

Statistical Analysis Plan for Study STP206-002  
October 31, 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

**Protocol No. STP206-002; Final Version 3.0, Amendment 2, 08Jul2018**

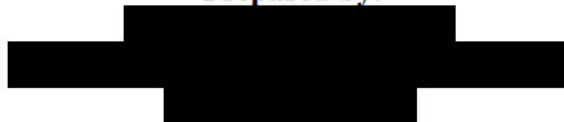
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**Statistical Analysis Plan**

**Prepared for:  
Leadiant Biosciences, Inc.**

**Final Version 3.0 31OCT2018**

**Prepared by:**

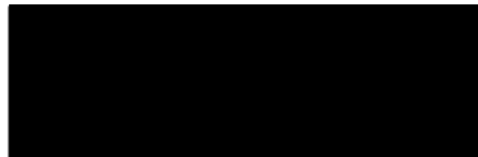


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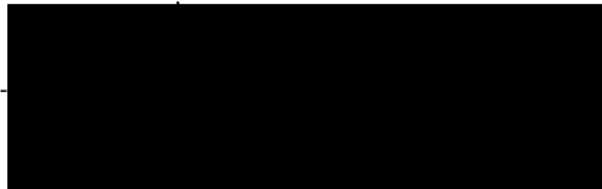
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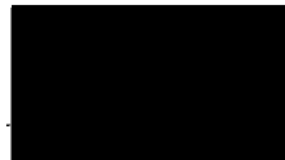


31 OCT 2018  
Date



Clinical Study Manager  
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## 1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

**Table 1: Abbreviations and Definitions of Terms**

<b>Abbreviation</b>	<b>Term</b>
AE	Adverse event
AGA	Appropriate for gestational age
BP	Blood pressure
BPD	Bronchopulmonary Dysplasia
BW	Birth Weight
CI	Confidence interval
CRA	Clinical Research Associate
CRF	Case report form
DSMC	Data safety and monitoring committee
ELBW	Extremely low birth weight
FDA	U.S. Food and Drug Administration
g	Gram
HR	Heart rate
IRB	Institutional review board
IVH	Intraventricular Hemorrhage
ITT	Intent-to-treat
LBP	Live Biotherapeutic Product
LBW	Low birth weight
LGA	Large for gestational age
MedDRA	Medical dictionary for regulatory activities
N	Number of subjects
NEC	Necrotizing Enterocolitis
PK	Pharmacokinetic
ROP	Retinopathy of prematurity
RR	Respiratory rate
SAS®	Statistical analysis software
SAE	Serious Adverse Event
SD	Standard deviation
SGA	Small for gestational age
SOC	System organ class
TEAE	Treatment-Emergent Adverse Event
Temp	Temperature

<b>Abbreviation</b>	<b>Term</b>
VLBW	Very low birth weight
WHO	World Health Organization

## 2 INTRODUCTION

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

### 2.1 Disease Background

Necrotizing Enterocolitis (NEC) is the most common serious acquired disease of the gastrointestinal tract in preterm infants<sup>1</sup> with the majority of NEC occurring in infants with birth weight (BW) below 1500 g.<sup>2</sup> 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<sup>3</sup>. These VLBW babies are at the highest risk for developing NEC. NEC has been reported to occur in approximately 10% of VLBW infants<sup>2</sup>, although the incidence varies among countries and neonatal centers. The mortality rate of VLBW infants with NEC is approximately 20%<sup>4, 5</sup>. In addition to the mortality rates, infants with NEC often have other complications and require other interventions and extended hospitalizations<sup>6</sup>. 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<sup>7</sup>.

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.

### 2.2 Description of Investigational Product

STP206 Live Biotherapeutic 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.

#### 2.2.1 Probiotics for the Prevention of NEC

There have been no clinical studies conducted to date with STP206 for the prevention of NEC in Neonates other than the current STP206-002 study.

[REDACTED]



## 2.3 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.

[REDACTED]

The hypothesis is, therefore, 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 of the protocol) 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.

## 3 STUDY OBJECTIVES

The study will be a sequential dose escalation study to examine the safety, tolerability, and preliminary NEC-preventative efficacy of two dose levels of STP206 in premature VLBW and ELBW neonates.

### 3.1 Sequential Dose Escalating Study

#### 3.1.1 Primary Objectives

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

##### 3.1.1.1 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.

## 4 STUDY DESIGN

### 4.1 General Design

Protocol STP206-002 is designed as a multi-center, randomized, double-blind, and placebo-controlled study with dose escalation to examine the safety, tolerability, and preliminary NEC-preventative efficacy of two doses of STP206 versus control in four sequentially decreasing BW strata.

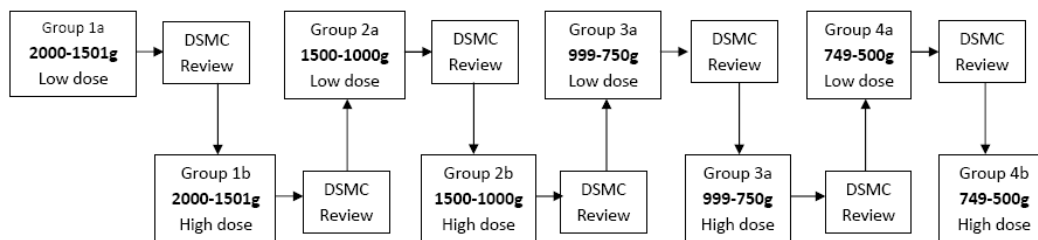
All neonates enrolled in the study will be randomized and will receive daily doses of blinded study treatment (STP206 or control) for between 2 and 11 weeks, through 34 weeks post-conceptual age or hospital discharge, whichever comes first. All neonates enrolled in the study will be placed under Universal 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 ( $1 \times 10^9$ ) CFU of [REDACTED] and approximately 100 million ( $1 \times 10^8$ ) CFU of [REDACTED] (total of 1.1 billion CFU)
  - High dose STP206: approximately 9 billion ( $9 \times 10^9$ ) CFU of [REDACTED] and approximately 900 million ( $9 \times 10^8$ ) 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 BW 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 – BW 2000 to 1501 g and Low dose STP206 versus control

- Study Group 1b – BW 2000 to 1501 g and High dose STP206 versus control
- Study Group 2a – BW 1500 to 1000 g and Low dose STP206 versus control
- Study Group 2b – BW 1500 to 1000 g and High dose STP206 versus control
- Study Group 3a – BW 999 to 750 g and Low dose STP206 versus control
- Study Group 3b – BW 999 to 750 g and High dose STP206 versus control
- Study Group 4a – BW 749 to 500 g and Low dose STP206 versus control
- Study Group 4b – BW 749 to 500 g and High dose STP206 versus control
- Each BW strata/STP206 dose group will consist of approximately 12 subjects.
- Within each BW 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 BW 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 BW 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 of 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 Protocol 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 the figure below.

Figure 1 – Treatment Group Sequence



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.

## 4.2 Discussion of Study Design

Not applicable.

## 4.3 Method of Assignment of Subjects to Treatment Groups

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 BW among treatment groups, randomization will be stratified by BW in four strata: 2000-1501g, 1500 to 1000 g, 999 to 750 g and 749 to 500 g.

## 4.4 Blinding

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 treatment is supplied in open-label fashion, the study will require unblinded site personnel to randomize subjects and prepare study treatments 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) to minimize bias in study conduct.

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

Only the staff who assist the process of preparing randomization assignments/labels for independent pharmacist, the designated unblinded site monitors, and the statistician who



assists preparing data for the independent Data Safety Monitoring Committee (DSMC) will be unblinded to the study.

#### **4.5 Determination of Sample Size**

The sample size of this study was not statistically determined.

### **5 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES**

#### **5.1 Changes in the Conduct of the Study**

Protocol version 2.0, Amendment 1, dated 06JAN2014, revised sections of the protocol to provide clarification regarding procedures/evaluations to be done. This Amendment was implemented prior to the start of subject enrollment.

Protocol version 3.0, Amendment 2, dated 08JUL2018, revised protocol to remove Part B of the study as well as the Month 18 Follow-up Visit. Data beyond Month 6 post dosing will only be presented in listings unless specifically detailed in this SAP.

#### **5.2 Changes from the Analyses Planned in the Protocol**

The definition of the Intent-to-treat analysis population was changed in this SAP to include all subjects that are randomized regardless of dosing status.

#### **5.3 Changes from Prior Versions of the SAP**



SAP V2.0: Sigma Tau Pharmaceuticals' name was updated to Leadiant Biosciences. [REDACTED] as the named statistical services vendor on STP206-002 [REDACTED]

SAP V3.0: Incorporates changes due to Protocol Amendment 2. See History of Protocol Changes, dated 08JUL2018 and redlined Protocol, version 3.0 for full description of changes.

### **6 BASELINE, EFFICACY AND SAFETY EVALUATIONS**

#### **6.1 Schedule of Evaluations**

The assessments to be conducted at each scheduled visit are displayed in the following table.

Schedule of Events <i>During</i> 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						
Vital Signs (Temp, BP, HR, RR, SpO <sub>2</sub> )	x	x						
Growth Assessment	x	x		x	x		x	
Fecal sample	x <sup>a</sup>	x <sup>a</sup>	x <sup>a</sup>	x <sup>f</sup>	x	x	x	
Retinopathy of Prematurity (ROP) <sup>c</sup>								x
Intraventricular Hemorrhage (IVH) <sup>d</sup>				x <sup>d</sup>	x <sup>d</sup>			
Bronchopulmonary Dysplasia (BPD) <sup>e</sup>								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<sub>2</sub>= 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 ( $\pm 3$  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.

**Table 2 Schedule of Events Post Dosing Period**

Protocol STP206-002 Schedule of Events <i>Post</i> 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

## 6.2 Time Point Algorithms

### 6.2.1 Relative Day

The date of first dose of study treatment will be considered as study day 1, and the day before the first dose of study treatment will be relative day -1. Study days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing study days).

For days on or after the first dose of study treatment:

Date of Assessment – Date of First Dose of study treatment + 1.

For days before the first dose of study treatment:

Date of Assessment – Date of First Dose of study treatment.

### 6.2.2 Windows

The time schedule described in the protocol for each scheduled activity will be followed as closely as possible. The time windows noted in Table 4 will be used for analysis purposes.

**Table 4: Analysis Visit Windows for Dosing Period and Post Dosing**

Nominal Visit during dosing period (Target Day)	Protocol Window	Study Day Analysis Visit Window Range
Baseline	Collected at birth, screening, or/and Week 1 Day 1 before study dosing	Sample assessment date < Date of First Dose of study treatment
1 Hour <sup>a</sup>	1 Hour ± 10 minutes	1 Hour ± 30 minutes



Nominal Visit during dosing period (Target Day)	Protocol Window	Study Day Analysis Visit Window Range
2 Hour <sup>a</sup>	2 Hour $\pm$ 10 minutes	2 Hour $\pm$ 30 minutes
3 Hour <sup>a</sup>	3 Hour $\pm$ 10 minutes	3 Hour $\pm$ 30 minutes
4 Hour <sup>a</sup>	4 Hour $\pm$ 10 minutes	4 Hour $\pm$ 30 minutes
8 Hour <sup>a</sup>	8 Hour $\pm$ 10 minutes	8 Hour $\pm$ 30 minutes
12 Hour <sup>a</sup>	12 Hour $\pm$ 10 minutes	12 Hour $\pm$ 30 minutes
16 Hour <sup>a</sup>	16 Hour $\pm$ 10 minutes	16 Hour $\pm$ 30 minutes
20 Hour <sup>a</sup>	20 Hour $\pm$ 10 minutes	20 Hour $\pm$ 30 minutes
24 Hour <sup>a</sup>	24 Hour $\pm$ 10 minutes	24 Hour $\pm$ 30 minutes
Week 1 (Day 1-4) <sup>b</sup>	day 1, day 2, day 3, day 4	day 1, day 2, day 3, day 4
Week 1 (Day 5-7) <sup>b,c,d</sup>	day 5, day 6, day 7	day 5, day 6, day 7
Week 2 (Day 14) <sup>b,d</sup>	13 to 16 days	13 to 17 days
Week 3 (Day 21) <sup>b</sup>	20 to 22 days	18 to 24 days
Week 4 (Day 28) <sup>b,d</sup>	25 to 32 days	25 to 32 days
Week 5 (Day 35) <sup>b</sup>	34 to 36 days	33 to 38 days
Week 6 (Day 42) <sup>b,d</sup>	41 to 42 days	39 to 45 days
Week 7 (Day 49) <sup>b</sup>	48 to 50 days	46 to 52 days
Week 8 (Day 56) <sup>b,d</sup>	55 to 57 days	53 to 59 days
Week 9 (Day 63) <sup>b</sup>	62 to 64 days	60 to 66 days
Week 10 (Day 70) <sup>b,d</sup>	69 to 71 days	67 to 73 days
Week 11 (Day 77) <sup>b</sup>	76 to 78 days	74 to 80 days
End of Dosing or Hospital Discharge <sup>b,d</sup> (for Growth Assessment, and fecal sample only)	Not specified	<b>For fecal sample:</b> sample assessment date - last dose date $\geq$ 0 <b>For growth assessment:</b> 0 $\leq$ sample assessment date - last dose date $\leq$ 5 days
<b>Nominal Visit during Post Dosing</b>		<b>Post Study Day Analysis Visit Window Range<sup>e</sup></b>
Post Dosing 1 Week <sup>d</sup>	5 to 9 days	6day $\leq$ (assessment date – expected last dose date+1) $\leq$ 13 days
Post Dosing 1 Month <sup>d</sup>	30 to 35 days	21 days $\leq$ (assessment date – expected last dose date+1) $\leq$ 35 days
Post Dosing 3 Month <sup>d</sup>	85 to 99 days	85 $\leq$ (assessment date – expected last dose date+1) $\leq$ 99 days

Nominal Visit during dosing period (Target Day)	Protocol Window	Study Day Analysis Visit Window Range
Post Dosing 6 Month <sup>d</sup>	181 to 195 days	181 ≤ (assessment date – expected last dose date+1) ≤ 195 days
Post Dosing 18 Month/End <sup>d</sup>	Not specified	520 ≤ (assessment date – expected last dose date+1) ≤ 576 days
Withdrawal Prior to Post Dosing 6 Month <sup>d</sup>	Not specified	assessment date ≥ date of withdrawal and (assessment date – expected last dose date+1) ≤ 181 days
Withdrawal between Post Dosing 6 and 18 Month <sup>d</sup>	Not specified	assessment date ≥ date of withdrawal and 196 days < (assessment date – expected last dose date+1) < 520 days

- a- Windows for vital sign measurements and physical examinations.
- b- Window for fecal sample.
- c- Window for IVH measurement.
- d- Windows for growth assessment (note that Post Dosing 18 Month data will only be presented in listings).
- e- Windows for Post Dosing may be adjusted to account for patients that terminated dosing early. For example, if a subject early terminates dosing at Week 10 but was expected to complete dosing at Week 11, then the Post Dosing window will be adjusted to reflect planned time point after expected dosing completion.

If a subject has more than 1 assessment occurring in the same visit window, the data from the visit closest to the scheduled study day will be used for summaries. If two assessments have the same distance from the scheduled study day, the assessment after the scheduled study day will be used for the analyses.

If multiple assessments occur as Baseline (screening or Day 1 prior to dosing), then the last assessment before the first study dose will be used for the analyses.

### 6.2.3 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. Subject's gestational age will be reported by the treating physician and/or Principal Investigator on the e-CRF. It is intended that neonates will receive blinded study treatment through 34 weeks post conceptional age. However, in the event of early hospital discharge, the minimum required dosing duration is provided in the table below.

<b>Gestational Age at Birth</b>	<b>Protocol Defined Gestational Age</b>	<b>Intended Dosing Duration Weeks (Days)</b>	<b>Minimum Required Cumulative Dosing Days<sup>ab</sup></b>
23 Weeks 0/7 days to 23 Weeks 6/7 days	23 weeks	11 (77)	54
24 weeks0/7 days to 24 Weeks 6/7 days	24 weeks	10 (70)	49
25 weeks0/7 days to 25 Weeks 6/7 days	25 weeks	9 (63)	45
26 weeks0/7 days to 26 Weeks 6/7 days	26 weeks	8 (56)	40
27 weeks0/7 days to 27 Weeks 6/7 days	27 weeks	7 (49)	35
28 weeks0/7 days to 28 Weeks 6/7 days	28 weeks	6 (42)	30
29 weeks0/7 days to 29 Weeks 6/7 days	29 weeks	5 (35)	25
30 weeks0/7 days to 30 Weeks 6/7 days	30 weeks	4 (28)	20
31 weeks0/7 days to 31 Weeks 6/7 days	31 weeks	3 (21)	15
32 weeks0/7 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

b –  $\geq 75\%$  of intended number of dosing days

### 6.3 Baseline Assessments

The following baseline assessments will be conducted prior to initial study treatment administration:

- 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 (Head circumference, body length, and body weight)
- Fecal sample, if produced
- Laboratory Assessments

- Peripheral Blood Culture (from NICU admission, if obtained)
- Prior medications

## 6.4 Efficacy Variables

### 6.4.1 Primary Efficacy Variable(s)

No primary efficacy variable is defined for this study.

### 6.4.2 Secondary Efficacy Variables

The secondary efficacy variables are:

- Incidence of suspected NEC (stage I)
- Incidence of confirmed NEC (stage II and higher)
- Incidence of Feeding intolerance
- Death
- Incidence of Sepsis
- Incidence of other neonatal complications of prematurity
  - ROP
  - IVH
  - BDP
  - Spontaneous Gastrointestinal Perforation
  - Patent ductus arteriosus requiring treatment with indomethacin, ibuprofen or surgery
- Number and percent of subject with STP206 organism (STP-6, STP-11) identified
- Time to first detection of STP206 organism (STP-6, STP-11)
- Number and percent of subjects that fall in the four growth classifications 1) appropriate for gestational age (AGA), 2) small for gestational age (SGA/Head-Spared), 3) SGA/Symmetric, and 4) large for gestational age (LGA). Where AGA is defined as both body weight (g) and head circumference (cm) are between 10th Percentile and 90th Percentile according to the gender specific growth Percentile charts. SGA/Head-Spared is defined as Body Weight (g) is <10th percentile, and Head circumference (cm) is between 10th Percentile and 90th Percentile according to the gender specific growth percentile charts. SGA/Head-Symmetric is defined as Both Body Weight (g) and Head circumference (cm) are <10th Percentile according to the gender specific growth percentile charts. LGA is defined as Both Body Weight (g) and Head circumference (cm) are >90th Percentile according to the growth percentile charts.

### **6.4.3 Exploratory Efficacy Variables**

Additional efficacy variables are:

- The incidence of suspected NEC (Stage I NEC) 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

### **6.5 Drug Concentration Measurements and Pharmacokinetic Parameters**

Not applicable to this study.

#### **6.5.1 Handling of Outliers**

There is no apriori plan to handle outliers for this study, except for observations deemed to be “extreme” outliers. These types of outliers may be excluded from summary analyses but will be included in listings. When an outlier is excluded from a summary table, a footnote will indicate the subject, value, and reason it was excluded.

### **6.6 Safety Assessments**

The following are the safety assessments:

- The incidence and severity of adverse events, serious adverse events, and changes in clinical parameters from baseline through six months after the last dose of blinded study treatment.
- Physical examination through six months after the last dose of the study treatment.
- Vital signs evaluation through six months after the last dose of the study treatment.
- Concomitant medications evaluations for infant through six months after the last dose of the study treatment.
- The assessment of the progression of standard neonatal growth parameters (head circumference, body length, and body weight) in STP206-treated subjects compared to control subjects through 60f corrected age.
- Number and percent of subjects with presence of STP206 organisms in fecal shedding in STP206-treated subjects compared to control subjects through the last dose of blinded study treatment

## **7 STATISTICAL METHODS**

### **7.1 General Methodology**

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 [N], mean, standard deviation [SD], median, 25<sup>th</sup> and 75<sup>th</sup> quartiles,



minimum [min], and maximum [max] values for continuous measures. Descriptive summaries will be presented for each treatment group, BW strata, and all BW strata combined.

All statistical comparisons performed on the data will be done for exploratory analysis purposes only.

## **7.2 Adjustments for Covariates**

Not applicable to this study.

## **7.3 Handling of Dropouts or Missing 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.

The study will require a minimum of nine evaluable subjects within each BW strata and dose group. If less than nine subjects complete the minimum required study treatment duration (see Section 6.2.3) and have a post dosing assessment, then replacement subjects will be enrolled to replace the original randomized subjects who do not meet the minimum required study treatment durations. The treatment assignment for the replacement subject will be the same as the original subject who needed to be replaced. Data from the subjects who are replaced will be analyzed in the ITT and Safety analysis.

## **7.4 Interim Analyses and Data Monitoring**

### **7.4.1 Formal Interim Analyses**

No formal interim analyses of study data are planned to occur during the study.

### **7.4.2 DSMC Analyses**

An independent DSMC will be used to review data generated in this study. A Charter for the DSMC outlining the membership, roles and responsibilities will be developed and finalized prior to the initiation of the study.

Available data on primary and secondary endpoints including adverse events will be included in each review. The DSMC can give recommendations of continuation of study, or 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 Protocol 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/BW group to assess whether proceeding to lower BW 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 – BW 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.

## **7.5 Multi-center Studies and Pooling of Centers**

This study will be conducted in up to 20 centers. Data from all sites will be pooled. The pooled data will be summarized and analyzed.

## **7.6 Multiple Comparisons/Multiplicity**

No adjustments for multiple comparisons or multiplicity will be made.

## **7.7 Use of an “Efficacy Subset” of Subjects**

Not applicable to this study.

## **7.8 Active-Control Studies Intended to Show Equivalence**

Not applicable to this study.

## **7.9 Examination of Subgroups**

A subgroup analyses will be conducted for subjects whose gestational age at birth is  $\leq 28$  weeks, and  $> 28$  weeks, respectively. Depending on the sample size, a subgroup analyses may be conducted for subjects whose gestational age at birth is  $\leq 26$  weeks, and 27 to 28, and  $\geq 29$  weeks.

# **8 STATISTICAL ANALYSIS**

All statistical analyses will be performed using SAS® (version 9.4 or higher).

Unless otherwise noted, summary tables will only include data up to the Month 6 Post-Dose visit. Data collected after that will only be included in listings.

Safety and efficacy data will be summarized using BW strata. If deemed necessary, additional analyses may be conducted on pooled data across cohorts, where incidence of clinical events

(NEC, sepsis, feeding intolerance, death, morbidity/complications of prematurity) may be presented.

## **8.1 Disposition of Subjects**

The number of subjects enrolled and the number of treated subjects will be summarized.

The number of subjects who completed the study, the number of treated subjects who discontinued from the study and the reasons for discontinuation from the study will also be summarized.

The Intent-to-treat (ITT) population will be used for this analysis.

The summary of subject disposition will be displayed by (i) dose group and BW stratum, (ii) by all BW strata combined for STP206 low dose, STP206 high dose and control group, and (iii) by investigation site and dose group.

## **8.2 Protocol Deviations**

Protocol deviations will be recorded by the designated site CRA and provided by Leadiant for consolidation. Deviations will be coded by Leadiant as Critical, Major, or Minor. The tracker of deviations will be provided to [REDACTED] for integration in the analysis reporting.

## **8.3 Analysis Populations**

### **8.3.1 Safety Population**

The safety population will be all randomized subjects who received any amount of blinded study treatment. Subjects will be analyzed according to the treatment they actually received.

### **8.3.2 Intent-to-Treat (ITT) Population**

The Intent-to-treat population will consist of all randomized subjects. Subjects will be analyzed according to the randomized treatment.

### **8.3.3 Per Protocol (PP) Population**

The per-protocol population will consist of all randomized subjects who meet the Minimum Required Cumulative Dosing Days as indicated in Protocol Section 11.2.3, or have a clinical outcome of NEC (confirmed case), and do not have a critical or major protocol deviation. Subjects will be analyzed according to the treatment they actually received. This population may be used for analysis if subjects are dosed incorrectly.



Leadiant will review protocol deviations/violations to determine if a subject completed the study according to the protocol. This population of subjects will be identified at the time when all the data has been entered into the database and cleaned, prior to database lock.

The major protocol deviations may include:

- Deviations from inclusion criteria
- Deviations from exclusion criteria
- Use of prohibited concomitant medications (e.g., Products containing probiotic bacteria are prohibited)
- Subjects not meeting the minimum cumulative required duration of study treatment

The primary and selected secondary analyses will be repeated using the per-protocol population.

### **8.3.4 Pharmacokinetics (PK) population**

Not applicable in this study.

## **8.4 Demographic and Other Baseline Characteristics**

All baseline summaries will be based on the ITT populations.

Maternal race, infant race, infant gender, whether the uses of resuscitation/stabilization support, supplement oxygen, PPV, CPAP, intubation, chest compression and epinephrine will be summarized using counts and percentages.

Maternal age, infant birth length (cm), BW (g), one- and five-minute Apgar score will be summarized with descriptive statistics (number of subjects [N], mean, standard deviation [SD], median, 25<sup>th</sup>, 75<sup>th</sup> quartiles, minimum [min], and maximum [max]).

Maternal Pregnancy History and Delivery of whether the mother consume/or use any alcohol, cigarette, or recreational drug will be summarized using counts and percentages.

The summary of Maternal History and Baseline Characteristics, Pregnancy History and Delivery, Infant History and Baseline Characteristics will be displayed by (i) dose group and BW stratum and (ii) by all BW strata combined for STP206 low dose, STP206 high dose and control group.

Maternal History and Baseline Characteristics, Pregnancy History and Delivery, Infant History and Baseline Characteristics will be presented in a listing.

## **8.5 Prior and Concomitant Therapy**

Summary of prior and concomitant therapy will be based on safety population.

The World Health Organization (WHO) Drug Dictionary September 2013 will be used to classify prior and concomitant medications by preferred term and WHO Anatomical Therapeutic Chemical (ATC) classification of ingredients. Prior medications are defined as any medication

given prior to and stopped before the subject receives the first dose of study medication (Day 1). Concomitant medications are defined as any medication given to the subject starting on or after the day the subject received the first dose of study treatment (Day 1) or given prior to the subject receiving the first dose of study treatment (Day 1) and continuing to receive it during the study.

If the start date of medication is unknown and the end date is known, then the medication will be considered:

- Prior to study treatment if the end date is prior to the subject receiving the first dose of study treatment (Day 1)
- Concomitant to study treatment if the end date is either on or after the first dose of study treatment (Day 1) or the end date is unknown.

If both the start and end dates are unknown, then the medication will be considered to be “concomitant on-treatment”. For the purposes of determining the medication reference to the onset date for partial dates, missing months will be imputed to ‘01’, and missing days will be imputed to ‘01.’

Prior and concomitant medication will be summarized giving the number and percentage of subjects (n, (n/N\*100)) by preferred name within each ATC, with ATC and preferred names sorted by descending frequency.

ATC classification level 3 will be used in summary tables and listings. If ATC classification level 3 is missing, then ATC classification level 2 will be used, however, if ATC classification level 2 is missing, then ATC classification level 1 will be used.

The summary of maternal medical history, infant prior and concomitant therapy will be displayed by (i) dose group and BW stratum and (ii) by all BW strata combined for STP206 low dose, STP206 high dose and control group.

## **8.6 Analysis of Efficacy Parameters**

Descriptive summaries will consist of frequencies and percentages for categorical measures and of the number of subjects [N], mean, standard deviation [SD], median, 25<sup>th</sup> and 75<sup>th</sup> quartiles, minimum [min], and maximum [max] values for continuous measures. Descriptive summaries will be presented for each treatment group, BW strata, and all BW strata combined.

The incidence rates of the exploratory variables for those who received STP206 vs. control will be summarized and displayed.

The analyses of efficacy variables will be performed for ITT population only.

Efficacy will be displayed by (i) dose group and BW stratum and (ii) by all BW strata combined for STP206 low dose, STP206 high dose and control group.

### ***8.6.1 Analysis of Primary Efficacy Variable***

Not applicable.

### ***8.6.2 Analysis of Secondary Efficacy Variables***

#### ***8.6.2.1 Endpoints***

- Incidence of suspected NEC (Stage I)
- Incidence of confirmed NEC (Stage II and higher)
- Incidence of sepsis/bacteremia
- Incidence of feeding intolerance
- Hospital Mortality (death occurred during inpatient hospitalization)
- Incidence of other neonatal complications of prematurity
  - ROP
  - IVH
  - BDP
  - Spontaneous Gastrointestinal Perforation
  - Patent ductus arteriosus requiring treatment with indomethacin, ibuprofen or surgery

The incidence rate of each outcome will be summarized separately. The secondary efficacy will be displayed by (i) dose group and BW stratum and (ii) by all BW strata combined for STP206 low dose, STP206 high dose and control group. Incidence rate of suspected NEC (stage I), confirmed NEC (stage II and higher) will be further summarized by two subgroups: gestational age at birth is less than and equal to 28 weeks, and greater than 28 weeks.

### ***8.6.3 Analysis of Pharmacokinetic Variables***

Not applicable.

### ***8.6.4 Subgroup Analyses***

In general, safety and efficacy data will be summarized based on BW strata and treatment group. Incidence rate of suspected NEC (stage I), confirmed NEC (stage II and higher) will be further summarized by two sub groups: gestational age at birth is less than and equal to 28 weeks, and greater than 28 weeks

### **8.6.5 Exploratory Analyses**

Exploratory analyses are as follows:

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

## **8.7 Analysis of Safety**

Safety population will be used for the analysis of Safety.

Safety data will be displayed by (i) dose group and BW stratum and (ii) by all BW strata combined for STP206 low dose, STP206 high dose and control group.

### **8.7.1 Extent of Exposure and Compliance to Study Treatment**

All exposure summaries will be presented by the safety population.

The extent of subject exposure to study treatment will be quantified using the parameters of total cumulative dose [REDACTED], Average daily dose, and duration of dosing. Total cumulative dose is defined as the actual cumulative dose of study treatment received during the entire dosing period. The average daily dose is defined as total cumulative dose divided by number of days elapsed from first dose to last dose, and the duration of dosing is defined as the total number of dosing days, in which a subject is actually receiving study treatment.

Total cumulative dose will be summarized using descriptive statistics (number of subjects [N], mean, standard deviation [SD], median, 25<sup>th</sup> and 75<sup>th</sup> quartiles, minimum [min], and maximum [max]). Average daily dose [REDACTED] will be summarized by descriptive statistics (number of subjects [N], mean, standard deviation [SD], median, minimum [min], and maximum [max]). The duration of dosing (days) will be summarized using descriptive statistics (number of subjects [N], mean, standard deviation [SD], median, minimum [min], and maximum [max]).

### **8.7.2 Adverse Events**

All AE summaries will be presented by the safety population.

All AE tables will include only treatment emergent AEs (TEAEs) unless otherwise noted. TEAEs are those which start or worsen in severity after the first dose of study medication. If it

cannot be determined if the AE started or worsened after the first dose of study treatment, it will be assumed to be a TEAE.

AEs will be assessed from the time the subject receives their initial dose of study medication up to 6 months following the last dose of study drug (note that some sites used 6 months gestational age rather than 6 months post last dose). All AEs reported during this period, regardless of severity relationship to blinded study treatment, will be recorded. The investigator's verbatim term of each adverse event will be mapped to the system organ class and preferred term using the MedDRA dictionary.

All AE tables will be summarized for each treatment group by system organ class (SOC) and preferred term (PT) using counts and percentages.

In order to count the number of subjects who experienced each AE, a subject experiencing the same AE multiple times will only be counted once for the corresponding preferred term. Similarly, if a subject experienced multiple AEs within the same SOC, that subject will be counted only once for that SOC. Adverse events will be presented in alphabetical order of SOC and within each SOC, in decreasing order of the total number of subjects who experienced each AE at the preferred term level.

Adverse events will also be presented by severity for Mild AE (Grade 1), Moderate AE (Grade 2) and Severe AE (Grade 3). In the case of multiple experiences with the same AE, the subject will be counted only once under the worst reported severity. Missing category will be presented to summarize any missing severity.

Serious adverse events (SAEs) will be presented by SOC and preferred term.

Adverse events will also be summarized by relationship. Treatment related AEs include those events that were rated by the investigator as possible or probable related. Missing category will be presented to summarize any missing relationship.

The following AE categories will be summarized:

- Overall AE summary
- AEs by SOC and preferred term
- Related AEs by SOC and preferred term
- Grade 3 AEs by SOC, preferred term and relationship to study treatment
- Treatment Related AEs with Grade 3 by SOC, preferred term
- AEs leading to discontinuation of study treatment by SOC, preferred term
- AEs leading to death by SOC, preferred term
- SAEs by SOC, preferred term

Additionally, the following listings will be produced:

- All AEs
- All SAEs
- AEs that resulted in discontinuation of study treatment
- AEs with an outcome of death

### **8.7.3 Clinical Laboratory Evaluations**

Blood cultures will be collected upon NICU admission (if SOC medium for the study site), and during the dosing period when sepsis is suspected. Data from blood cultures will be provided in a listing.

Site cultures will be collected if an infection of a normally sterile site (e.g., UTI, peritonitis) is suspected. Data from site cultures will be provided in a listing.

### **8.7.4 Other Observations Related to Safety**

Growth assessments during the dosing period and post dosing period will be summarized as AGA, SGA/Head-Spared, SGA/Symmetric, LGA at the following time points: Pre-dose, Week 1 (Days 5-7), Week 2, 4, 6, 8, 10, and Post Dosing 1 Week, Post Dosing 1, 3 6 Month, and Early Withdrawal Prior to post dosing 6 Months. Four classifications (AGA, SGA/Head-Spared, SGA/Symmetric, and LGA) according to the growth chart for males and females will be summarized and displayed. Classifications will be based on weight and head growth measurements<sup>13</sup> specified in Appendix D of the protocol and the WHO standard growth charts [https://www.cdc.gov/growthcharts/who\\_charts.htm](https://www.cdc.gov/growthcharts/who_charts.htm).

Information on feeding method (bottle, breast, and tube) and content of feedings (formula or breast milk), abdominal evaluation, etc will be summarized by number and percent of subjects.

Physical examination will be summarized by the number and percent of subjects with abnormal findings at the following time points: Pre-dose, and 3 hours Post Dosing.

Vital signs (BP, HR, RR, and Temperature) will be summarized as descriptive statistics (N, mean, SD, median, 25<sup>th</sup> and 75<sup>th</sup> quartiles, minimum, and maximum) and change from baseline at the following time points: Pre-dose, 1 hour, 2, 3, 4, 8, 12, 16, 20 and 24 hours post dosing.

The number and percentage of subjects with presence of STP206 organisms in fecal samples will be summarized, and the quantity (CFU) of the STP206 organisms detected from fecal shedding will be further summarized as descriptive statistics (N, mean, SD, median, 25<sup>th</sup> and 75<sup>th</sup> quartiles, maximum, and minimum) at the following time points: Pre-dose, Week 1 Days 1- 4), Week 1 (Days 5-7), Week 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, End of Dosing or Hospital Discharge, whichever occurs first.

## 9 COMPUTER SOFTWARE

All analyses will be performed by [REDACTED] using Version 9.4 or higher version of SAS® software. All summary tables and data listings will be prepared utilizing SAS® software.

## 10 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]

[REDACTED]

[REDACTED]

[REDACTED]



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

## 11 TABLES AND LISTINGS

Programming shells for the tables and listings are provided in a separate document. However, below is a schedule of the tables and listings planned in this SAP. Note that additional tables and listings may be created after this SAP is finalized and therefore will not be listed below (table and listing numbers may change accordingly).

NUMBER	TABLE
14.1.1.1.1	End of Treatment Disposition of Subject by Birth Weight Stratification (2000 - 1501 g, 1500 – 1000 g)\Intent-to-treat Population
14.1.1.1.2	End of Treatment Disposition of Subject by Birth Weight Stratification (999 - 750 g, 749 – 500 g)\Intent-to-treat Population
14.1.1.1.3	End of Treatment Disposition of Subjects Across All Birth Weight Stratifications\Intent-to-treat Population
14.1.1.1.5	End of Study Disposition of Subject by Birth Weight Stratification (2000 - 1501 g, 1500 – 1000 g)\Intent-to-treat Population
14.1.1.1.6	End of Study Disposition of Subject by Birth Weight Stratification (999 - 750 g, 749 – 500 g)\Intent-to-treat Population
14.1.1.1.7	End of Study Disposition of Subjects Across All Birth Weight Stratifications\Intent-to-treat Population
14.1.2.1.1	Maternal Demographic Characteristics by Birth Weight Stratification (2000 - 1501 g, 1500 – 1000 g)\Intent-to-treat Population
14.1.2.1.2	Maternal Demographic Characteristics by Birth Weight Stratification (999 - 750 g, 749 – 500 g)\Intent-to-treat Population
14.1.2.1.3	Maternal Demographic Characteristics Across All Birth Weight Stratifications\Intent-to-treat Population
14.1.2.2.1	Maternal Smoking/Alcohol History by Birth Weight Stratification (2000 - 1501 g, 1500 – 1000 g)\Intent-to-treat Population
14.1.2.2.2	Maternal Smoking/Alcohol/Drug Use History by Birth Weight Stratification (999 - 750 g, 749 – 500 g)\Intent-to-treat Population



14.1.2.2.3	Maternal Smoking/Alcohol/Drug Use History Across All Birth Weight Stratifications\Intent-to-treat Population
14.1.2.3.1	Maternal Reproductive History by Birth Weight Stratification (2000 - 1501 g, 1500 – 1000 g)\Intent-to-treat Population
14.1.2.3.2	Maternal Reproductive History by Birth Weight Stratification (999 - 750 g, 749 – 500 g)\Intent-to-treat Population
14.1.2.3.3	Maternal Reproductive History Across All Birth Weight Stratifications\Intent-to-treat Population
14.1.2.4.1	Maternal Pregnancy/Delivery History by Birth Weight Stratification (2000 - 1501 g, 1500 – 1000 g)\Intent-to-treat Population
14.1.2.4.2	Maternal Pregnancy/Delivery History by Birth Weight Stratification (999 - 750 g, 749 – 500 g)\Intent-to-treat Population
14.1.2.4.3	Maternal Pregnancy/Delivery History Across All Birth Weight Stratifications\Intent-to-treat Population
14.1.3.1	Infant Baseline Characteristics by Birth Weight Stratification (2000 - 1501 g, 1500 – 1000 g)\Intent-to-treat Population
14.1.3.2	Infant Baseline Characteristics by Birth Weight Stratification (999 - 750 g, 749 – 500 g)\Intent-to-treat Population
14.1.3.3	Infant Baseline Characteristics Across All Birth Weight Stratifications\Intent-to-treat Population
14.1.3.5	Infant Baseline Characteristics by Birth Weight Stratification (2000 - 1501 g, 1500 – 1000 g)\Per Protocol Population
14.1.3.6	Infant Baseline Characteristics by Birth Weight Stratification (999 - 750 g, 749 – 500 g)\Per Protocol Population
14.1.3.7	Infant Baseline Characteristics Across All Birth Weight Stratifications\Per Protocol Population
14.1.3.9	Infant Baseline Characteristics by Birth Weight Stratification (2000 - 1501 g, 1500 – 1000 g) and Gestational Age Group (<= 28 Weeks vs > 28 Weeks)\Intent-to-treat Population
14.1.3.10	Infant Baseline Characteristics by Birth Weight Stratification (999 - 750 g, 749 – 500 g) and Gestational Age Group(<= 28 Weeks, > 28 Weeks)\Intent-to-treat Population
14.1.3.11	Infant Baseline Characteristics Across All Birth Weight Stratifications and by Gestational Age Group(<= 28 Weeks, > 28 Weeks)\Intent-to-treat Population

14.1.3.13	Infant Baseline Characteristics by Birth Weight Stratification (2000 - 1501 g, 1500 – 1000 g) and Gestational Age Group (<= 28 Weeks vs > 28 Weeks)\Per Protocol Population
14.1.3.14	Infant Baseline Characteristics by Birth Weight Stratification (2000 - 1501 g, 1500 – 1000 g) and Gestational Age Group (<= 28 Weeks vs > 28 Weeks)\Per Protocol Population
14.1.3.15	Infant Baseline Characteristics by Birth Weight Stratification (999 - 750 g, 749 – 500 g) and Gestational Age Group(<= 28 Weeks, > 28 Weeks)\Per Protocol Population
14.1.4.1.1	Maternal Prior Medications by Drug Class and Preferred Name by Birth Weight Stratification (2000-1501 g,1500–1000 g)\Safety Population
14.1.4.1.2	Maternal Prior Medications by Drug Class and Preferred Name by Birth Weight Stratification (999 - 750 g, 749 – 500 g)\Safety Population
14.1.4.1.3	Maternal Prior Medications by Drug Class and Preferred Name Across All Birth Weight Stratifications\Safety Population
14.1.4.2.1	Maternal Concomitant Medications by Drug Class and Preferred Name by Birth Weight Stratification (2000-1501 g,1500–1000 g)\Safety Population
14.1.4.2.2	Maternal Concomitant Medications by Drug Class and Preferred Name by Birth Weight Stratification (999 - 750 g, 749 – 500 g)\Safety Population
14.1.4.2.3	Maternal Concomitant Medications by Drug Class and Preferred Name Across All Birth Weight Stratifications\Safety Population
14.1.4.3.1	Infant Prior Medications by Drug Class and Preferred Name by Birth Weight Stratification (2000 - 1501 g, 1500 – 1000 g)\Safety Population
14.1.4.3.2	Infant Prior Medications by Drug Class and Preferred Name by Birth Weight Stratification (999 - 750 g, 749 – 500 g)\Safety Population
14.1.4.3.3	Infant Prior Medications by Drug Class and Preferred Name Across All Birth Weight Stratifications\Safety Population
14.1.4.4.1	Infant Concomitant Medications by Drug Class and Preferred Name by Birth Weight Stratification (2000 - 1501 g, 1500 – 1000 g)\Safety Population
14.1.4.4.2	Infant Concomitant Medications by Drug Class and Preferred Name by Birth Weight Stratification (999 - 750 g, 749 – 500 g)\Safety Population
14.1.4.4.3	Infant Concomitant Medications by Drug Class and Preferred Name Across All Birth Weight Stratifications\Safety Population
14.2.2.1	Incidence Rate of NEC by Birth Weight Stratification (2000 - 1501 g, 1500 – 1000

	g)\Intent-to-treat Population
14.2.2.2	Incidence Rate of NEC by Birth Weight Stratification ((999 - 750 g, 749 – 500 g)\Intent-to-treat Population
14.2.2.3	Incidence Rate of NEC Across All Birth Weight Stratifications\Intent-to-treat Population
14.2.2.6	Incidence Rate of NEC by Birth Weight Stratification (2000 - 1501 g, 1500 – 1000 g) and Gestational Age Group\(<= 28 Weeks, > 28 Weeks)\Intent-to-treat Population
14.2.2.7	Incidence Rate of NEC by Birth Weight Stratification ((999 - 750 g, 749 – 500 g) and Gestational Age Group\(<= 28 Weeks, > 28 Weeks)\Intent-to-treat Population
14.2.2.8	Incidence Rate of NEC Across All Birth Weight Stratifications and Gestational Age Group\(<= 28 Weeks, > 28 Weeks)\Intent-to-treat Population
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