study Group 2a – Birth weight 1500 to 1000 g and Low dose STP206 versus control
- Study Group 2b – Birth weight 1500 to 1000 g and High dose STP206 versus control
- Study Group 3a – Birth weight 999 to 750 g and Low dose STP206 versus control
- Study Group 3b – Birth weight 999 to 750 g and High dose STP206 versus control
- Study Group 4a – Birth weight 749 to 500 g and Low dose STP206 versus control
- Study Group 4b – Birth weight 749 to 500 g and High dose STP206 versus control

- Each birth weight strata/STP206 dose group will consist of 12 subjects.
- Within each birth weight strata/STP206 dose group, subjects will be randomized in a 2:1 ratio to either the STP206 or control group.
- Enrollment of neonates into study groups will occur sequentially. Enrollment into the high dose group within a birth weight stratum will not proceed until after the safety data from the low dose group is reviewed by the study independent Data Safety Monitoring Committee (DSMC). Similarly, enrollment into the next lower birth weight stratum will not proceed until the safety data from the high dose group of the prior weight stratum is reviewed by the study independent DSMC. If, at any point during the study the DSMC determines that the high dose of STP206 is not safe and well tolerated, weight de-escalation will continue with the low dose of STP206.

The sequencing of treatment groups for the study is shown in Figure 1. Enrollment will begin with neonates weighing 2000 - 1500 g at the low dose of STP206 (Group 1a). Safety data through the last dose of blinded study treatment will be evaluated by the DSMC (see Section 7.7). Subsequent cohorts will not open for enrollment before the data from the previous cohort has been reviewed by the DSMC. If the safety data review conducted by the DSMC determines there are no safety concerns, study groups will open sequentially as illustrated in Figure 1.

Figure 1: Treatment Group Sequence



All neonates enrolled will receive daily doses of blinded study treatment through 34 weeks of post-conceptional age or neonatal intensive care unit (NICU) discharge, whichever comes first. While in the NICU, neonates will be evaluated daily for signs/symptoms of NEC, feeding volumes/feeding tolerance, AEs, and concomitant medications. Physical examinations and vital signs will be performed daily during the dosing period and at the end of dosing/NICU discharge. Growth assessments will be performed every other week while in the NICU and at the end of dosing/NICU discharge. Assessments for complications of prematurity, including retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), and bronchopulmonary dysplasia (BPD) will be

performed at protocol defined timeframes (see Section 11.2). Neonates enrolled in the study will have fecal/meconium samples collected daily through 4 days following the start of dosing and weekly thereafter until NICU discharge to determine fecal shedding of [redacted] (STP6) and [redacted] (STP11).

Following completion of blinded study treatment dosing, neonates will be evaluated at 1 week, 1 month, 3 months, and 6 months for safety and growth assessments.

7.1.1. Stopping Criteria

The following stopping events reported to Leadiant will be evaluated by the DSMC to assess whether the events merit a temporary suspension or stopping study enrollment:

- Any death due to an AE assessed to be directly related to the administration of STP206
- Isolation of an STP206 organism from a normally sterile site (including bacteremia but excluding peritonitis in association with intestinal necrosis) in any subject

All reports of stopping events will be forwarded to the DSMC for review. If either of the above events occurs, enrollment will be suspended temporarily while the DSMC is evaluating the event. Subjects on blinded study drug will continue dosing during the assessment of the event.

If a stopping criterion is met, the DSMC will perform an unblinded review of the event to assess causality and its overall impact on subject safety and provide its recommendations to Leadiant. If an event, in the opinion of the DSMC, is related to the administration of STP206, dosing of all ongoing study subjects will be halted, and the study will be suspended temporarily. FDA will be notified of all DSMC's recommendations before taking any actions with the study.

A flow diagram for the process of evaluating infections of normally sterile sites that are suspected to be associated with STP206 organisms (*i.e.,* gram positive bacilli) is provided in Appendix E.

7.1.2. Study Periods

Subject participation will be classified into four study periods:

- Screening Period – from the time of informed consent through administration of the first dose of study drug.
- Treatment Period – this will be the period when subjects are actively being administered blinded study treatment.
- Immediate Follow-up Period – this period will begin the day following the last dose of blinded study treatment through 30 days following administration of the last dose.
- Long-Term Follow-up Period – this period will begin after completion of the immediate follow-up period.

7.1.3. Recruitment and Enrollment

The total duration of recruitment for the study will be approximately 4 years.

7.1.3.1. Recruitment Definitions

- Screen Failure - Neonates for whom parental informed consent is obtained and do not proceed to study treatment (e.g., withdrawal of parental consent, does not meet entry criteria). Screening data will be documented in the study specific Screening Log. Reasons for screen failure will be documented in the subject's source documents and in the Screening Log.
- Enrolled – Neonates who pass all screening evaluations and are randomized to blinded study treatment.
- Treated – Neonates who are enrolled and receive at least one dose of blinded study treatment.
- Treatment Discontinuation – Neonates who receive blinded study treatment but fail to complete treatment through 34 weeks of post-conceptional age or hospital discharge.
- Study Discontinuation – Neonates who complete blinded study treatment but not all follow-up visits
- Completed Subject - Neonates who complete treatment and all follow-up visits

7.2. Study Treatments

7.2.1. Rationale for Dose Selection and Choice of Control Groups

The STP206 doses and treatment duration selected for this study are based upon [redacted] studies [redacted] evaluating [redacted] The doses planned for this study (total of 1.1 x 10^9 CFU for low dose and 9.9x10^9 CFU for high dose) bracket the average dose administered in these studies.

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	

[redacted] The dosing duration planned for this study (through 34 weeks of post-conceptional age or hospital discharge, whichever comes first) is consistent with the dosing durations employed in these studies. The dosing duration is also supported by the knowledge that neonates will be at minimal risk of NEC and will be discharged at a post-conceptional age of 34 weeks.

The control group (standard of care plus STP206 reconstitution vehicle) will provide a comparison of incidence of clinical events and study endpoints in a blinded fashion and minimize bias.

7.3. Assignment of Subjects to Treatment

Neonates enrolled into the study will be randomized to receive either STP206 or control in a 2:1 ratio based upon a pre-prepared, computer generated, centralized randomization schedule.

To assure a balance in birth weight among treatment groups, randomization will be stratified by birth weight.

After obtaining informed consent and completion of screening assessments, neonates passing screening will be eligible for enrollment. The unblinded site research pharmacist (or other designated site personnel who has no role in screening, enrolling or qualifying study subjects) will obtain a randomization number and treatment assignment through an automated randomization system.

The unblinded research pharmacist is responsible for maintaining treatment assignments in a secure place with restricted access to assure the integrity of the study blind and prevent the identity of treatment assignments from becoming known to blinded staff at the research facility.

7.4. Study Duration

The total duration of the study will be approximately 55 months.

7.4.1. Duration of Treatment and Subject Participation

Subjects enrolled in this study will receive a variable number of daily doses of STP206 or vehicle based on their gestational age. Based on the study entry criteria, treatment will be between 2 and 11 weeks in duration determined by the subject gestational age at birth. All neonates will be followed the 6-month postdosing visit.

The total duration of study participation for each study subject will be between 28 and 39 weeks.

7.5. Methods Used to Minimize Bias

Eligible study subjects for whom parental consent is obtained will be consecutively enrolled and randomized to receive STP206 or control using a centralized randomization system (see Section 7.3) in an effort to minimize subject selection bias.

All staff performing study assessments will be blinded to the identity of the treatment assignment to which the infant has been randomized in an effort to minimize bias in study assessments. Fecal shedding results will not be shared with the study sites during the course of the study as these results may potentially unblind study staff to the identity of treatment.

As study drug is supplied in open-label fashion, the study will require unblinded site personnel to randomize subjects and prepare study drugs for administration. The study will use a third party (e.g., pharmacist or other designated site personnel who has no role in screening, enrolling, or qualifying study subjects) blind to minimize bias in study conduct.

As there may be a visual difference between STP206 and control treatments (white vs. clear, respectively), an opaque syringe will be used to administer the blinded study treatment.

7.6. Appropriateness of Study Measurements

The physical examinations and AE assessments used in this study are standard measures of monitoring safety during the course of clinical trials. The assessments and monitoring used to diagnose NEC and complications of prematurity are standard methods utilized in NICUs and are appropriate to assess study objectives. Growth measurements used in this study are standard for the determining neonatal growth.

Fecal shedding will be monitored by validated qPCR assays developed specifically for the detection of the STP206 organisms in feces.

Identification of STP206 organisms in cultures of normally sterile sites will be assessed using validated qPCR assays that were developed for the detection of the components of STP206 from isolates.

7.7. Study Monitoring Committees

An independent DSMC will be used to review data generated in this study, provided as a separate document. A Charter for the DSMC outlining the membership, roles and responsibilities was developed and finalized prior to the initiation of the study and submitted to the FDA on 03 December 2013 (SN 0030).

Available data on primary and secondary endpoints, including AEs, will be included in each review. The DSMC can give recommendations regarding continuation of study, temporary hold on study while additional data is further analyzed, or termination of the study. The DSMC will also review events that may constitute stopping criteria (see Section 7.1.1) on an as needed basis. Unscheduled DSMC review of study data may occur at any time on an as-needed basis if requested by the DSMC.

The DSMC will review data for each dose/birth weight group to assess whether proceeding to lower birth weight and/or higher STP206 doses is warranted. Data reviewed at each DSMC meeting will follow the following schedule:

- For the first group of subjects (Study Group 1a – Birth weight 2000 to 1501 g and low dose STP206), data will be reviewed through the completion of dosing.
- For the next six DSMC reviews (Study Groups 1b through 4a), data the current dose group will be reviewed through the completion of dosing along with 30-day post dosing data from the prior dose group.
- For the final DSMC review (Study Group 4b), data through 30-days post dosing will be reviewed.

8. STUDY DRUG AND TREATMENTS

8.1. Description of Study Drug(s)

8.1.1. STP206

STP206 Live Biotherapeutic is a combination of defined quantities of lyophilized [redacted] (STP6) and [redacted] (STP11) components of drug product. The product components will be individually reconstituted with water for injection (USP) prior to administration.

8.1.2. Control

The control for this study will be water for injection (USP), the vehicle used to reconstitute STP206.

8.2. Supply and Labeling

8.2.1. How Supplied

8.2.1.1. STP206

The individual components of STP206, [redacted] (STP6) and [redacted] (STP11), will be supplied separately in individual 3-mL-glass vials covered with rubber stoppers and aluminum caps with color-coded plastic flip-tops.

- Each vial of STP6 contains between 5 x 10^8 and 5 x 10^{10} CFU per vial and identified with a white flip-top.
- Each vial of STP11 contains between 5x10^7 and 5x10^9 CFU per vial and identified with a violet flip-top.

STP6 and STP11 components of STP206 drug product will be packaged in the separate boxes containing 50 vials per box.

8.2.1.2. Control / Vehicle

Control/vehicle, *i.e.*, water for injection (USP), will not be supplied by Leadiant; it will be provided by the research sites conducting the study.

8.2.2. Labeling

Each vial of the STP206 drug product will be labeled with the product component name and a viable cell (CFU) count per vial, Investigational use statement, and a statement cautioning the product is only for oral use. The vial label will also have extra space for recording of dispensing date and ID of the subject to whom the drug was administered. The samples of vial labels are provided in Figure 2.

Figure 2: Sample of STP6 and STP11 Vial Labels

Sample Label
[redacted] STP6 (5 x 10^8 to 5 x 10^{10} cfu/vial)
FOR ORAL USE ONLY
Caution: New Drug - Limited by Federal Law to Investigational Use

Sample Label
[redacted] STP11 (5 x 10^7 to 5 x 10^9 cfu/vial)
FOR ORAL USE ONLY
Caution: New Drug - Limited by Federal Law to Investigational Use

Each box of [redacted] (STP6) and [redacted] (STP11) will be labeled with the box number, protocol number, product name, lot number, manufacture date, Investigational use statement, storage condition, preparation and administration instructions and manufacturer and sponsor information. The samples of box labels are provided in Figure 3.

Figure 3: The Box Label Samples for Components of STP206 Drug Product

Sample Label

Box # [XX]
Protocol STP206-002 *****FOR ORAL USE ONLY*****
Contains 50 vials of [redacted] STP6 (5×10^8 to 5×10^{10} cfu/vial)

Lot No. 08SBF03 **Date of Mfg.: 07Nov2008**
Store at 2 – 8 °C
Caution: New Drug - Limited by Federal Law to Investigational Use
Reconstitute with Water for Injection and co-administer with [redacted] STP11 per protocol instructions
Manufactured by: [redacted]
Manufactured for: Leadiant Biosciences, Inc.
9841 Washingtonian Blvd., Suite 500
Gaithersburg, MD 20878
(800) 447-0169

Sample Label

Box # [XX]
Protocol STP206-002 *****FOR ORAL USE ONLY*****
Contains 50 vials of [redacted] STP11 (5×10^7 to 5×10^9 cfu/vial)
Lot No. 09SLF01 **Date of Mfg.: 12Mar2009**
Store at 2 – 8 °C
Caution: New Drug - Limited by Federal Law to Investigational Use

Reconstitute with Water for Injection and co-administer with [redacted] STP6 per protocol instructions

Manufactured by: [redacted]
Manufactured for: Leadiant Biosciences, Inc.
9841 Washingtonian Blvd., Suite 500
Gaithersburg, MD 20878
(800) 447-0169

8.3. Storage Conditions

8.3.1. STP206

The vials of individual components of STP206, [redacted] (STP6) and [redacted] (STP11) will be stored under monitored refrigerated conditions (2 - 8°C) prior to reconstitution for use in the research pharmacy at each site.

8.4. Preparation for Administration

8.4.1. STP206

Each vial of STP6 [redacted] and STP11 [redacted] will be reconstituted using with 1.0 mL of water for injection of USP quality in the research pharmacy (Note: STP206 must not be reconstituted at the subject's bedside). The appropriate volume of the reconstituted bacterial suspension will be removed from STP6 and STP11 vials by sterile syringes and stored in the individual syringes until administered. The reconstituted STP206 must be administered within 2 hours following reconstitution.

The following dose volumes will be administered:

- For the low dose of STP206, 0.1 mL of STP6 and 0.1 mL STP11 will be drawn up for administration (0.2 mL total).
- For the high dose of STP206, 0.9 mL of STP6 and 0.9 mL of STP11 will be drawn up for administration (1.8 mL total).

The syringes with the reconstituted STP206 will be labeled with the protocol number, subject identification (randomization number and initials), date and time of preparation, dose volume, and the words "contains STP6 or vehicle" [redacted] or "contains STP11 or vehicle" [redacted].

8.4.2. Control

Syringes containing the matching volume of vehicle for both STP6 and STP11 will be used as the control. Syringes will be labeled in the same manner as syringes with STP206 to maintain study blinding.

8.5. Study Drug Accountability

The Food and Drug Administration requires accounting for the disposition of all study material (active or control). The Investigator is responsible for ensuring that a current record of study drug disposition is maintained and dispensed only at an official study site by authorized personnel as required by applicable regulations and guidelines. Records of product disposition as required by federal law consist of the date received, date dispensed/administered, quantity dispensed/administered, and the subject to whom the material was administered.

The Investigator or designee authorized by the Investigator will be responsible for maintaining accurate records of the shipment, dispensing/return of the study drug by the study site, and return of used/undispensed study drug to Leadiant. Drug accountability records must be available for inspection by Leadiant or its representative and is subject to inspection by a regulatory agency (*e.g.*, FDA, EMA) at any time. Copies of the records will be provided to Leadiant at the conclusion of the study.

At the termination of the study, all unused investigational product must be returned to Leadiant (or destroyed, if not feasible to return to Leadiant). A written explanation will be required for any product not returned to Leadiant, stating the reason it was not returned. An Investigational Product Return Form and the study drug accountability form must be maintained in either the pharmacy or

study site. Study drug accountability records will be reviewed by an unblinded monitor on a routine basis.

9. STUDY POPULATION

9.1. Number of Subjects

The study will be conducted at up to 20 active centers.

This study will require at least nine evaluable neonates (*i.e.,* completing minimum dosing duration described in Section 11.3.2 and having a post-dosing assessment performed) per treatment group for each of the eight treatment groups. It is not expected that there will be a high percentage of neonates that do not meet evaluability criteria. Thus, to achieve the required number of evaluable neonates, it is anticipated that approximately 100 to 110 neonates will be enrolled in this study.

There are no limitations on the number of subjects that may be enrolled at each center.

9.2. Inclusion Criteria

1. Neonates with birth weights between 2000-500g
2. Ability to start treatment within four (4) days after birth.
3. Gestational age between 23 and 32 weeks at birth.
4. Obtaining of informed consent from the subject's appropriate legally authorized representative(s) (e.g., one or both parents, legal guardian), as defined by local law and IRB/IEC requirements, after those individuals have been provided with a full understanding of the study purpose and procedures.
5. Parent(s) who agree to allow the Principal Investigator and his/her staff to follow the procedures and assessments required by the protocol.

9.3. Exclusion Criteria

1. Infants with, or at high probability for, early onset sepsis (positive blood cultures or with the expectation of empirical antimicrobial therapy for ≥5 days).
2. Infants with persistent pulmonary hypertension of the newborn (PPHN)
3. Congenital chromosomal anomalies.
4. Congenital or acquired gastrointestinal pathology that preclude feeds within 7 days after birth (e.g., cleft lip is not an exclusion criterion, but a duodenal atresia is).
5. Infants in extremis to whom no further intensive care is offered by attending neonatologist (e.g., infant being provided only hospice/comfort care).
6. Other conditions of the infant, which in the opinion of the attending neonatologist, preclude participation.
7. Positive maternal HIV status.
8. Participation in another interventional clinical trial.

9. Small for gestational age neonates, i.e. neonates that weigh less than the 10th percentile for their gestational age according to the Estimated Fetal Weight Percentile Chart in Appendix D.

9.4. Post-Enrollment Restrictions

9.4.1. Concomitant Medications

Products containing probiotic bacteria are prohibited. There are no other restrictions on concomitant medications.

9.4.2. Concurrent Treatments

There are no restrictions on concurrent treatments other than those described under clinical management (Section 10.6).

9.4.3. Dietary Restrictions

Dietary management of neonates is described in Section 10.6.1.

9.5. Withdrawal of Enrolled Subjects

In the absence of a medical contraindication or significant protocol violation, every effort will be made by the Principal Investigator to keep subject in the study. The primary reason for a subject withdrawing prematurely should be selected from the following standard categories:

- Adverse Event - clinical or laboratory events that in the judgment of the Principal Investigator require discontinuation of study medication in the best interests of the subject.
- Death – death of the subject, whether study related or not.
- Withdrawal of Consent – subject's parents desire the subject to be withdrawn from further participation in the study in the absence of a medical need to withdraw determined by the Principal Investigator.
- Lost to follow-up - the subject did not return for follow-up visit(s) following the completion of study treatment and hospital discharge despite attempts to contact the subject's parents to maintain scheduled appointments.
- Protocol Non-compliance - the subject's participation in the study failed to meet protocol requirements, which had a direct impact on subject safety and evaluability of the subject's data. The violation necessitated premature termination from the study.
- Subject meets withdrawal criteria – the subject's condition meets the criteria for withdrawal from the study (Section 9.5.1).
- Other - causes of premature termination from the study other than the above (e.g., termination of study by Leadiant, subject relocated).

9.5.1. Withdrawal Criteria

Subjects will be withdrawn from the study if the subject meets any of the following criteria after the initiation of study treatment:

- Necrotizing enterocolitis (Bell stage II or worse)

- Any event requiring stopping of all enteral intake for more than 7 days

9.5.2. Withdrawal Procedures

All subjects who are withdrawn from the study will have a post dosing assessment completed. All subjects who received blinded study treatment, with the exception of those for whom consent is withdrawn, will be followed for all subsequent study assessments per study protocol.

9.5.3. Replacement of Discontinued Subjects

The study will require a minimum of nine evaluable subjects per treatment group. If more than three subjects do not complete the minimum required duration of study treatment (see Section 11.3.2) and have a post dosing assessment, subsequent subjects not meeting the minimum required duration of study treatment and follow-up assessments will be replaced.

10. DESCRIPTION OF STUDY PROCEDURES

The Schedule of Assessments for the study is provided in Appendix A.

All neonates enrolled in the study will be placed under Universal Precautions and all study personnel with subject contact are trained in appropriate NICU infection control practices.

10.1. Informed Consent

After being provided with a full understanding of the study purpose and procedures, the subject's appropriate legally authorized representative(s) (e.g., one or both parents, legal guardian) as defined by local law and IRB/IEC requirements will provide written informed consent and HIPAA authorization using the current version of the IRB-approved informed consent form and HIPAA authorization forms. Consent from both parents (as opposed to only one) will be obtained, if required by the local IRB in accordance with IRB requirements.

The Principal Investigator (PI) and other site personnel as assigned by the PI will be responsible for obtaining informed consent and HIPAA authorization after the study has been explained to the subject's parents/legal guardian and all questions have been answered. The original signed consent form will be filed in the subject's records in accordance with institutional policy and a copy will be provided to the subject's parents/legal guardian. The consent process will be documented in the subject's source documents and the Informed Consent Log supplied for the study.

Written informed consent must be obtained prior to performing any study related procedures.

If a protocol amendment requires revision to the informed consent form, the revised IRB-approved form must be used to obtain and document re-consent from the subject's parents/legal guardian for all subjects currently enrolled in the study.

For mothers below the age of consent and who are emancipated minors, state and local regulations will determine how informed consent and HIPAA authorization are obtained.

10.2. History and Baseline Characteristics

The following history and demographic data will be collected:

- Maternal History and Baseline Characteristics – age, ethnicity, race, ongoing medical conditions, concomitant medications, fertility medications taken for this pregnancy (if

applicable), reproductive history, maternal smoking during pregnancy, alcohol use during pregnancy, and recreational drug use during pregnancy.

- Pregnancy History and Delivery – pregnancy complications (description and dates), multiple gestation, gestational age/gestational week at time of delivery, type of delivery, and medications at delivery or around time of delivery. For cesarean section specify whether elective or emergent; for vaginal deliveries specify whether spontaneous, induced, forceps- or vacuum-assisted.
- Infant History and Baseline Characteristics – sex, race, birth date and time, 1- and 5-minute Apgar Scores, birth weight (g), head circumference (cm), length (cm), cord pH and base deficit (if obtained), birth resuscitation/stabilization support used (supplemental oxygen, PPV, CPAP, intubation, chest compression, epinephrine), pre-enrollment medications (e.g., surfactant, antibiotics), date/time of NICU admission. Birth weight will be characterized in relation to gestational age.[35]

10.3. Safety Procedures

10.3.1. Physical Examination

Physical examinations will be performed that will include assessments of the following body systems:

- Head, Eyes, Ears, Nose, Throat (HEENT)
- Cardiovascular
- Respiratory
- Central nervous system
- Abdomen/Gastrointestinal
- Genitourinary
- Musculoskeletal
- Dermatologic/Skin

Physical examination findings will be noted in the subject medical records. The screening and Day 1 physical examinations will be recorded on a CRF for the subject. Subsequent physical examinations performed in the NICU will not be recorded on a CRF but all adverse findings meeting the definition of an AE (see Section 12.2.1), independent of relationship or severity, will be recorded on the CRF as either adverse events or complications of prematurity.

10.3.2. Vital Signs

Vitals signs will include:

- Temperatures (˚C) - axillary or by skin probe
- Heart rate (BPM) - measured by auscultation
- Respiratory rate (breaths/minute) – measured by observation

- Blood pressure (mmHg) – measured by either non-invasive (oscillometric) or invasive (arterial pressure transducers) techniques
- SpO_2 (pulse oximetry in %)

Vital signs will be noted in the subject medical records. The screening and Day 1 vital signs will be recorded on a CRF for the subject. If there are multiple measurements obtained as standard of care during these study days, the first assessments obtained after noon will be used for the study. The date and time of when these assessments were obtained will be recorded. Subsequent vital signs performed in the NICU will not be recorded on a CRF, but all adverse findings will be recorded on the CRF as AEs.

10.3.3. Growth Assessments

The following assessments of growth will be collected:

- Head circumference (cm) using standard measuring tape
- Body length (cm) using standard measuring tape
- Body weight (g) using digital scale

10.3.4. Imaging Examination

Cranial ultrasonography will be performed to ascertain presence/absence of intraventricular hemorrhage (IVH). If IVH is noted, the grade of the IVH will be recorded.

10.3.5. Adverse Event Assessment

AEs occurring in neonates will be determined based upon physical findings, functional findings, laboratory findings, and routine observation of the neonate. AEs will be assessed from the time of initial administration of blinded study treatment through 6 months following completion of dosing and be recorded regardless of severity or relationship to blinded study treatment. Ongoing AEs will be followed by standard NICU practice until resolution or stabilization. For each AE, the following information will be recorded:

- Onset date and time
- Resolution date and time
- Severity/intensity (see Section 12.2.5)
- Relationship to study drug (see Section 12.2.4)
- Serious or non-serious (see Section 12.2.3)
- Actions taken to manage/treat the event
- Outcome of the event - resolved, resolved with sequelae, ongoing, death

Complications of prematurity (see Section 10.5.2) will be recorded separately and not recorded as AEs.

10.3.5.1. Assessment and Treatment of Sepsis

The Investigator will initiate a work-up for suspected sepsis (including the involvement of either one of the two bacteria strains in STP206) for full evaluation, diagnosis, and treatment, if indicated by clinical signs and symptoms.

In the case of suspected sepsis, the Investigator will:

- Perform full clinical evaluation of the subject.
- Study drug treatment will be suspended temporarily. Study drug treatment may be re-initiated at the discretion of the Investigator based on the subject's clinical condition (see Section 10.8.2).
- Obtain peripheral blood cultures (*i.e.,* not through a central line) for aerobic and anaerobic pathogens to identify the offending pathogen(s) prior to initiating antibiotic treatment. If obtaining a culture prior to initiation of antibiotics is not possible, a culture should be collected as soon as possible following initiation of antibiotic treatment.
- If the site's local laboratory identifies gram positive bacilli in the blood culture, a sample of the isolate will be forwarded to the central laboratory for qPCR analysis to confirm, if the offending bacteria are [redacted] STP11 or [redacted] STP6.
- Start treatment with antibiotics, as appropriate.
- Clinical management, monitoring (*e.g.,* clinical signs, vital signs, X-rays, and laboratory investigations) and supportive care of the subject will be based upon the treatment protocol(s) of the institution and the discretion of the treating physician and/or Principal Investigator based upon the individual subject requirements and changes in clinical status over time.
- Feeding will be continued or adjusted based upon subject stability as determined by the treating physician and/or Principal Investigator (*e.g.,* stable neonates may continue to be on enteral feeds, while infants with respiratory distress or suspected NEC will receive nothing by mouth (NPO) and be maintained on intravenous fluids).
- If the initial cultures obtained were positive, obtain a repeat set of aerobic and anaerobic cultures to assess response to antibiotic treatment.

The Investigator will maintain and/or obtain medical records pertaining to the management, treatment, and outcome of the event for the purpose of AE/SAE reporting.

The incidence of sepsis with [redacted] is extremely rare and is NOT an anticipated event. Guidelines to the Investigator are provided in the study protocol for monitoring and documentation in the unlikely case the event occurs. Any sepsis occurring during the study is considered an SAE (*i.e.,* other important medical event; see Section 12.2.3) and will be reported as described in Section 12 of study protocol.

If the central laboratory identifies [redacted] (STP11) or [redacted] (STP6) in the isolate provided from the local laboratory, the study enrollment will be halted and a DSMC meeting will be convened to review the case (see Appendix E).

10.3.5.2. Assessment and Treatment of Other Infections

In the event an infection of a normally sterile site (other than sepsis) is suspected, the following guidelines for the evaluation, monitoring and treatment should be followed.

The Investigator will:

- Perform full clinical evaluation of the subject
- Study drug treatment will be suspended temporarily. Study drug treatment may be re-initiated at the discretion of the Investigator based as the subject's clinical condition (see Section 10.8.2).
- Obtain aerobic and anaerobic cultures of the infected site to identify the offending pathogen(s) prior to initiating antibiotic treatment as appropriate based upon the location of the infection and the clinical need for cultures. If cultures are indicated, they should be obtained prior to initiation of antibiotics. If obtaining a culture prior to initiation of antibiotics is not possible, a culture should be collected as soon as possible following initiation of antibiotic treatment.
- If the site's local laboratory identifies gram positive bacilli in the culture, a sample of the isolate will be forwarded to the central laboratory for qPCR analysis to confirm if the offending bacteria are [redacted] (STP11) or [redacted] (STP6).
- Start treatment with antibiotics, as appropriate.
- The subject will be managed based upon the treatment protocol(s) of the institution and the discretion of the treating physician and/or Principal Investigator. Clinical management, monitoring (e.g., clinical signs, vital signs, X-rays, and laboratory investigations) and supportive care will be adjusted to individual subject requirements and changes in clinical status over time.
- If initial site cultures were positive and if permissible, obtain a repeat set of aerobic and anaerobic cultures to assess response to antibiotic treatment.

The Investigator will maintain and/or obtain medical records pertaining to the management, treatment, and outcome of the event for the purpose s of AE/SAE reporting.

If the central laboratory identifies [redacted] STP11 or [redacted] STP6 in the isolate provided from the local laboratory, the study enrollment will be halted and DSMC meeting will be convened to review the case (see Appendix E).

10.4. Fecal Sample Collection

Fecal sampling for shedding will be performed.

Prior to dosing, a baseline stool sample will be collected, if available, followed by collections during and following the completion of blinded study drug administration. Post dosing samples will be collected until discharge as outlined in the schedule of procedures.

Diapers of infants will be checked at least every 6 hours per standard NICU practice. During the first 4 days of dosing, all fecal samples will be collected. After Day 4, samples will be collected one

time per week. If there are multiple samples per day, only a single sample will be collected for processing.

Fecal samples will be collected, processed and shipped to a central laboratory as described in the study laboratory manual. For samples that cannot be processed and frozen immediately after collection, the sample (diaper) may be stored under refrigerated conditions until freezing. Freezing of samples must occur within 12 hours of collection. The time of collection and freezing of the samples will be recorded.

Fecal samples will be analyzed for [redacted] using qPCR**.**

10.5. Clinical Event Assessments

10.5.1. Feeding Tolerance

Neonates will have feeding method (tube, bottle, or breast), feeding content (breast milk, donor milk or preterm formula), daily feeding volumes (for tube and bottle feeds), and presence/absence of feeding tolerance recorded daily.

Neonates will have feeding tolerance evaluated by abdominal evaluation (any excessive distension beyond what is expected with a feed, redness of abdominal wall, firmness, presence of normal bowel sounds).

Neonates who are placed on NPO status for at least 12 hours will be considered to have feeding intolerance.

10.5.1.1. Management of Feeding Intolerance

Feeding intolerance will be determined by the attending physician Investigator based on the evaluations in Section 10.5.1 and his/her clinical experience.

Any subject diagnosed with feeding intolerance will have:

- An abdominal X-ray performed to evaluate for pneumatosis intestinalis, intestinal perforation, and/or biliary air.
- For subjects without the diagnosis of NEC or spontaneous intestinal perforation, management will be determined by the attending physician Investigator.
- As indicated, and at the discretion of the attending physician Investigator, blood cultures and a CBC will be obtained.
- The subject will be placed on NPO status for approximately 48 hours. During NPO status, STP206 may continue.
- Antibiotic treatment will be initiated and continued for approximately 48 hours.

Treatment for a time-frame less than 48 hours will not be considered a protocol violation. If, however, antibiotic therapy and NPO status are maintained for greater than 72 hours, the diagnosis of NEC will be considered.

If NEC is diagnosed, study drug administration will be immediately discontinued.

10.5.2. Relevant Neonatal Morbidities/Complications of Prematurity

10.5.2.1. Necrotizing Enterocolitis

Necrotizing Enterocolitis, (see Appendix B for diagnostic and staging criteria) will be assessed through physical findings (abdominal distension & tenderness) and feeding tolerance. If NEC is suspected, an abdominal X-ray will be obtained to determine the presence of pneumatosis intestinalis, portal venous air, or free air.

If NEC is diagnosed, study drug administration will be discontinued immediately.

10.5.2.2. Retinopathy of Prematurity

Ophthalmologic examinations are required for all preterm neonates for Retinopathy of Prematurity (ROP) as per NICU ROP protocols by ophthalmologists with expertise in the diagnosis of ROP, commonly using indirect ophthalmoscope after pupillary dilation.

Retinopathy of Prematurity of any stage (see Appendix B for diagnostic and staging criteria) will be assessed through ophthalmologic examinations performed by a certified pediatric ophthalmologist. Ophthalmologic assessments for ROP will be performed per NICU standard protocols.

10.5.2.3. Bronchopulmonary Dysplasia

Assessments for bronchopulmonary dysplasia (BPD) will be performed per NICU standard protocols by the attending physician. BPD will be defined as oxygen requirement at 36 weeks post-conceptional age to keep oxygen saturation levels above 90%. BPD will be diagnosed and assessed for severity, using the criteria provided in Appendix B.

10.5.2.4. Intraventricular Hemorrhage

Cranial ultrasound will be performed at between 5 and 7 days of age and at 28 days (±3 days) of age for assessment of intraventricular hemorrhage (IVH). The Day 28 cranial ultrasound will be performed only if clinically indicated and the subject is still in the hospital. If the subject is discharged from the hospital prior to 28 days of age or the procedure is not clinically indicated, the cranial ultrasound does not need to be performed. If the 28-day procedure is not performed, the reason the procedure was not performed will be documented in the source document and the CRF.

IVH will be diagnosed and graded (Grade II, III, or IV) using the criteria provided in Appendix B.

10.5.2.5. Other Complications of Prematurity

Study staff will evaluate neonates for the following other clinical events:

- Spontaneous gastrointestinal perforation
- Patent ductus arteriosus requiring treatment with indomethacin, ibuprofen or surgery
- Late onset sepsis
- Late onset Candida sepsis

10.6. Clinical Management

10.6.1. Dietary Management

The following guidelines are suggested for the dietary management of infants:

- Tube vs. non-tube feeds – Tube feeds will be provided to infants who are unable to feed at breast or by bottle adequately, or who take prolonged duration per feeding (e.g. >30 minutes).
- Content of Enteral Feeds – Enteral feeding will consist of either breast milk, donor milk or preterm formula. Maternal breast milk is preferred.
- Suggested Feeding Volumes – suggested feeding volumes will be based upon birth weight as follows:
  - 2000 – 1501 g – starting at 20-40 mL/kg/day; increase feeds over 5-10 days to 150 mL/kg/day
  - 1001 – 1500 g – starting at 20 mL/kg/day; increase feeds over 5-10 days to 150 mL/kg/day
  - 500 – 1000 g – starting at 20 mL/kg/day; increase feeds over 7-15 days to 140 mL/kg/day
- Total Parenteral Nutrition (TPN) (for infants on NPO status) – TPN will be provided under the discretion of the attending neonatologist.

10.6.2. Prophylactic Treatments

Neonates may be started on empiric antimicrobial therapy (*e.g.,* ampicillin with an aminoglycoside) for the first 36 to 72 hours after birth per NICU procedures. If the culture at 48 hours after initiation of antimicrobial therapy shows "no growth, therapy should be discontinued. This empiric antimicrobial therapy should be discontinued once the initial blood culture is reported as "no growth" by 48 hours. Infants who are critically ill and considered to have clinical sepsis despite negative cultures may have antimicrobials continued.

Prophylactic exogenous surfactant (e.g., Survanta, Infasurf, Curosurf) may be administered to subjects in this study under the discretion of the attending neonatologist.

Indomethacin prophylaxis for intraventricular hemorrhage may be administered in accordance with NICU procedures for extremely low birth weight infants. (See also Appendix C for guidelines regarding antibiotic susceptibility.)

10.6.3. Cardiovascular Monitoring and Management

Cardiovascular status will be assessed during routine physical assessments (see Section 10.3.1).

If cardiac problems are diagnosed, appropriate treatment will be initiated by the attending physician Investigator in accordance with standard NICU practice.

10.6.4. Respiratory Monitoring and Ventilatory Management

Respiratory status will be assessed during routine physical assessments by the attending physician Investigator using the NICU's standard practices (see Section 10.3.1).

Supplemental oxygen should be administered to infants who are unable to maintain adequate oxygen saturation (generally considered >90%) on room air. This supplemental oxygen is normally provided by oxygen hood or nasal cannula.

Infants who continue to have low oxygen saturation despite supplemental oxygen will require additional support, as determined by the attending physician Investigator in accordance with standard NICU practice.

10.7. Pharmacokinetic and Pharmacodynamic Assessments

10.7.1. Pharmacokinetic Assessments

None.

10.7.2. Pharmacodynamic Assessments

None.

10.8. Study Medication Administration and Compliance

10.8.1. Dosage and Administration

Dosing of blinded study drug will be initiated within 4 days (i.e., 96 hours) after birth. Dosing is intended to consist of a single daily bolus dose administered as part of a scheduled feeding. However, in neonates who are volume restricted, the total daily dose may be divided and given twice daily (BID) or three times daily (TID) until full amount can be tolerated in one dose. In neonates where the dose volume is less than the maximum volume tolerated, dosing may be supplemented with regular feeding. In neonates receiving continuous feeds, the feed will be interrupted for dose administration and then immediately restarted. The date, time and volume of each dose administration will be recorded.

In neonates who are still on tube feeds, the dose will be given by feeding tube prior to feeding. If dosing at the time of feeding is not possible, the dose may be given and then the line flushed with sterile water to assure delivery of the full dose. In larger neonates who feed orally by breast or bottle for all feeds and do not have a feeding tube in place, the dose will be fed directly into the mouth before a feed using a syringe intended for oral drug administration. In the event the dose is spit up, the neonate will not be re-dosed. Regurgitation of the dose will be noted in the source document and the case report form.

Prior to administration, subject identification will be verified against the labeled syringes to ensure that the correct IP is given.

The times of product reconstitution and dose administration will be recorded. Reconstituted components of STP206 should be administered within 2 hours following reconstitution.

10.8.2. Suspension of Study Drug Administration

Study drug administration will be suspended temporarily in subjects with a case of suspected sepsis (see Section 10.3.5.1) or infection of a normally sterile site (see Section 10.3.5.2). Study drug may be re-initiated at the discretion of the Investigator, if the subject's clinical condition permits and:

- Cultures are negative for gram positive bacilli or,

- STP-206 organisms are not confirmed by central laboratory analysis.

Additionally, dosing of blinded study treatment may be withheld at the discretion of the physician Investigator. The reason for suspension of blinded study treatment will be documented in the subject's source documents and the case report form.

Neonates will be discontinued from the study if:

- Dosing is suspended for greater than seven consecutive days or
- More than two suspensions of oral dosing of five or more consecutive days each in duration are required.

If the neonate is placed on NPO status for suspected NEC and the NPO status is maintained for greater than 24 hours, dosing of blinded study drug will be suspended until NPO status is removed.

If NEC is diagnosed, study drug administration will be immediately discontinued.

10.8.3. Dose Adjustments

STP206 dosage adjustments will not be permitted during the study.

10.8.4. Assessment of Study Medication Compliance

All doses of blinded study drug will be administered by study staff in the NICU. Subject source records must document the administration of each dose of blinded study drug.

10.9. Recording of Concomitant Medications

All changes in prior and new prescription and non-prescription medications, including blood products, supplemental oxygen, vitamins, supplements, and vaccinations, from the start of screening through the 6-month post-treatment study visit are to be recorded.

10.10. Compliance

The PI and the study personnel will verify compliance with the study requirements, procedures and schedule of events. The PI, or physician Sub-Investigator, listed on Form FDA 1572 will be present for the initial administration of blinded study treatment and available for the post-dose monitoring and evaluation for all neonates. The PI or physician sub-investigator will be available by pager at all other times throughout the study for the management of the subjects enrolled in this clinical trial. Non-compliance with any study evaluations/procedures will be documented in the subject's source documents and CRFs.

11. SCHEDULE OF STUDY PROCEDURES

11.1. Screening

Parental/legal guardian informed consent must be obtained prior to performing any study procedures.

The following screening procedures will be performed before the first dose of blinded study treatment:

- History and baseline characteristics, including:

  - Maternal history and baseline characteristics
  - Pregnancy history and delivery information
  - Infant history and baseline characteristics
- Physical Examination
- Vital Signs
- Growth Assessment
- Fecal sample, if produced
- Laboratory Assessments
  - Blood Culture (from NICU admission, only if obtained per NICU standard procedures)
- Record concomitant medications

11.2. Assessment Schedule for Complications of Prematurity

11.2.1. Necrotizing Enterocolitis (NEC)

Assessments of signs and symptoms of NEC will be performed daily while the neonate is hospitalized. If NEC is suspected, abdominal X-rays will be performed (see Appendix B).

11.2.2. Retinopathy of Prematurity (ROP)

Retinopathy of Prematurity (ROP) of any stage (see Appendix B for diagnostic and staging criteria) will be assessed through ophthalmologic examinations performed by a certified pediatric ophthalmologist.

Ophthalmologic assessments for ROP will be performed per NICU standard protocols.

11.2.3. Intraventricular Hemorrhage (IVH)

Cranial ultrasound will be performed at between 5 and 7 days of age and at 28 days (±3 days) of age for assessment of IVH. The Day 28 cranial ultrasound will be performed only if clinically indicated and the patient is still in the hospital. If the patient is discharged from the hospital prior to 28 days of age or the procedure is not clinically indicated, the cranial ultrasound does not need to be performed. If the 28-day procedure is not performed, the reason the procedure was not performed will be documented in the source document and the CRF.

11.2.4. Bronchopulmonary Dysplasia (BPD)

Assessments for BPD will be performed per NICU standard protocols by the attending physician Investigator and defined as oxygen requirement at 36 weeks post-conception age to keep oxygen saturation levels above 90%.

11.3. Dosing Period

11.3.1. Daily Assessments During Dosing

During the dosing period, the following assessments will be performed daily:

- Physical Examination and vital signs
- Assessments of signs and symptoms of NEC
- Assessment of AEs
- Assessment of concomitant medication changes
- Assessment of feeding volumes and tolerance

11.3.2. Dosing Duration

The subject's gestational age at birth will dictate how many weeks of dosing will be administered as outlined in the table below. For the initial 2 weeks of daily dosing, neonates should not miss more than 2 doses per week. It is intended that neonates receive blinded study treatment for between 2 to 11 weeks based upon the protocol-defined gestational age. However, in the event of early hospital discharge, the minimum required dosing duration is provided in Table 2.

Table 2: Dosing Duration Guidelines

Gestational Age at Birth	Protocol Defined Gestational Age	Intended Dosing Duration Weeks (Days)	Minimum Required Cumulative Dosing Days [a,b]
23 weeks 0/7 days to 23 weeks 6/7 days	23 weeks	11 (77)	54
24 weeks 0/7 days to 24 weeks 6/7 days	24 weeks	10 (70)	49
25 weeks 0/7 days to 25 weeks 6/7 days	25 weeks	9 (63)	45
26 weeks 0/7 days to 26 weeks 6/7 days	26 weeks	8 (56)	40
27 weeks 0/7 days to 27 weeks 6/7 days	27 weeks	7 (49)	35
28 weeks 0/7 days to 28 weeks 6/7 days	28 weeks	6 (42)	30
29 weeks 0/7 days to 29 weeks 6/7 days	29 weeks	5 (35)	25
30 weeks 0/7 days to 30 weeks 6/7 days	30 weeks	4 (28)	20
31 weeks 0/7 days to 31 weeks 6/7 days	31 weeks	3 (21)	15
32 weeks 0/7 days to 32 weeks 6/7 days	32 weeks	2 (14)	10

a. Over the first 2 weeks of dosing, neonates should receive study drug for a minimum of 5 of the 7 dosing days, per week
b. ≥70% of intended dose

11.3.2.1. Week 1: Day 1 (Start of Dosing)

Subjects who pass screening evaluations and are eligible for enrollment will be randomized to study treatment.

Prior to dosing, the following study procedures will be performed:

- Physical Examination
- Vital Signs

- Growth Assessment
- Changes in concomitant medications since the screening assessment
- Fecal sample: all fecal samples produced will be collected daily through Day 4 and then once weekly afterward.

Blinded study treatment will be administered to the neonate and the time of administration recorded. Following the initial dose administration, the neonate will be observed continuously by a member of the study staff over the first 60 minutes following administration of study drug and following procedures will be conducted:

- Vital signs every hour (±10 minutes) for 4 hours, then every 4 hours (± 30 minutes) through 24 hours following dose administration
- Physical Examination at 3 hours (±1 hour) following dose administration

11.3.2.2. Week 1: Days 2-7

Subject will be dosed once per day on days 2 through 7.

Fecal sample: All fecal samples produced will be collected daily through Day 4 and then once weekly afterward.

On Day 7 (±1 day), the following procedure will be performed:

- Growth Assessment

11.3.2.3. Week 2

Subject will continue to be dosed once daily on days 8 through 14.

On day 14 (± 1 day) the following procedures will be performed:

- Growth Assessment
- Fecal sample

11.3.2.4. Week 3

Subject will continue to be dosed once daily on days 15 through 21.

On day 21 (±1 day) the following procedures will be performed:

- Fecal sample

11.3.2.5. Week 4

Subject will continue to be dosed once daily on days 22 through 28.

On day 28 (±1 day) the following procedures will be performed:

- Growth Assessment
- Fecal sample

11.3.2.6. Weeks 5, 7, 9, and 11

Subject will continue to be dosed once daily.

On Days 35, 49 and 63 (±1 day) the following procedure will be performed:

- Fecal sample

11.3.2.7. Weeks 6, 8 and 10

Subject will continue to be dosed once daily.

On day 42, 56 and 70 (±1 day) the following procedures will be performed:

- Growth Assessment
- Fecal sample

11.3.2.8. End of Dosing/Hospital Discharge

Dosing will continue until a post-conception age of 34 weeks, or until hospital discharge, whichever comes first. If a subject stops study drug dosing prior to the post-conception age of 34 weeks, the following procedures will be completed on the day the subject receives his/her last dose of blinded study treatment:

- Physical examination
- Vital Signs
- Growth Assessment
- Fecal sample
- Assessment of AEs
- Assessment of concomitant medication changes

Discharge evaluations will be performed by a physician-Investigator who is a board-certified staff neonatologist and be performed per standard NICU practice.

11.3.3. Post Dosing Assessments

11.3.3.1. 1 Week

The following procedures will be performed at one week (±2 days) following completion of dosing:

- Physical Examination
- Vital Signs
- Growth Assessment
- Assessment of AEs
- Assessment of concomitant medication changes

11.3.3.2. 1 Month

The following procedures will be performed between 30 to 35 days following completion of dosing:

- Physical Examination
- Vital Signs

- Growth Assessment
- Assessment of AEs
- Assessment of concomitant medication changes

11.3.3.3. 3 Months

The following procedures will be performed between 85 and 99 days following completion of dosing:

- Physical Examination
- Vital Signs
- Growth Assessment
- Assessment of AEs
- Assessment of concomitant medication changes

11.3.3.4. 6 Months/End of Study

The following procedures will be performed between 181 and 195 days following completion of dosing:

- Physical Examination
- Vital Signs
- Growth Assessment
- Assessment of AEs
- Assessment of concomitant medication changes

11.4. Early Withdrawal Study Assessments

For subjects who withdrawal from the study prior to the 6-month post-dosing follow-up, the following procedures will be performed:

- Physical Examination
- Vital Signs
- Growth Assessment
- Assessment of AEs
- Assessment of concomitant medication changes

For subjects who withdrawal from the study prior to the 6-month follow-up assessment, the following procedures will be performed:

- Growth Assessment

12. ADVERSE EVENTS

12.1. Assessment Period

AEs will be assessed from the time the subject receives their initial dose of study medication through 6 months following the last dose of study drug. All AEs reported during this period, regardless of severity relationship to blinded study treatment, will be recorded.

12.2. Definitions

12.2.1. Adverse Event

An **adverse event** (AE) is any untoward medical event associated with the use of a drug in humans, whether or not considered drug-related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality.

Based upon the above definition of an AE, physical examination findings/abnormalities (inclusive of severity, nature and duration of the finding) that, in the opinion of the principal investigator, are expected to be observed in this patient population would not be considered untoward medical events and do not require reporting as AEs.

An untoward medical event which occurs outside the period of follow-up as defined in the protocol will not be considered an AE. Worsening of a medical condition for which the efficacy of the study drug is being evaluated will not be considered an AE.

12.2.2. Unexpected Adverse Event

An **unexpected adverse event** is an AE that is not listed in the Investigator Brochure (IB) or an AE not listed in the IB at the specificity or severity that has been observed.

For example, under this definition, the AE of **hepatic necrosis** would be considered "unexpected" (by virtue of greater severity) if the investigator brochure had referred previously only to elevated **hepatic enzymes** or **hepatitis**. Similarly, **cerebral thromboembolism** and **cerebral vasculitis** would be considered "unexpected" (by virtue of greater specificity) if the IB listed only **cerebral vascular accidents**. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

12.2.3. Serious Adverse Event

A **serious adverse event** (SAE) is an AE that in the view of either the investigator or sponsor, results in any of the following outcomes:

- Results in death
- Is life-threatening (an event that in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death; it does not include an event that had it occurred in a more severe form, might have caused death)
- Requires in-patient hospitalization or prolongation of existing hospitalization

- Is a congenital anomaly or birth defect
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is an important medical event
  An important medical event that may not be immediately life-threatening or result in death or hospitalization but based upon appropriate medical judgment, may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The term "severe" is often used to describe the intensity (severity) of an event; the event itself may be of relatively minor medical significance (such as a severe headache). This is not the same as "serious", which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning.

In addition to the above definitions of SAEs, all occurrences of confirmed bacteremia will also be considered an SAE (*i.e.,* other important medical event).

12.2.4. Relationship to Study Drug

The Investigator must attempt to determine if an AE is in some way related to the use of the study drug. This relationship should be described based upon the following definitions:

- ***Unrelated/Not Related:*** The AE is clearly due to causes distinct from the use of the study drug, such as a documented pre-existing condition, the subject's clinical state, environmental factors, the effect of other concomitant medications or treatments administered.
- ***Unlikely:*** The AE does not follow a reasonable temporal sequence from administration of the study drug, does not follow a known response pattern to the study drug, and could readily have been due to other causes such as the subject's clinical state, environmental factors, the effect of other concomitant medications or treatments administered.
- ***Possible:*** The AE follows a reasonable temporal sequence from administration of the study drug and follows a known response pattern to the study drug, *BUT,* the AE could readily have been produced by the subject's clinical state, environmental factors, the effect of other concomitant medications or treatments administered.
- ***Probable:*** The AE follows a reasonable temporal sequence from administration of the study drug and follows a known response pattern to the study drug *AND* cannot be reasonably explained by the subject's clinical state, environmental factors, the effect of other concomitant medications or treatments administered. The event improves upon discontinuation of the study drug.
- ***Definite/Related:*** The AE follows a reasonable temporal sequence from administration of the study drug and follows a known response pattern to the study drug. Based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug. The AE improves upon discontinuation of the study drug and reappears upon repeat exposure.

12.2.5. Severity (Intensity)

For AEs that are quantifiable (e.g. blood pressure, lab assessments), the Investigator will assess the severity (intensity) of all AEs according to the following grading system:

- Grade 1 – (Mild AE) - event does not require medical intervention
- Grade 2 – (Moderate AE) - event is treatable with standard medical intervention
- Grade 3 – (Severe AE) - event requires intensive medical intervention

12.3. Reporting Adverse Events

All new events, as well as those that worsen in intensity or frequency relative to baseline, which occur must be captured. The Investigator or his/her staff should elicit information regarding the occurrence of adverse events through physical examination results, review of laboratory results, and, if appropriate, questioning of the neonate's parents/guardians.

Information to be recorded for each AE includes:

- A medical diagnosis of the event (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event should be recorded)
- The date and time of onset of the event
- The date and time of resolution of the event
- Assessments of severity, causal relationship, and seriousness of the AE (see definitions in Sections 12.2.3, 12.2.4, and 12.2.5)
- Action(s) taken (if any) for management of the AE
- Outcome of the AE: subject recovered (without sequelae); subject recovered with sequelae; event ongoing; subject died

All AEs will be followed until resolution or stabilization.

12.3.1. Reporting Complications of Prematurity

Complications of prematurity will not be classified as AEs, but as study outcomes.

12.4. Reporting Serious Adverse Events

All serious events, regardless of relationship to study drug, must be reported to Leadiant as described below.

- SAEs that are fatal or life–threatening must be reported to Leadiant or their designee by telephone ***immediately*** after site personnel first become aware of the event. Within 24 hours, the Leadiant Serious Adverse Event Form must be faxed to the medical monitor or designee regardless of whether full information regarding the event is known or not. If full information is not known, additional follow-up by the Investigator will be required.
- All other SAEs must be reported to the Leadiant medical monitor or designee within 24 hours by phone, e-mail or fax after becoming aware of the event. Within 48 hours, the Leadiant Serious Adverse Event Form must be faxed to the medical monitor or designee

regardless of whether full information regarding the event is known or not. If full information is not known, additional follow-up by the Investigator will be required.

All SAE reports will be reported to a representative of Leadiant as described in the Study Reference Manual.

All SAEs will be evaluated by the Leadiant medical monitor or designee. If meeting the requirements for expedited reporting, Leadiant will report the AE to all regulatory authorities with jurisdiction over ongoing trials with the study drug and to all other investigators involved in clinical trials with STP206.

The Investigator must report all SAEs, reported to regulatory authorities in an expedited manner to the reviewing IRB. For all other SAEs, the Investigator must report all SAEs in accordance with the requirements of the reviewing IRB.

12.4.1. Reporting of Other Adverse Events of Special Interest

In addition to reporting of SAEs, the following AEs that do not meet serious criteria will be reported to Leadiant within 48-hours using the Leadiant Serious Adverse Event Form:

- Any discontinuation of study drug dosing due to a severe (i.e., Grade 3) AE. These AEs will be reported to FDA by Leadiant.
- Any infection confirmed to be due to [redacted] that is not reported as an SAE. Infections due to STP206 bacteria will be reported to the FDA by Leadiant.

In addition, per FDA's request during a teleconference held on 22 July 2014, blinded desk copies of all cases of NEC resulting in surgery or death that did not meet expedited reporting requirements to qualify as a 7- or 15-day IND safety report will be submitted to the FDA via a Clinical Information Amendment to the IND.

13. STATISTICS

13.1. Sample Size Determination

The sample size for this study will not be determined statistically.

13.2. Statistical Methodology

13.2.1. General Analysis Considerations

All summaries and statistical analyses will be performed using SAS, Version 9.4 or higher. Descriptive summaries will consist of frequencies and percentages for categorical measures and of the number of subjects, mean, standard deviation, median, minimum, and maximum values for continuous measures. Descriptive summaries will be presented for each treatment group. Any statistical comparisons performed on the data will be done for exploratory analysis purposes only.

13.2.2. Analysis Populations

The safety population will be all randomized subjects who received at least one dose of blinded study drug. The Intent-to-treat (ITT) population will consist of all randomized subjects who received study medication and have at least one post-baseline evaluation.

13.2.3. Data Analysis

Details regarding the data analyses planned for the study will be outlined in the statistical analysis plan (SAP). Any changes to planned methods and analyses will be described and justified in the SAP, as appropriate. The SAP will be finalized prior to database lock.

13.2.3.1. Efficacy Data Analysis

The following efficacy parameters will be compared between those who received STP206 vs. control:

- Feeding intolerance
- Death
- NEC incidence
- Incidence of sepsis
- Incidence of other neonatal complications of prematurity (ROP, IVH, BDP, etc)

Details regarding the analysis of efficacy data will be provided in the SAP.

13.2.3.2. Safety Data Analysis

AEs will be assessed from the time the subject receives the initial dose of study drug through 6 months following the last dose. AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) and summarized in frequency tables displaying counts and percentages by body system, preferred term, and treatment group. Subjects reporting multiple events will only be counted once.

In addition, AEs will be summarized by relationship to study drug and by severity. For assessing relationship to study drug, any event with a study drug relationship marked as “possible”, “probable” or “definite/related” on the CRF will be considered related to study drug.

All SAEs will also be summarized in a frequency table.

Medical history (maternal, pregnancy and infant), concomitant medications, and physical examination findings, will also be summarized by treatment group at each timepoint where data was collected.

Information on method (bottle, breast, tube) and content of feedings (formula or breast milk) will be summarized.

13.2.3.3. Pharmacokinetic Data Analysis

None.

13.2.3.4. Fecal Shedding Data Analysis

Fecal shedding [redacted] for each treatment group will be assessed by quantitative and/or qualitative methods. Counts will be summarized as a continuous measure and will be summarized descriptively by treatment at each time point. Qualitative responses will be categorized and analyzed by counts and percentages and summarized by treatment at each time point.

In addition, change from baseline will be calculated and summarized descriptively by treatment to determine whether fecal shedding values return to baseline levels.

Duration of fecal shedding will be summarized descriptively by treatment group.

13.2.4. Handling Missing, Repeated, Unused, and Spurious Data

It is not anticipated that there will be a need to adjust for missing data in this study. All data for this study will be analyzed as collected on the CRF. If the need arises to account for any special circumstances presented by the data, details of how it will be handled will be documented in the SAP.

13.2.5. Reporting of Deviations to Statistical Methodology

Any deviations to the protocol defined analysis will be documented in the SAP. Deviations in analyses described in the SAP will be documented in the study report.

13.3. Interim Analysis

An interim analysis is not planned.

13.4. Statistical Criteria for Termination of the Study

There are no statistical criteria for stopping the study.

14. ADMINISTRATIVE

14.1. Changes to Study Protocol

14.1.1. Protocol Amendments

Protocol changes must be in the form of a written amendment approved by Leadiant.

Protocol amendments and necessary revisions to the informed consent form must be submitted by the Investigator to the local IRB and such amendments will only be implemented after written approval of the requisite IRB. Protocol changes to eliminate an immediate hazard to a study subject may, at the direction of Leadiant, be implemented immediately by the Investigator. The Investigator must then immediately inform the IRB and obtain required approvals.

If a protocol amendment requires revision to the informed consent form, the revised IRB-approved form must be used to re-consent subjects currently enrolled in the study and the new form must be used to obtain consent from new subjects prior to enrollment.

All amendments will be submitted to local regulatory authorities by Leadiant as required by local regulation.

14.1.2. Protocol Deviations

Deviations to the protocol will not be permitted without the prior approval of Leadiant. All departures from this protocol will be recorded as protocol deviations, regardless of whether the deviation was approved by Leadiant. If Leadiant approves a protocol deviation, a written waiver will be provided to the Investigator. The original waiver will be filed in the site regulatory files and a copy filed with the study records for the subject.

Deviations from the protocol involving informed consent, eligibility criteria, study drug administration, and the administration of prohibited treatments will require written IRB notification by the Investigator.

14.2. Study Termination

Leadiant reserves the right to temporarily or permanently discontinue the study at any site and at any time. Reasons for study discontinuation may include, but are not limited to, the following:

- Investigator non-compliance with the protocol, Good Clinical Practice guidelines or regulatory requirements
- Insufficient enrollment to complete the study within the prescribed timeframe
- Safety concerns
- Drug supply issues
- Discontinuation of the study protocol and/or all studies with STP206
- Request to discontinue the study by a regulatory or health authority

Leadiant will promptly inform all Investigators and the requisite regulatory authorities, if the study is suspended or terminated for safety reasons. In the case of such suspension or termination, Leadiant will provide the Investigator with instructions regarding the disposition of subjects (e.g., termination of treatment, subject follow-up) currently on the study. The Investigator will promptly notify the IRB and implement subject disposition instructions.

Should the study be terminated prematurely, all unused study drug(s), unused case report forms and any other investigational study material will be returned to the Sponsor.

14.3. Ethics

14.3.1. Compliance Statement

This study will be conducted in accordance the principles of the Declaration of Helsinki, the International Conference on Harmonization Guidance on Good Clinical Practice and the requirements of federal regulatory authorities regarding the conduct of clinical trials and the protection of human subjects.

14.3.2. Institutional Review Board/Ethics Committee

The Investigator will submit the protocol and subsequent amendments, the Investigator's Brochure and subsequent revisions, the informed consent and any other material used to inform subject/subjects about the study to the local IRB for approval prior to enrolling any subject/subjects into the study. The IRB should be duly constituted according to applicable regulatory requirements.

Approval must be in the form of a letter signed by the Chairperson of the IRB or the Chairperson's designee, must be on IRB stationary and must include the protocol by name and/or designated number. IRB approval of the informed consent form must be clearly indicated in the IRB approval letter (indicating version/date of the version approved) or by other means utilized by the IRB (e.g., IRB approval stamp on the approved version of the form). If an Investigator is a member of the IRB, the approval letter must stipulate that the Investigator did not participate in the final vote, although the Investigator may participate in the discussion of the study.

The Investigator will also report the progress of the study to the IRB on an annual basis or more frequently, as required by the IRB. The Investigator will also promptly inform the IRB of:

- SAEs that the Sponsor reports to regulatory authorities in an expedited manner
- All changes in research activity
- Protocol deviations, as required by Leadiant or the IRB
- Other reports, as required by the IRB
- The completion, termination, or discontinuation of the study, and
- A final summary of the final results at the conclusion of the study, as required by the IRB

Copies of all correspondence between the Investigator and the IRB will be provided to Leadiant.

14.3.3. Informed Consent

The Investigator will obtain written informed consent from the subject's appropriate legally authorized representative(s) (e.g., one or both parents, legal guardian), as defined by local law and IRB/IEC requirements, after those individuals have been provided with a full understanding of the study purpose, prior to performing any study-related procedures. The consent form used to document informed consent from study participants must contain the elements of informed consent as described in 21 CFR, Part 50.

The study records (*i.e.,* subject source documents and applicable study logs) will document that informed consent was obtained prior to subject participation in the study.

14.3.4. Health Insurance Portability and Accountability Act

The Investigator must obtain authorization from the subject's mother to use and/or disclose protected heath information (PHI) in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

For mothers below the age of consent and who are emancipated minors, state and local regulations will determine how HIPAA authorization is to be obtained.

HIPAA authorization may be obtained as part of the informed consent form or in a separate document and will include:

- Identification of the parties that can use and disclose PHI
- Identification of the parties to whom PHI may be disclosed
- A description of the PHI
- A description of the purpose for use and disclosure

- Information pertaining to the subject's rights related to authorization
- Information about the expiration of the authorization and how to revoke authorization
- A statement about what may happen if authorization is not provided
- A statement that once information has been disclosed, it may be disclosed again without further authorization.

14.3.5. Confidentiality of Subject Records

It is the responsibility of the Investigator to ensure that the confidentiality of all subjects participating in the study and all of their medical information is maintained. Case report forms and other documents submitted to Leadiant must not contain the name of a study participant. Each subject in the study will be identified by a unique identifier that will be used on all CRF's and any other material submitted to Leadiant. All case report forms and any identifying information must be kept in a secure location with access limited to the study staff directly participating in the study.

Personal medical information may be reviewed by representatives of Leadiant, the IRB or regulatory authorities in the course of monitoring the progress of the study. Every reasonable effort will be made to maintain such information as confidential.

The results of the study may be presented in reports, published in scientific journals or presented at medical meetings; however, subject names will never be used in any reports about the study.

14.3.6. Conflict of Interest

The Investigator shall acknowledge, by signing the Investigator's Statement/ Signature Page (Section 15), that the participation in this clinical study by the Investigator and his/her sub-investigators presents no conflict of interest with the study.

14.4. Investigator Obligations

The Investigator is responsible for complying with the obligations of clinical investigators, as described in ICH GCP guidelines, the Declaration of Helsinki, and U.S. federal regulations as defined in 21 CFR Parts 50, 54, 56, and 312. These obligations include, but are not limited to, the following:

1. Protect the rights, safety and welfare of subjects under the Investigator's care.
2. Conduct the study in accordance with the approved study protocol.
3. Conduct the study in accordance with GCP guidelines and applicable federal, state and local regulations and laws.
4. Ensure that the staff involved with the conduct of the study are knowledgeable on the study agents used, the study protocol, study procedures, and reporting requirements.
5. Properly obtain informed consent and HIPAA authorization from each subject (or the subject's legal representative) enrolled using the current IRB-approved forms.
6. Supply study drug only to those subjects who are participating in the study and are under the direct supervision of the Investigator or an authorized sub-investigator. The Investigator must not supply the study drug to any person not authorized to receive it.

7. Prepare and maintain accurate and complete case histories for all subjects participating in this trail that document all study procedures performed and record all data required for this study protocol.
8. Report all SAEs to the sponsor and IRB (as necessary) within the timeframes described in this protocol.
9. Report any changes in research activity and unanticipated problems involving risk to study participants promptly to the IRB.
10. Report all protocol deviations promptly to Leadiant. Significant deviations will require prompt notification to the IRB.
11. Provide the IRB with copies of reports of SAEs submitted by Leadiant to regulatory authorities in an expedited manner (e.g., IND Safety Reports).
12. Provide Leadiant with complete and accurate financial information to allow submission of complete and accurate certification and disclosure statements to FDA as required.

It is required that either the Principal Investigator, or an appropriately delegated, licensed physician sub-investigator, administer or oversee the care of study subjects and review study data (e.g., AEs, laboratory data, treatment response data) in a timely manner.

14.5. Financial Disclosure

All Investigators and sub-investigators listed on any FDA 1572 form supplied by the Investigator will disclose the following information as required by 21 CFR, Part 54:

1. Any financial arrangement entered into between Leadiant and the Investigator/sub-investigator whereby the value of the compensation to the Investigator/sub-investigator for conducting the study could be influenced by the outcome of the study.
2. Any significant payments totaling more than $25,000 USD, exclusive of the costs of conducting this or other clinical studies, from Leadiant, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria
3. Any proprietary interest in the test product
4. Any significant equity interest in Leadiant Biosciences in excess of $50,000 USD

The Investigator/sub-investigator shall promptly update financial disclosure information if any changes occur during the course of the study and for one year following completion of this study. This financial disclosure requirement includes the finances of the spouse and the dependent children of the Investigator/sub-investigator.

14.6. Quality Control and Quality Assurance of Study Data

14.6.1. Monitoring and Audits

During the course of the study, a clinical monitor assigned by Leadiant will make regularly scheduled visits to the investigational site to review the progress of the study. The frequency of monitoring visits will depend on the enrollment rate and performance at each site. During each visit, the monitor will review various aspects of the study including, but not limited to:

- Compliance with the protocol
- Compliance with the principles of Good Clinical Practice and regulatory requirements
- Review of written informed consent forms for subjects enrolled
- Comparison of source documentation to data recorded on case report forms to assure the completeness and accuracy of data collected
- Continued acceptability of facilities and staff
- Assessment of proper study drug accountability and storage

During scheduled monitoring visits, the Investigator and the investigational site staff must be available to meet with the study monitor in order to discuss the progress of the study, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other study-related inquiries of the monitor.

In addition to the above, representatives of Leadiant's auditing staff or government inspectors may review the conduct/results of the study at the investigational site. The Investigator must promptly notify Leadiant of any audit requests by regulatory authorities. The Investigator will cooperate with the auditor(s), make available to the auditor all requested documentation, and ensure that issues detected during the course of these audits are satisfactorily resolved. The Investigator will supply Leadiant with copies of all documentation and correspondence related to regulatory agency audits as outlined in the Clinical Study Agreement between Leadiant and the Investigator and/or Institution. If the results of the audit result in an FDA-483 (or similar document from another regulatory agency), the Investigator will promptly provide a copy to Leadiant and will provide a copy of the draft response to Leadiant prior to submission to the regulatory agency.

14.6.2. Data Processing and Data Quality Assurance

Case report forms/eCRFs will be reviewed for correctness against source document data by Leadiant's monitor. If any entries into the CRF/eCRF are incorrect, incomplete or illegible, the monitor will request the Investigator or the study site staff to make appropriate corrections.

Data edit and consistency checks will be applied to review for missing, out of range, or inconsistent data. Discrepancies will be provided to the investigational site for resolution. The discrepancy will be clarified by site personnel and the data corrected.

A quality control (QC) audit of the database will be performed to assure accuracy of the database prior to database lock. Discrepancies noted during the audit will be corrected. Error rates determined during the QC audit must be within the acceptable error rate defined by the data management plan (DMP) prior to lock of the database.

14.7. Study Records

The Investigator is responsible for preparing and maintaining adequate records to enable the conduct of the study to be documented. Study records include, but are not limited to, regulatory documentation (Section 14.7.1) and subject records (Sections 14.7.2 and 14.7.3).

14.7.1. Regulatory Documentation

Prior to initiating the study, the Investigator will provide Leadiant the following documents:

- A signed FDA Form 1572
- A current curriculum vitae for the Principal Investigator and each sub-investigator listed on the FDA Form 1572
- Copy of the current medical licenses for the Investigator and physician sub-investigators
- Written IRB approval of the protocol, informed consent form and any other material provided to potential study participants with information about the study (e.g., advertisements)
- A copy of the IRB-approved informed consent document and HIPAA authorization
- Current IRB membership list for the reviewing IRB and/or multiple project assurance number or an IRB organization number under the Federal Wide Assurance program (www.ohrp.osophs.dhhs.gov)
- A signed Investigator Protocol Agreement (see Section 15)
- Completed financial disclosure form for the Investigator and all sub-investigators
- Local reference laboratory documentation, including current laboratory certification, current laboratory normal values, and director's CV

During the course of the study, the Investigator will maintain current records to document regulatory compliance with the study including: the study protocol and amendments, all versions of the Investigators Brochure in effect during study conduct, signed Investigator Agreement protocol page(s), FDA 1572 forms, curricula vitae of the Investigator and sub-investigators, medical licenses of the Investigator and physician sub-investigators, financial disclosure of the Investigator and sub-investigators, IRB approvals of the protocol, protocol amendment(s), informed consent form(s), IRB membership list, IRB-approved informed consent form(s), IRB correspondence, protocol deviations, study logs (as provided by Leadiant), drug dispensing and accountability records, safety reports, and all correspondence pertaining to the conduct of the study. Regulatory documentation will be reviewed by Leadiant or its representatives during monitoring visits to assure regulatory compliance.

14.7.2. Source Documents

The Investigator will maintain records separate from the case report forms in the form of clinical charts, medical records, original laboratory, radiology and pathology reports, pharmacy records, subject diary cards, etc. The Investigator will document in the clinic chart or medical record the name and number of the study and the date on which the subject signed informed consent prior to the subject's participation in the study. Source documents must completely reflect the nature and extent of the subject's medical care and must be available for verification against case report form

entries, when the Leadiant or its representatives visit the investigational site. All information obtained from source documents will be kept in strict confidentiality.

14.7.3. Case Report Forms

All site-generated study data will be entered either onto case report forms (CRFs) supplied by Leadiant or into an electronic Case Report Form (eCRF) via an electronic data capture (EDC) system. The CRFs/eCRFs are not to be used as the primary method for collection of study data (unless otherwise described in this section of the study protocol) and CRF/eCRF entries must be supported by source documents maintained by the Investigator. Only those site staff authorized at the initiation of the study may enter data onto the case report forms or into an EDC system.

For studies using paper CRFs, all entries must be legible and made in black pen. If an entry error is made, a single line will be placed through the incorrect entry. The correct entry will then be made, with the correction dated and initialed by the authorized person making the entry. Any corrections to data entered into the CRF must be made in such a way that the original entry is not obscured. Resolutions to data clarification forms (DCFs) issued by Leadiant, or its designated data management contractor will be maintained with the CRFs for each subject.

The Investigator is responsible for the completeness and accuracy of all CRF/eCRF data as certified by the Investigator's dated signature on designated CRF/eCRF pages.

14.7.4. Access to Study Records

The Investigator will make available all records pertaining to the conduct of this study to Leadiant and its representatives, and auditors from domestic and foreign regulatory authorities to facilitate monitoring visits and study audits.

14.7.5. Records Retention

The Investigator will retain the records of the study for 2 years following the date that a marketing application for the study drug is approved, or if no marketing application is filed, or if such an application is not approved, for 2 years after the IND has been closed. Leadiant will notify Investigators when retention of study records is no longer required. All study records must be maintained in a safe and secure location that allows for timely retrieval, if needed.

Study records that must be retained include copies of case report forms, signed informed consents, regulatory documentation, source documents, clinic charts, medical records, laboratory results, radiographic reports, and other study-specific documentation.

Should the Investigator relocate or retire or should there be any changes in the archival arrangements for the study records, Leadiant must be notified. The responsibility for maintaining the study records may be transferred to another suitable individual, but Leadiant must be notified of the identity of the individual assuming responsibility for maintaining the study records and the location of their storage. If no other individual at the investigational site is willing to assume this responsibility, Leadiant will assume responsibility for maintaining the study records.

14.8. Publication Policy

Publication of study data is addressed in the Clinical Trial Research Agreement between Leadiant and the Investigator(s) and/or Institution(s).

14.9. Financing and Insurance

Financing and Insurance are addressed in the Clinical Trial Research Agreement between Leadiant and the Investigator and/or Institution.

15. INVESTIGATOR AGREEMENT

I have reviewed Amendment 2 to Leadiant Biosciences Protocol STP206-002, entitled "A Phase Ib Randomized, Placebo Controlled Study of the Safety and Efficacy of Once Daily Dosing of STP206 in Premature Very Low Birth Weight and Extremely Low Birth Weight Neonates" and agree that it contains all the information necessary to conduct the study as required. I will conduct the trial in accordance with the principles of ICH Good Clinical Practice and the Declaration of Helsinki.

I will maintain as confidential all written and verbal information provided to me by Leadiant Biosciences, including but not limited to, the protocol, case report forms, investigators' brochure, material supplied at investigator meetings, minutes of teleconferences, etc. Such material will only be provided as necessary to site personnel involved in the conduct of the trial, the IRB or IEC, or local regulatory authorities.

I will obtain written informed consent from each prospective trial subject or each prospective trial subject's legal representative prior to conducting any protocol-specified procedures. The consent form used will have the approval of the local IRB or IEC.

I will maintain adequate source documents and record all observations, treatments and procedures pertinent to trial subjects in their medical records. I will accurately complete the case report forms supplied by Leadiant Biosciences in a timely manner. I will ensure that my facilities and records will be available for inspection by representatives of Leadiant Biosciences, the local IRB or IEC or local regulatory authorities. I will ensure that I and my staff are available to meet with representatives of Leadiant Biosciences during regularly scheduled monitoring visits.

I will notify Leadiant Biosciences, or it's designated representative, within 24 hours of any serious adverse events. Following this notification, a written report describing the SAE will be provided to Leadiant Biosciences, or it's designated representative, as soon as possible, but no later than three days following the initial notification.

My signature below indicates that my participation in this clinical study presents no conflict of interest for me or my sub-investigators with the study.

_____

Investigator's Name (Print)

_____ _____

Investigator's Signature **Date**

16. REFERENCES

1. Lee JS, Polin RA. Treatment and prevention of necrotizing enterocolitis. *Seminars in Neonatology* 2003;8:449-59.
2. Kosloske AM. Epidemiology of necrotizing enterocolitis. *Acta Paediatrica Suppl* 1994;396:2-7.
3. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Mathews MS, Osterman MJK. Births: Final data 2008. *National Vital Statistics Reports*; 2010: 59 (1): National Center for Health Statistics.
4. Caplan MS, Jilling T. New concepts in necrotizing enterocolitis. *Current Opinion in Pediatrics* 2001;13:111-115.
5. Holman RC, Stoll BJ, Clarke MJ, Glass ERI. The epidemiology of necrotizing enterocolitis infant mortality in the United States. *American Journal of Public Health* 1997;87:2026-2031.
6. Bisquera JA, Cooper TR, Bersth CL. Impact of necrotizing enterocolitis on length of stay and hospital charges in very low birth weight infants *Pediatrics* 2002; 109:423-428.
7. Stoll BJ, Hansen N, Farnaroff AA, Hintz SR, Vohr B, Higgins RD. Neurodevelopmental and growth impairment among extremely low-birth weight infants with neonatal infection. *JAMA* 2004;292:2357-2365.

[redacted]

[redacted]

24. Lin HC, Su BH, Chen AC, Lin TW, Tsai CH, Yeh TF, Oh W. Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants *Pediatrics* 2005;115:1-4.

25. Lin HC, Hsu CH, Chen HL, Chung MY, Hsu JF, Lien R, Tsao LY, Chen CH, Su BH. Oral probiotics prevent necrotizing enterocolitis in very low birth weight preterm infants: a multicenter, randomized, controlled trial *Pediatrics* 2008;122:693-700.

26. Samanta M, Sarkar M, Ghosh P, Ghosh P, Sinha M, Chatterjee S. Prophylactic probiotics for prevention of necrotizing enterocolitis in very low birthweight newborns. *Journal of Tropical Pediatrics* 2009; 55(2):128-131.

27. Bin-nun A, Bromiker R, Wilschanski M, Kaplan M, Rudensky B, Caplan M, Hammerman C. Oral probiotics prevent necrotizing eneterocolitis in very low birth weight neonates. *J Pediatr* 2005; 147:192-6.

28. Dani C, Biadaioli R, Bertini G, Martelli E Rubaltelli FF. Probiotics feeding in prevention of urinary tract infection, bacterial sepsis and necrotizing enterocolitis in preterm infants. A prospective double-blind study. *Biol Neonate* 2002;82:103-8.

29. Costalos C, Skouteri V, Gounaris A, Sevastiadou S, Triandafilidou A, Ekonomidou, Kontaxaki F, Petrochilou V. Enteral Feeding of premature infants with *Saccharomyces boulardii*. *Early Human Development* 2003;74:89-96.

30. Hoyos AB. Reduced incidence of necrotizing enterocolitis associated with enteral administration of *Lactobacillus acidophilus* and *Bifidobacterium infantis* to neonates in the intensive care unit. *Int J Infect Dis* 1999;3:197-202

[redacted]

35. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. Obstet Gynecol. 1996; 87(2):163-8.

APPENDIX A - SCHEDULE OF ASSESSMENTS

Schedule of Events *During* Dosing Period								
Procedure	**Screening**	**Week 1 Day 1**	**Week 1 Days 2-4**	**Week 1 Days 5-7**	**Weeks 2, 4, 6, 8, 10**	**Weeks 3, 5, 7, 9, 11**	**End of Dosing or Hospital Discharge**	**Unique Events Scheduling**
Informed Consent	x							
Demographics	x							
Medical History (maternal)	x							
Pregnancy/Delivery History (maternal)	x							
Concomitant Medication history (maternal)	x							
Medical History (infant)	x							
Physical Examination	x	x	←	→	→	→	[b]	
Vital Signs (Temp, BP, HR, RR, SpO_2)	x	x	←	→	→	→	[b]	
Growth Assessment	x	x		x	x		x	
Fecal sample	x[a]	x[a]	x[a]	x[f]	x	x	x	
Retinopathy of Prematurity (ROP)[c]								x
Intraventricular Hemorrhage (IVH)[d]				x [d]	x[d]			
Bronchopulmonary Dysplasia (BPD)[e]								x
Randomize subject		x						
NEC Evaluation (daily)		x	x	x	x	x		
Assessment of Feeding Volumes and Tolerance (daily)		x	x	x	x	x		
Adverse Event Assessment (daily)		x	x	x	x	x	x	
Concomitant Medications (Infant) (daily)		x	x	x	x	x	x	
Study Drug Administration (daily)		x	x	x	x	x		

AE=adverse event; BP=blood pressure; BPD=bronchopulmonary dysplasia; HR=heart rate; IVH=intraventricular hemorrhage; NEC=necrotizing enterocolitis; NICU=neonatal intensive care unit; ROP=retinopathy of prematurity; RR=respiratory rate; SpO_2= pulse oximetry.

a. If available.

b. To be performed daily in NICU per standard NICU procedures, adverse findings to be recorded as AEs or complications of prematurity.

c. To be performed at per standard NICU protocols for assessment of ROP.
d. Cranial ultrasound will be performed at between 5 and 7 days of age and at 28 (±3 days) of age for assessment of IVH; if neonate is discharged from the hospital prior to 28 days of age or the procedure is not clinically indicated, the cranial ultrasound may be deferred
e. Assessments for BDP will be performed per NICU standard protocols by the attending physician and is defined as oxygen requirements at 36 weeks post conceptional age to keep oxygen saturation levels above 90%.
f. Day 7 only.

Protocol STP206-002
Schedule of Events *Post* Dosing Period

Procedure	**Week 1 ±2 days**	**1 Month (Day 30 -35)**	**3 Months (Day 85 – 99)**	**6 Months (Day 181 – 195)**	**Early Withdrawal| Prior to 6 Months**
Physical Examination	x	x	x	x	x
Vital Signs (Temp, BP, HR, RR)	x	x	x	x	x
Growth Assessment	x	x	x	x	x
Adverse Event Assessment	x	x	x	x	x
Concomitant Medications Evaluation (Infant)	x	x	x	x	x

APPENDIX B – DIAGNOSTIC CRITERIA FOR NEONATAL MORBIDITY

Necrotizing Enterocolitis (NEC)

Modified Bell's Staging Criteria for NEC

Stage	Systemic	Intestinal Signs	Radiologic Signs
IA - Suspected NEC	Temperature instability, apnea, bradycardia, lethargy	Elevated pre-gavage residuals, mild abdominal distension, emesis, guaiac. positive stool	Normal or intestinal dilation, mild ileus
IB - Suspected NEC	Temperature instability, apnea, bradycardia, lethargy	Bright red blood from rectum	Normal or intestinal dilation, mild ileus
IIA - Definite NEC Moderately ill	Temperature instability, apnea, bradycardia, lethargy	Bright red blood from rectum, **PLUS** absent bowel sounds, ± abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis
IIB - Definite NEC	Temperature instability, apnea, bradycardia, lethargy **PLUS** mild metabolic acidosis, mild thrombocytopenia	Bright red blood from rectum, absent bowel sounds, **PLUS** definite abdominal tenderness, ± abdominal cellulitis or right lower quadrant mass	Intestinal dilation, ileus, pneumatosis intestinalis **PLUS** portal vein gas, ± ascites
IIIA - Advanced NEC, Severely ill Bowel intact	Temperature instability, apnea, bradycardia, lethargy, mild metabolic acidosis, mild thrombocytopenia **PLUS** hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, disseminated intravascular coagulation, neutropenia	Bright red blood from rectum, absent bowel sounds, definite abdominal tenderness, ± abdominal cellulitis or right lower quadrant mass **PLUS** signs of generalized peritonitis, marked tenderness, and distention of abdomen	Intestinal dilation, ileus, pneumatosis intestinalis portal vein gas, definite ascites
IIIB - Advanced NEC, Severely ill Bowel perforated	Temperature instability, apnea, bradycardia, lethargy, mild metabolic acidosis, mild thrombocytopenia **PLUS** hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, disseminated intravascular coagulation, neutropenia	Bright red blood from rectum, absent bowel sounds, definite abdominal tenderness, ± abdominal cellulitis or right lower quadrant mass **PLUS** signs of generalized peritonitis, marked tenderness, and distention of abdomen	Intestinal dilation, ileus, *pneumatosis intestinalis* portal vein gas, definite ascites **PLUS** pneumoperitoneum

From: Ped. Clinics of North America, February 1986, Walsh, M., Kliegman, R., Necrotizing enterocolitis: Treatment based staging criteria.

Retinopathy of Prematurity

ROP is categorized in zones, with stages depicting the severity of the disease. The smaller and younger the infant at birth, the more likely the disease will involve the central zones with advanced stages.

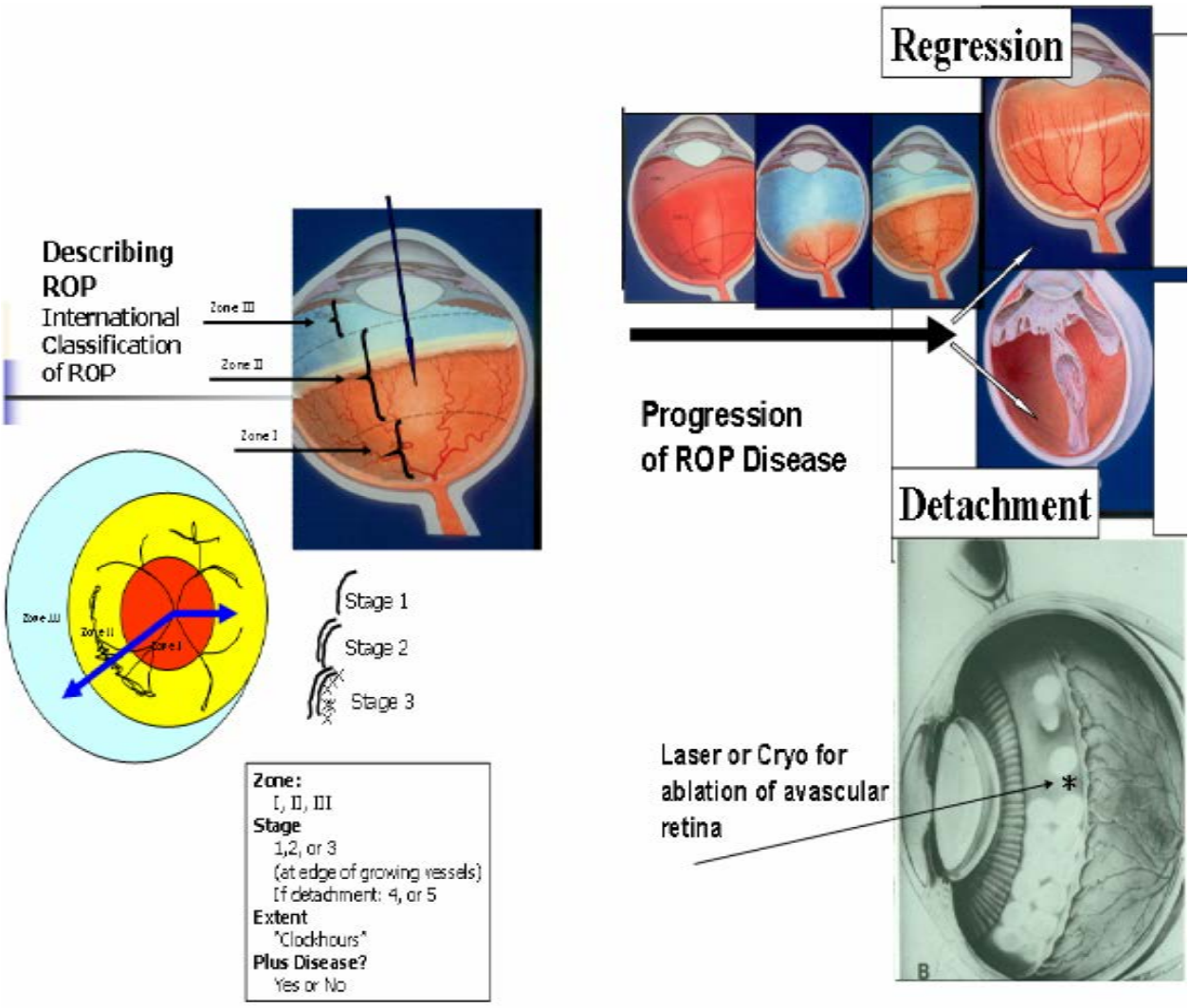
ROP is categorized by the lowest zone and the highest stage observed in each eye.

Zones

- Zone 1- is the most labile. The center of zone 1 is the optic nerve. It extends twice the distance from the optic nerve to the macula in a circle. Using a 28-diopter lens, if any portion of the optic nerve is in the same view as the ridge of ROP, that is considered zone 1.
- Zone 2 - is a circle surrounding the zone 1 circle with the nasal ora serrata as its nasal border.
- Zone 3 - is the crescent that the circle of zone 2 did not encompass temporally.

Stages

- Stage 0: This is the mildest form of ROP. It is immature retinal vasculature. No clear demarcation of vascularized and nonvascularized retina is present. Only a suggestion of the border is noted on examination.
- Stage 1: A fine, thin demarcation line between the vascular and avascular region is present. This line has no height and no thickness.
- Stage 2: A broad, thick ridge clearly separates the vascular from the avascular retina.
- Stage 3: The extraretinal fibrovascular proliferation (neovascularization) may be present on the ridge, on the posterior surface of the ridge or anteriorly toward the vitreous cavity. The neovascularization gives the ridge a velvety appearance, a ragged border.
- Stage 4: This stage is a subtotal retinal detachment beginning at the ridge. The retina is pulled anteriorly into the vitreous by the fibrovascular ridge.
- Stage 5: This stage is a total retinal detachment in the shape of a funnel.


Describing ROP
International Classification of ROP
Zone III
Zone II
Zone I
Stage 1
Stage 2
Stage 3
Zone:
I, II, III
Stage
1,2, or 3
(at edge of growing vessels)
If detachment: 4, or 5
Extent
"Clockhours"
Plus Disease?
Yes or No
Regression
Progression of ROP Disease
Detachment
Laser or Cryo for ablation of avascular retina
*
B

Bronchopulmonary Dysplasia

- Clinical signs and symptoms consistent with neonatal lung disease
- The subject meets specific NICHD diagnostic criteria specified in the table below.

National Institute of Child Health and Human Development Criteria for Diagnosis of Bronchopulmonary Dysplasia (BPD)*

< 32 Wk Gestational Age†	**Diagnosis†**
Need for < 30% O_2 at 36 wk PMA or discharge, whichever comes first	Mild to Moderate BPD
Need for ≥ 30% O_2, positive pressure or both at 36 wk PMA or discharge, whichever comes first	Severe BPD

*NOTE: These criteria are in addition to the baseline requirement of > 21% O_2 for at least 28 days.
†Assessed at 36 wk postmenstrual age (PMA).

Intraventricular Hemorrhage

Hemorrhage noted on cranial ultrasonography:

- Grade I - Hemorrhage of subependymal region and/or germinal matrix
- Grade II - Subependymal hemorrhage with extension into lateral ventricles without ventricular enlargement
- Grade III - Subependymal hemorrhage with extension into lateral ventricles with ventricular enlargement
- Grade IV - Intraparenchymal hemorrhage

APPENDIX C – ANTIBIOTIC SUSCEPTIBILITY

In the event of an infection due to [redacted] STP6 or [redacted] STP11, the minimum inhibitory concentrations (MICs) for 20 commonly used antibiotics are presented in the [redacted]

	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

APPENDIX D – ESTIMATED FETAL WEIGHT PERCENTILE CHART

Girls

AGA (10-90th %tile) Measurements at Birth

Gestation*	Weight (g)	Head (cm)
23	477 – 687	19.5 – 22.2
24	524 – 772	20.3 – 23.2
25	584 – 885	21.1 – 24.1
26	645 – 1,004	22 – 25.1
27	719 – 1,147	22.8 – 26.2
28	807 – 1,310	23.7 – 27.3
29	915 – 1,489	24.6 – 28.4
30	1,052 – 1,693	25.6 – 29.4
31	1,196 – 1,897	26.5 – 30.3
32	1,352 – 2,116	27.4 – 31.2
33	1,545 – 2,379	28.3 – 32.1
34	1,730 – 2,661	29.1 – 33.1
35	1,869 – 2,985	29.8 – 34
36	2,028 – 3,339	30.5 – 34.8
37	2,260 – 3,651	31.1 – 35.4
38	2,526 – 3,847	31.7 – 35.7
39	2,724 – 3,973	32 – 36
40	2,855 – 4,070	32.3 – 36.1
41	2,933 – 4,142	32.6 – 36.3

*Choose gestation based on weeks completed.
(25/2 = 25 weeks, 25/6 = 25 weeks)

Weight	Head	Classification
10-90%	10-90%	AGA
<10%	10-90%	SGA/Head-Spared
<10%	<10%	SGA/Symmetric
>90%	>90%	LGA

Olsen IE, Groveman S, Lawson ML, Clark R, Zemel B. New intrauterine growth curves based on U.S. data. Pediatrics 2010;125:e214-e224.

Boys

AGA (10-90th %tile) Measurements at Birth

Gestation*	Weight (g)	Head (cm)
23	509 – 727	20 – 22.7
24	561 – 813	20.8 – 23.6
25	626 – 926	21.7 – 24.6
26	704 – 1,065	22.5 – 25.7
27	789 – 1,218	23.5 – 26.8
28	884 – 1,385	24.3 – 27.9
29	988 – 1,560	25.2 – 28.8
30	1114 – 1,761	26.1 – 29.8
31	1267 – 1,984	27 – 30.8
32	1433 – 2,218	27.8 – 31.8
33	1625 – 2,488	28.7 – 32.7
34	1810 – 2,763	29.5 – 33.6
35	1980 – 3,084	30.3 – 34.5
36	2170 – 3,432	31 – 35.3
37	2401 – 3,736	31.7 – 36
38	2652 – 3,986	32.2 – 36.4
39	2833 – 4,129	32.5 – 36.6
40	2950 – 4,232	32.8 – 36.8
41	3039 – 4,319	33 - 37

*Choose gestation based on weeks completed.
(25/2 = 25 weeks, 25/6 = 25 weeks)

Weight	Head	Classification
10-90%	10-90%	AGA
<10%	10-90%	SGA/Head-Spared
<10%	<10%	SGA/Symmetric
>90%	>90%	LGA

Olsen IE, Groveman S, Lawson ML, Clark R, Zemel B. New intrauterine growth curves based on U.S. data. Pediatrics 2010;125:e214-e224.

APPENDIX E – REVIEW OF INFECTIONS SUSPECTED TO INVOLVE STP206 ORGANISMS