PROTOCOL NUMBER GIFT-02

A MULTI-CENTER, RANDOMIZED DOUBLE-BLIND, THREE-ARM, PARALLEL-GROUP TRIAL TO ASSESS THE EFFICACY AND SAFETY OF NTRA-9620 IN INFANTS WITH SHORT BOWEL SYNDROME (SBS) FOLLOWING SURGICAL RESECTION

10 JANUARY 2017

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INVESTIGATIONAL NEW DRUG PROTOCOL

NTRA-9620
(INSULIN FOR ORAL ADMINISTRATION)

PROTOCOL NUMBER GIFT-02
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SPONSOR:
NUTRINIA LTD.
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SPONSOR SIGNATURE PAGE

This protocol has been reviewed and approved by Nutrinia, Ltd. By my signature, I approve this document.

_____ _____
Date

_____ _____
Date

_____ _____
Medical Monitor
Sarina Tanimoto, MD, PhD, MBA
Date

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
Ca	Calcium
CFR	Code of Federal Regulations
cGCP	Current Good Clinical Practice(s)
cGMP	Current Good Manufacturing Practices
cm	Centimeter
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
dL	Deciliter
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EKG	Electrocardiogram
EN	Enteral Nutrition
FAS	Full Analysis Set
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practice(s)
GGT	Gamma-glutamyl Transpeptidase
GI	Gastrointestinal
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICH-GCP	International Conference on Harmonization-Good Clinical Practice(s)
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IU	Insulin Unit(s)
IV	Intravenous
K	Potassium
kg	Kilogram
MAR	Missing at Random
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MD	Maltodextrin
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram

Abbreviation	Explanation
mITT	Modified Intent-to-Treat
mL	Milliliter
Na	Sodium
npo	Nothing by Mouth
OMM	Own Mother's Milk
%PN	Percent Parenteral Nutrition
PC_PN	Percent Change in Percent Parenteral Nutrition
PN	Parenteral Nutrition
PP	Per-Protocol
RA	Regulatory Authority
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBS	Short Bowel Syndrome
SOC	Standard of Care
TPN	Total Parenteral Nutrition
U	Units
US	United States (of America)
WBC	White Blood Cells
Y	Year

STATEMENT OF COMPLIANCE

This clinical trial will be conducted in compliance with the protocol, International Conference on Harmonization Good Clinical Practice Guidelines E6 (ICH-GCP), and the applicable regulatory requirements.

INVESTIGATOR SIGNATURE PAGE

I have read and understood the protocol and agree to implement the study in accordance with the procedures set forth in the protocol and in accordance with the Sponsor's guidelines, all applicable government regulations, and the International Conference on Harmonization Good Clinical Practice Guidelines E6 (ICH-GCP).

I will provide adequate protocol training to my associates, colleagues and employees assisting in the conduct of the study.

I will obtain Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval of the protocol and the subject Informed Consent Form (ICF) prior to enrollment of subjects in the study. I understand that any modifications to the protocol made during the course of the study must first be approved by the IRB/IEC except when such modification is made to remove an immediate hazard to a subject.

I will ensure that a fully executed subject ICF is obtained on behalf of each subject prior to initiation of any study procedures.

I will promptly report any Serious Adverse Event (SAE) (within 24 hours for related SAEs and within 48 hours for unrelated SAEs) that occurs during the course of the study in accordance with the procedures described in Section 7 of the protocol.

I will allow the Sponsor, Nutrinia Ltd. and its agents, as well as the United States (US) Food and Drug Administration (FDA) and other regulatory agencies, to inspect study facilities and pertinent records at reasonable times and in a reasonable manner, ensuring subjects confidentiality. If I am notified that this study is to be inspected by a regulatory agency, I will notify the Sponsor as soon as possible thereafter (within one week of receipt of notification).

Investigator's Name	Investigator's Signature	Date

Site Name: _____

Site Address: _____

_____

PROTOCOL SYNOPSIS

Protocol Number	GIFT-02
Study title	A Multi-Center, Randomized, Double-Blind, Three-Arm, Parallel-Group Trial to Assess the Efficacy and Safety of NTRA-9620 in Infants with Short Bowel Syndrome (SBS) Following Surgical Resection
Sites	Approximately 40 worldwide
Indication	NTRA-9620 (8 insulin units (IU)/kg/day or 4 IU/kg/day) is intended to treat infants with SBS to improve intestinal absorption of nutrients and fluids.
Primary Objective	The primary objective is to evaluate the efficacy and safety of NTRA-9620 compared with placebo when added to standard of care (SOC) in pediatric subjects (aged 28 weeks post-menstrual age to 52 weeks chronological age) with SBS within 4 months from surgical resection who are on parenteral nutrition (PN) support.
Study Design	This multi-center, randomized, double-blind, three-arm, parallel-group trial is designed to assess the efficacy and safety of two doses (8 IU/kg/day and 4 IU/kg/day) of NTRA-9620 or matching placebo at two time points (12 and 24 weeks post randomization) administered to infants less than 52 weeks chronological age with SBS (following surgical resection). The study will be conducted in approximately 40 clinical trial sites worldwide. Subjects will continue on SOC nutrition after the 24 week intervention period. A final study visit will be conducted at Week 28, 4 weeks after the end of dosing. All subjects will be further followed for long-term safety through Week 104; these safety data will be reported as an addendum to the final clinical study report.
Dosage & Regimen	All three groups will receive NTRA-9620 or matching placebo four times per day for 24 weeks. Group 1: NTRA-9620 2 IU/kg for each dose (8 IU/kg per day). Group 2: NTRA-9620 1 IU/kg for each dose (4 IU/kg per day). Group 3: Matching placebo for each dose.
Sample Size	Approximately 50 subjects per treatment arm (150 subjects).
Study Population	Subjects who are at least 28 weeks post-menstrual age[1] and up to 52 weeks chronological age and, after their major surgical resection, have less than or equal to 70% of their expected bowel length remaining and require at least 70% parenteral support (PN/IV) at study entry.
Inclusion Criteria	Subjects must meet *all* of the following criteria to be included: 1) Subject must be at least 28 weeks post-menstrual age and up to 52 weeks chronological age at enrollment. 2) Subject weight must be at least 500 grams (17.6 ounces) at time of enrollment. 3) Clinically diagnosed with SBS requiring PN/IV secondary to surgical resection of the intestine. 4) After major surgical resection leading to SBS, the subject has maximally 70% of expected bowel length preserved or an ostomy in place such that ≤ 70% of the small bowel is available for absorption[2].

[1] Post menstrual age is defined as gestational plus chronological age

[2] % bowel left is calculated as the amount of small bowel remaining of the total expected bowel.

	5) Subject can tolerate at least 10 mL/kg/day of enteral nutrition (EN) for at least 7 days at time of enrollment. 6) At time of enrollment subject is on at least 70% of prescribed PN/IV and no more than 30% of EN based on total caloric intake for at least 7 days prior to study entry. 7) Subject is randomized into the trial within 4 months from the surgical resection that has led to the diagnosis of SBS. 8) Subject's parent(s) or legal guardian(s) provide written informed consent. 9) Subject's parent(s) or legal guardian(s) understand and are willing to comply with all study procedures and requirements.
Exclusion Criteria	Subjects meeting *any* of the following criteria at study entry will be excluded: 1) Subject has undergone any bowel lengthening procedure. 2) Subject has a malabsorption disorder such as: • Congenital etiology (such as microvilli inclusion disease, tufting enteropathy) • Untreated Hirchsprung's disease 3) Significant motility disorder such as: • Pseudo obstruction • Severe gastroschisis defined as: primary reason for PN support is due to persistent feeding intolerance of less than 20 ml/kg/day EN intake or signs and symptoms (i.e., abdominal distention, vomiting) requiring prokinetic agents. 4) Any known inherited abnormality (e.g., Fanconi syndrome,) that is not related to SBS. 5) Prior bowel resection due to isolated spontaneous intestinal perforation. 6) < 10 cm of remaining small bowel left with no colon. 7) Uncontrolled systemic infection, acute gastroenteritis, pneumonia, cardiovascular or other abnormality including EKG findings that in the opinion of the investigator makes the infant unstable and at significant risk of not completing the first 12 weeks of the study. 8) Subjects with known hyperinsulinemia[3]. 9) Subjects with unexplained or recurrent hypoglycemia with blood glucose ≤ 50 mg/dL within 48 hours of treatment initiation. 10) Subjects with severe anemia of Hemoglobin less than 60 g/L and requiring transfusion within 48 hours of treatment initiation to avoid a life threatening event. 11) Subjects who require pancreatic enzyme replacement therapy. 12) Subject is currently receiving oral or injectable insulin for any reason. 13) Participation in another interventional clinical study within the past 30 days that may interfere with the results of this study. 14) History or current use of growth factors or glutamine. 15) In the opinion of the investigator, the subject has any other medical condition that would make participation in this study either unsafe or would compromise the potential benefit of insulin treatment.

[3] Full definition of hyperinsulinemia is provided below (Section 3.4.5).

Study Visit Schedule (See Appendix B: Schedule of Study Procedures)	Subjects diagnosed with SBS resulting from surgical resection may be evaluated for qualification to this study after their parent(s) or legal guardian(s) have given written informed consent. Screening assessments will include medical history and demographics, inclusion and exclusion criteria, maternal data, weight and body length, head circumference, vital signs, electrocardiogram (EKG) in triplicate, physical examination, urinalysis, hematology, blood chemistry, PN intake, EN intake and concomitant medications. During the 24-week treatment period, subjects are expected to be on PN/IV for all or most of the treatment period and thus are expected to be hospitalized for approximately 12 weeks, but they may be released sooner according to local institution's SOC. Each subject will receive the study treatment 4 times daily concomitantly with enteral feedings. Treatment will continue for the full 24 weeks regardless of the %PN (i.e., treatment should be continued even if subject is weaned off PN). EN includes SOC infant formula, donor breast milk, or own mother's milk (as detailed in Appendix A). Once the subject is released for home care, the caregivers, including any at-home medical professionals, will be trained on the proper procedures for dosing NTRA-9620 or matching placebo and how to record study information in the daily diary. Dose interruptions over the 24 week study treatment period will only be allowed at investigator discretion (i.e., NPO for procedure.) No dose interruption should last more than 7 consecutive days. During the first 12 weeks where the subject is likely to be hospitalized, there should be no more than 10 days of dose interruption. During weeks 12 to 24, where the subject may be at home or at a secondary facility, there should be no more than 15 days of dose interruption. During the study, the investigator will follow a recommended PN/IV and EN feeding protocol (Appendix A). Both the volume and the caloric value of PN/IV and EN consumed will be recorded at each study visit (as described in, Appendix B). Vital signs, body weight, body length, head circumference, and gastric residuals (through Week 12 only if it is done as part of the SOC), adverse events, and concomitant medications will be collected by weekly assessments throughout Week 12 and at least once every two weeks between Week 12 and Week 24. In addition, at Week 12, assessments will include full physical examination, hematology, chemistry, urinalysis, anti-insulin antibodies, and plasma citrulline. The non-routine use of oral antibiotics and probiotics are allowed if it is part of the SOC. Recording of parenteral and enteral nutritional intake will be continued until the end of the 24-week treatment period. Once released for home care, the subject will return to the clinic as needed according to standard medical practice or at least every two weeks between Week 12 and Week 24 for assessments, replenishment of study medications, and adjustment of the PN/IV and EN protocols. At the end of the treatment period (Week 24) subjects will discontinue administration of study medication. At this time, subjects will be given a full physical examination. Assessments will include body weight, body length, head circumference, vital signs, hematology, chemistry, urinalysis, plasma citrulline, concomitant medications, PN, EN and AEs. The primary portion of the study will be considered complete when the last randomized subject finishes the 24 week treatment period and a 4 week initial safety follow-up period (Week 28). At Week 28, the same assessments as in Week 24 visit will take place, except for plasma citrulline. In addition, anti-insulin antibodies will be assessed. Additional long-term safety and follow-up evaluations will be conducted at 52 and 104 weeks after initiation of treatment. Each visit during the follow-up period will include body weight, body length, head circumference, parenteral nutrition intake, enteral nutrition intake, re-hospitalizations and adverse events. In addition, growth parameters and nutritional support information from routine care visits at the primary site will be recorded in the eCRF. These data will include Bayley's neurodevelopmental cognitive, language and motor domains at 2Y corrected age.

Study Duration	Each subject is expected to be treated in the study for 24 weeks, and to participate for up to 104 weeks including the long-term safety follow-up period: The primary portion of the study is 28 weeks: 24 weeks of treatment plus a 4 week initial safety follow-up. The total length of the study is 104 weeks: 28 weeks of the primary portion plus 76 weeks of long-term safety and follow-up evaluations.
Primary Efficacy Endpoints	This trial has two co-primary endpoints. The first co-primary endpoints are the percent changes in %PN ($PC\_PN_{0\text{-}t}$) from baseline based on caloric intake to 12 weeks and again to 24 weeks. Each endpoint is calculated as: $$PC\_PN_{0-t} = 100 \times \frac{\%PN_{Baseline} - \%PN_t}{\%PN_{Baseline}}$$ where: t = 12 or 24weeks. %PN = % Parenteral Nutrition (feeding) calculated as parenteral calories divided by calculated total caloric requirements (the Schofield equation (1)). • Each PC_PN_{0-t} observation will be computed as an average over a single week. • Thus, for example, PC_PN at 12 weeks will be the average of PC_PN over days 78 to 84. PC _PN at 24 weeks will be the average of PC_PN over days 162 to 168. The study will have shown benefit if either $PC\_PN_{0\text{-}12}$ or $PC\_PN_{0\text{-}24}$ in the treated group is statistically significantly superior to placebo. The second co-primary endpoints are responder endpoints. The outcome variable for each subject will be the same outcome as for the first primary, but the statistical test will be calculated as continuous responder comparison at 12 weeks and again at 24 weeks.
Secondary Efficacy Endpoints	**Key Secondary Endpoint** Time to reduction of PN to less than 10% of the total caloric intake on 14 consecutive days. **Other Secondary Endpoints** a) Time to wean off [4]parenteral nutrition b) Number of patients reaching readiness to wean[5] off at 12 and 24 weeks from baseline. c) Time to 50% PN/IV reduction from baseline in %PN based on total calories. d) Time to 50% PN/IV reduction from baseline in %PN based on volume. e) Number of patients reaching 50% PN/IV reduction from baseline in %PN based on total calories at 12 and 24 weeks. f) Number of patients reaching 50% PN/IV reduction from baseline in %PN based on volume at 12 and 24 weeks. g) Percent change from baseline in %PN/IV based on total calories. h) Percent change from baseline in %PN/IV based on volume. i) Percent change from baseline in PN/IV fluid volume during treatment period. j) Change in Z-scores (Fenton) from baseline during the treatment period k) Percent change from baseline in %EN based on total calories. l) Percent change from baseline in %EN based on total volume. m) Change from baseline in liver enzymes (ALT, GGT, and total and direct bilirubin). n) Change from baseline in plasma citrulline levels.

[4] Wean off defined as complete cessation of parenteral nutrition and achieving full enteral autonomy for two weeks.

[5] Reduction to PN of less than 10% of the total caloric intake for 14 consecutive days is defined as readiness to wean off.

	o) Change from baseline in body weight during the treatment period. p) Weekly average of hours on prescribed PN/IV during the last month of treatment. q) General safety variables including episodes of significant feeding intolerance compared to placebo.
Statistical Analysis of Endpoints	**First Co-Primary Endpoints** The primary endpoints (measured at 12 weeks and 24 weeks) will each be analyzed using an analysis of covariance model with PC_PN_{0-12} and PC_PN_{0-24} serving as the dependent variable for each respective analysis. Treatment group and the randomisation stratification variables will serve as factors and the baseline %PN value will serve as a covariate in each analysis. In each analysis, the higher dose group will be compared to placebo group first. The high-dose comparison will be tested at the 0.025 two-sided significance level at each timepoint. If the high-dose comparison at a particular timepoint is significant at $p < 0.025$, then the low-dose comparison with placebo (at the same timepoint) will be tested at the 0.025 level. **Second Co-Primary Endpoints** The results will be displayed on a graph where the *x*-axis displays the percent reduction in %PN and the *y*-axis shows the proportion of infants who meet each response threshold (from 0 to 100%). The continuous responder curves for each dose vs. placebo will be compared using the Mann Whitney U test based on the 12 week data and another graph and analysis will make the similar comparison at 24 weeks. A positive outcome for the continuous responder analyses will be a one-sided p-value less than 0.10. The trial will have shown benefit if any group comparison stated above is shown to be superior to placebo on both of the co-primary endpoints at the same time (12 or 24 weeks, or both), each at the stated significance level. **Key Secondary Endpoint** The key secondary endpoint will be analyzed using a stratified log-rank test with factors for treatment group and the randomization stratification variables. Separate analyses will be carried out for each dose group. Time to the endpoint will be taken as the 14th day of consecutive less than 10% PN.
Sample Size	The sample size is based on testing the superiority of the high dose of NTRA-9620 compared to placebo on the primary endpoints of percent change in %PN from baseline to time "t" (PC_PN0-t) where "t" = 12 and 24 weeks. On the basis of historical data, the assumed reduction in PC_PN0-t is 30% and 42% in placebo and NTRA-9620, respectively, at both 12 and 24 weeks. A common within-group standard deviation of 20% has been assumed for both arms. Given the above specifications, and based on the use of a two-sided, two-sample comparison of means at the alpha = 0.025 level of significance, a sample of 45 subjects per group would provide approximately 80% power to demonstrate superiority. Since some subjects may not complete the entire trial, an additional 10% of subjects will be enrolled per arm (50 subjects per arm) to account for this potential loss. Thus, the proposed sample size is 150 subjects. (Note that the protocol provides for a sample size recalculation; the procedure described in the protocol will be followed).
Safety Analysis	The safety analyses will be descriptive and narrative in nature, with SAEs and AEs coded using MedDRA and tabulated by body system, preferred term, treatment group, severity and relation to procedure. Descriptive statistics will be provided by treatment group as appropriate.

1. INTRODUCTION

1.1. BACKGROUND

The majority of the target population consists of preterm and term infants suffering from conditions soon after birth that result in the loss of or damage to the small bowel. Given that the natural development and maturation of the intestine occurs during the third trimester and first year of life, the additional insult of bowel loss at this critical period of time makes this group a high risk population for prolonged intestinal failure requiring potentially lifelong parenteral nutrition (PN). All infants in this group of patients require PN post-operatively. Early enteral (EN) feeding should be promoted as soon as possible to enhance gastrointestinal (GI) maturation, growth and functional development. Infants should be weaned off PN as enteral tolerance to feeding is enhanced (2).

Intestinal failure in the context of Short Bowel Syndrome (SBS) is associated with dependency on PN for a prolonged period of time. Evidence suggests that the survival rate after massive small bowel resection depends on the ability of the residual bowel to adapt while decreasing the probability of PN associated co-morbidities. Moreover, successful adaptation allows patients with SBS to grow and remain healthy while receiving oral nutrition or EN. As indicated, the most important therapy for children with SBS is the early introduction of EN.

Insulin, which plays a role in intestinal growth, cell maturation, and differentiation, has been shown to enhance intestinal adaptation. Nutrinia is developing an insulin formulation, NTRA-9620, to enhance EN intake in infants with SBS following surgical resection. NTRA-9620 is an oral insulin formulation for local GI therapy aimed at accelerating the natural course of intestinal adaption and maturation.

NTRA-9620 is an oral formulation of insulin for local GI therapy without systemic insulin exposure aimed at increasing intestinal adaption.

Evidence supports the fact that intestinal adaptation is enhanced and sustained when growth factors are provided immediately following intestinal loss (3). This adaptation is likely to be further augmented when growth factors are administered during early development, the most critical period of gut growth. The dual effects of NTRA-9620 to enhance both adaptation and enteral tolerance at this vital time are major strengths of the product concept.

Benefits of accelerating adaptation over placebo can be translated to being eligible for an average of 2-3 fewer hours a day “attached” to PN, which is associated with the following:

1. Insulin’s receptor-mediated structural effects on the GI tract such as increased rate of enterocyte proliferation, villous height, and crypt depth that leads to better gut adaptation (4).

2. Adequate enteral nutrients absorption for supporting the infant's growth and development, and, in the long-term, improved nutrition early in life that leads to better growth and development has been linked to overall improved health outcomes in this population (2).
3. Minimizing exposure to toxic constituents such as lipids and dextrose which may result in less metabolic stress on the growing infant (5).
4. Reduction of PN-associated co-morbidities such as parenteral nutrition-associated liver disease (PNALD), bacterial overgrowth, catheter-associated bloodstream infections, cholestatic liver disease, and death (6, 7).
5. As PN/IV requirements decrease, this can potentially be translated to an opportunity to advance cycling of PN/IV. This is an important opportunity to introduce oral rehabilitation strategies during the daytime awake hours and then provide the remaining PN/IV support overnight for example.
6. Less opportunities of necessity to handle fragile central line access that may predispose to infection or malfunction (8).
7. Increased oral stimulation to feed, EGF secretion leading to gut development and reduced malnutrition, thus enhanced growth and associated development
8. Increased hours of normal development behavior as a child grows without being "attached" or connected to a line (9, 10).
9. Less hours of necessary specialized supervision, which reduce the costs and provides support in parents.

Therefore, acceleration in the reduction in the percent PN and enhancement of EN intake during this period of gut adaptation is hypothesized to be the most appropriate method to assess progress towards full enteral autonomy, even if the latter takes years to achieve.

1.2. NONCLINICAL ASSESSMENTS AND CLINICAL STUDIES IN INFANTS

Nutrinia's nonclinical program was designed to assess whether oral administration of human recombinant insulin in newborn animals affects serum glucose levels, as well as to assess other safety measurements. Nutrinia has conducted several pre-clinical safety studies in lambs, calves, piglets, and poultry. The newborn animals were exposed to various levels of insulin in their nutrition, up to two orders of magnitude higher than the insulin levels in expressed milk. The results consistently demonstrated that oral insulin administration at an early stage of life did not affect blood glucose, insulin levels, or histological, biochemistry, and hematology parameters.

Nutrinia performed in vivo studies in newborn animals with NTRA-2112, a compound similar to NTRA-9620. The animals were dosed with higher levels of insulin and for a longer duration than will be used in the proposed study. These studies did not result in hypoglycemic events or

changes in blood chemistry or hematology. In addition to the available nonclinical data, Nutrinia's clinical experience with a 26-33 week pre-term infant population treated for 24 to 28 days with oral insulin did not result in hypoglycemic events or changes in blood chemistry or hematology.

Studies with orally administered insulin in neonatal mini-pigs at 8 IU/day (4) adult rats at 26 IU/day (11, 12) and human infants at 4 IU/day showed no local adverse effects. In fact, the data showed evidence that the local effects were beneficial such as an increase in mucosal surface area and villous height and crypt depth. Daily dosing for mini-pigs, rats, and human infants were 4 days, 4 to 12 days, and 24 to 28 days, respectively. These studies suggest that repeated daily doses of oral insulin present no risk of local adverse effects.

Recombinant human insulin is approved for chronic, daily, parenteral administration to pediatric patients as young as two years old who have Type I diabetes. Nutrinia's patient population is younger than the patient population for the approved product; however, nonclinical and clinical data support that this difference is not likely to result in any new systemic adverse effects, for two reasons: systemic absorption of insulin is very unlikely, and the systemic effects of insulin are well understood and, although unlikely to happen, can be readily detected and managed.

The daily insulin dose levels in the proposed clinical trial (4 IU/kg/day and 8 IU/kg/day) were safe and free of local or systemic adverse effects in neonatal mini-pigs (18 IU/kg), adult rats (26 IU/kg), and human infants (4 IU/kg). The results obtained to date support the initiation of this clinical trial. The dose levels are supported by a long-term GLP local GI toxicity study in neonatal minipigs NTRA-9620 with two dose levels (4 IU/kg/day and 40 IU/kg/day).

The Investigator's Brochure describes the methods and results from these safety studies.

2. PURPOSE AND STUDY OBJECTIVES

2.1. PURPOSE

This Phase IIb clinical study is a multiple dose safety and efficacy study intended to assess whether NTRA-9620 (4 IU/kg/day or 8 IU/kg/day) is beneficial in infants with SBS if administered following surgical resection to improve intestinal absorption of nutrients and fluids.

2.2. STUDY OBJECTIVES

The objectives of this clinical study are to evaluate the efficacy and safety of NTRA-9620 compared with placebo when added to standard of care (SOC) in pediatric subjects (aged 28 weeks post-menstrual age to 52 weeks chronological age) with SBS within 4 months from resection who are on parenteral nutrition support.

3. STUDY DESIGN

3.1. DESCRIPTION OF STUDY DESIGN

This multi-center, randomized, double-blind, three-arm, parallel-group trial is designed to assess the efficacy and safety of two doses (4 IU/kg/day and 8 IU/kg/day) of NTRA-9620 compared to matching placebo at two time points (12 and 24 weeks post randomization) administered to infants less than 52 weeks chronological age with SBS (following surgical resection). The study will be conducted at up to 40 clinical trial sites in North America, Europe and Israel. All subjects will be enrolled after their parent(s) or legally authorized guardian(s) sign an IRB/IEC approved informed consent form (ICF). Subjects entering the study will be diagnosed with SBS; they will have at most 70% of their expected bowel length preserved or functioning, requiring PN by intravenous (IV) infusion; they will have a total body weight of at least 500 grams (17.6 ounces) and be at least 28 weeks of gestation in age at the time of entry into the study. At time of study entry, subjects should be able to tolerate at least 10 mL/kg/day of EN but not less than 70% of PN based on caloric intake for at least 7 days.

Each subject, after parent(s) or legal guardian(s) consent to the study, will complete screening assessments. Screening evaluations will include assessment of entry criteria, medical history, as well as a complete physical examination, blood chemistry, hematology and urinalysis evaluations, EKG and concomitant mediations.

After meeting all screening and baseline criteria, subjects will be randomized in a 1:1:1 ratio to either 8 IU/kg/day NTRA-9620, 4 IU/kg/day NTRA-9620, or matching placebo. Randomization, which will be performed centrally, will be stratified by estimated percent length of the remaining small intestine ($L < 50\%$ or $50\% \leq L \leq 70\%$; where L is remaining length of small intestine relative to the expected length for gestational age (13)) and presence or absence of an ileocecal valve. Randomization will take place as close as possible to treatment initiation and not more than 24 hours before the first dose of study medication.

During the 24-week treatment period, subjects are expected to be on PN/IV for all or most of the treatment period and thus are expected to be hospitalized for approximately 12 weeks, but they may be released sooner according to local institution's SOC.

All subjects will receive SOC PN/IV and enteral feedings containing NTRA-9620 or matching placebo. NTRA-9620 or matching placebo will be dosed to target an insulin dose of 1 IU/kg or 2 IU/kg administered four times a day, spaced as equally over 24 hours as possible (ideally at every six hours, but no less than 3 hours between any two doses). The study medications can be reconstituted in normal (0.9%) or half normal (0.45%) saline (NaCl) and administered concomitantly with SOC infant formula, donor breast milk, or own mother's milk (OMM) used for enteral feeds. During the hospitalization period, dosing will be performed as a bolus administration four times a day. In home care, subjects will receive NTRA-9620 or matching placebo four times a day as well.

Subjects will continue treatment for the full 24 weeks of dosing regardless of the %PN use (i.e., even if subject is weaned off PN). Dose interruptions over the 24 week study treatment period will only be allowed at investigator discretion (i.e., nothing by mouth (npo) for procedure.) No dose interruption should last more than 7 consecutive days. During the first 12 weeks when the subject is likely to be hospitalized, the subject should experience no more than 10 days of dose interruption. During weeks 12 to 24, when the subject may be at home or at a secondary facility, the subject should experience no more than 15 days of dose interruption. The daily PN and EN intake for each subject will be recorded in a study diary. Subjects will be assessed weekly or once every two weeks as described on the Schedule of Study Procedures (Appendix B) for the treatment period. Most subjects will remain hospitalized for at least 12 weeks to collect accurate PN amounts, but some may be released from the institution per local SOC. Subjects will continue treatment for the full 24 weeks of dosing regardless of the %PN use (i.e., even if subject is weaned off PN). Enteral nutrition includes SOC infant formula, donor breast milk, or own mother's milk (as detailed in Appendix A). Subjects will continue on SOC feedings after the 24 week intervention period. A final study statistical analysis of efficacy and safety will be conducted at Week 28, 4 weeks after the end of dosing. All subjects will be further followed for long-term safety through Week 104; these safety data will be reported as an addendum to the final clinical study report.

3.2. DOSE RATIONALE

This is a placebo–controlled, two dose level study. The choice of the proposed dosing regimen of 1 IU/kg or 2 U/kg 4 times a day (4 IU/kg/day and 8 IU/kg/day respectively) is based on a series of studies in SBS animal models and on two independent clinical studies. Moreover, Nutrinia conducted a repeated-dose, local GI toxicology study with NTRA-9620 (4 IU/kg/day and 40 IU/kg/day) to support the proposed clinical doses (4 IU/kg/day and 8 IU/kg/day).

In the first clinical study, pre-term infants (26-29 weeks of gestational age) were dosed 4 IU/kg/day for 28 days in order to assess whether enteral administration of insulin to preterm infants would enhance GI adaptation and reduce enteral feeding intolerance without adverse effects (14). No drug-related adverse effect, such as hypoglycemia, was observed after administration of insulin. The infants who received insulin had higher lactase activity and less feeding intolerance than the controls (30% shorter time to full enteral feeds; fewer gastric residuals per infant). Thus, the proposed dosing regimen was effective and did not suggest any safety concerns.

A second clinical study was performed with the same dosing regimen in infants and young children with SBS (15). Infants in the trial had 8-40 cm remaining bowel and were not expected to wean off Total Parenteral Nutrition (TPN). On average, enteral intake increased from 45.6% ± 30.6 (Mean ± SD) to 58.9% ± 28.2, and ALT blood levels decreased from 194 ± 128 U/L to 136 ± 79 U/L. Two (2/10) infants were weaned off PN and stayed off PN. None of the children developed insulin antibodies. In that study, oral insulin supplementation in pediatric SBS was not associated with side effects.

The choice of the proposed dosing regimen of 4 or 8 IU/kg/day is based on a series of studies in SBS animal models and predominantly on 2 clinical studies as described above. No dose used previously raised any safety concerns. The dose levels are supported by a GLP local GI toxicity study assessed in neonatal minipigs (26-week GLP repeat-dose toxicity study in minipigs).

The lower dose of 4 IU/kg/day has been previously used in SBS children (15) and in preterm infants (14), showing promising efficacy results. The suggested second dose level is double the clinically tested dose, remaining below the dose level used in the 26-week GLP repeat-dose toxicity study in minipigs.

The decision to divide the dose into 4 daily administrations is based on previous clinical experience. The rationale is to prolong the local intestinal exposure to insulin. Each dose will be compared against placebo in each primary and secondary analysis.

3.3. DOSING

All three groups will receiveNTRA-9620 or matching placebo four times per day.

Group 1: NTRA-9620 2 IU/kg for each dose (8 IU/kg per day)

Group 2: NTRA-9620 1 IU/kg for each dose (4 IU/kg per day)

Group 3: Matching placebo

3.4. STUDY ENDPOINTS

3.4.1. Co-Primary Endpoints

This trial has two co-primary endpoints.

The first co-primary endpoints is the percent change in %PN ($PC\_PN_{0\text{-}t}$) from baseline[6] based on caloric intake to 12 weeks and again to 24 weeks. The 12 and 24 week endpoints are calculated as:

$$PC\_PN_{0-t} = 100 * \frac{\%PN_{Baseline} - \%PN_t}{\%PN_{Baseline}}$$

Where

- t = 12 or 24 weeks
- %PN = % Parenteral Nutrition (feeding) will be calculated as parenteral calories divided by calculated total caloric requirements (the Schofield equation (1)).
- $PC\_PN_{0\text{-}t}$ observations will be computed as an over a single week.

Thus, PC_PN at 12 weeks will be the average of PC_PN over Days 78 to 84.
PC_PN at 24 weeks will be the average of PC_PN over days 162 to 168.

[6] Baseline: prior to treatment. Baseline measurement period should be at least 7 days.

The second co-primary endpoints are responder endpoints. The outcome variable for each subject will be the same outcome as for the first primary, but the statistical test will be calculated as continuous responder comparisons at 12 weeks and again at 24 weeks.

3.4.2. Secondary Endpoints

3.4.2.1. Key Secondary Endpoints

Time to reduction of PN to less than 10% of the total caloric intake on 14 consecutive days.

3.4.2.2. Secondary Endpoints

Other Secondary Endpoints

a) Time to wean off [7] parenteral nutrition
b) Number of patients achieving readiness to wean off [8] at 12 and 24 weeks from baseline
c) Time to 50% PN/IV reduction from baseline in %PN based on total calories.
d) Time to 50% PN/IV reduction from baseline in %PN based on volume.
e) Number of patients reaching 50% PN/IV reduction from baseline in %PN based on total calories at 12 and 24 weeks
f) Number of patients reaching 50% PN/IV reduction from baseline in %PN based on volume at 12 and 24 weeks.
g) Percent change from baseline in %PN/IV based on total calories.
h) Percent change from baseline in %PN/IV based on volume.
i) Percent change from baseline in PN/IV fluid volume during treatment period.
j) Change in Z-scores (Fenton) from baseline during the treatment period.
k) Percent change from baseline in %EN based on total calories.
l) Percent change from baseline in %EN based on total volume.
m) Change from baseline in liver enzymes (ALT, GGT, and total and direct bilirubin).
n) Change from baseline in plasma citrulline levels.
o) Change from baseline in body weight during the treatment period.
p) Weekly average of hours on prescribed PN/IV during the last month of treatment.
q) General safety variables including episodes of significant feeding intolerance compared to placebo

[7] Wean off defined as complete cessation of parenteral nutrition and achieving full enteral autonomy for two weeks.
[8] Reduction to PN of less than 10% of the total caloric intake for 14 consecutive days.

3.4.3. Study Population

Subjects in this trial are between 28 weeks post-menstrual age[9] and 52 weeks chronological age and, after their major surgical resection, have less than or equal to 70% of their expected bowel length remaining and require at least 70 % parenteral support (PN/IV) at study end.

3.4.4. Inclusion Criteria

Subjects must meet *all* of the following criteria to be included:

1) Subject must be at least 28 weeks post-menstrual age and up to 52 weeks chronological age at enrollment.
2) Subject weight must be at least 500 grams (17.6 ounces) at time of enrollment.
3) Clinically diagnosed with SBS requiring PN/IV secondary to surgical resection of the intestine.
4) After major surgical resection leading to SBS, the subject has maximally 70% of expected bowel length preserved or an ostomy in place such that ≤ 70% of the small bowel is available for absorption[10].
5) Subject can tolerate at least 10 mL/kg/day of EN for at least 7 days at time of enrollment.
6) At time of enrollment subject is on at least 70% of prescribed PN/IV and no more than 30% of enteral nutrition based on total caloric intake for at least 7 days prior to study entry.
7) Subject is randomized into the trial within 4 months from the surgical resection that has led to the diagnosis of SBS
8) Subject's parent(s) or legal guardian(s) provide written informed consent.
9) Subject's parent(s) or legal guardian(s) understand and are willing to comply with all study procedures and requirements.

3.4.5. Exclusion Criteria

Subjects meeting *any* of the following criteria at study entry will be excluded:

1) Subject has undergone any bowel lengthening procedure.[11]
2) Subject has a malabsorption disorder such as:
    - Congenital etiology (such as microvilli inclusion disease, tufting enteropathy)
    - Untreated Hirchsprung's disease
3) Significant motility disorder such as:
    - Pseudo obstruction

[9] Post menstrual age is defined as gestational plus chronological age
[10] % bowel left is calculated as the amount of small bowel remaining of the total expected bowel.
[11] This criteria would be relevant throughout the intervention duration.

- Severe gastroschisis defined as: primary reason for PN support is due to persistent feeding intolerance of less than 20 ml/kg/day EN intake or signs and symptoms (i.e., abdominal distention, vomiting) requiring prokinetic agents.

4) Any known inherited abnormality (e.g., Fanconi syndrome,) that is not related to SBS.
5) Prior bowel resection due to isolated spontaneous intestinal perforation.
6) < 10 cm of remaining small bowel left with no colon.
7) Uncontrolled systemic infection, acute gastroenteritis, pneumonia, cardiovascular or other abnormality including EKG findings that in the opinion of the investigator makes the infant unstable and at significant risk of not completing the first 12 weeks of the study.
8) Subjects with known hyperinsulinemia (16)[12].
9) Subjects with unexplained or recurrent hypoglycemia with blood glucose ≤ 50 mg/dL within 48 hours of treatment initiation.
10) Subjects with severe anemia (hemoglobin less than 60 g/L) and requiring transfusion within 48 hours of treatment initiation.
11) Subjects who require pancreatic enzyme replacement therapy.
12) Subject is currently receiving oral or injectable insulin for any reason.
13) Participation in another interventional clinical study within the past 30 days that may interfere with the results of this study.
14) History or current use of growth factors or glutamine.
15) In the opinion of the investigator, the subject has any other medical condition that would make participation in this study either unsafe or would compromise the potential benefit of insulin treatment.

4. STUDY PROCEDURES AND ASSESSMENT

See Appendix B: Schedule of Study Procedures for timing of the assessments.

4.1. DEFINITIONS OF STUDY PROCEDURES

4.1.1. Informed Consent

Prior to initiation of any study procedure, each subject's parent(s) or legal guardian(s) will undergo an Informed Consent process in which they voluntarily confirm their willingness to include their child in the trial, after having been informed of all aspects of the trial relevant to their decision about their child's participation. The investigator, or a person designated by the investigator, will fully inform the subject's parent(s) or legal guardian(s) of all pertinent aspects of the trial. In addition, the investigator or designee will inform the subject's parent(s) or legal

[12] In order to define hyperinsulinemia all criteria must be met:
a. *Glucose requirements > 6-8 mg/kg/min to maintain blood glucose above 2.6-3 mmol/litre*
b. *Laboratory blood glucose < 2.6 mmol/litre (mg/liter)*
c. *Detectable insulin at the point of hypoglycaemia with raised C peptide*
d. *Inappropriately low blood free fatty acid and ketone body concentrations at the time of hypoglycaemia*
e. *Glycaemic response after the administration of glucagon when hypoglycaemic*
f. *Absence of ketonuria*

guardian(s) that they are free to refuse to enter their child in the study or to withdraw the child from the study at any time, for any reason. The subject's parent(s) or legal guardian(s) should also be informed that formal training for home care and dosing of the study medication to the infant will be required.

The ICF approved by the IRB/IEC will contain a description of the study's purpose, procedures, inconveniences, and potential risks, and anticipated benefits.

Prior to a subject's participation in the trial, an ICF will be signed and personally dated by the subject's parent(s) or legal guardian(s) and by the person who conducted the Informed Consent discussion.

If a subject's parent(s) or legal guardian(s) is unable to read, the Informed Consent may be read to the subject's parent(s) or legal guardian(s), provided that an impartial witness is present during the entire Informed Consent discussion. After the written ICF is read and explained to the subject's parent(s) or legal guardian(s) and after they have orally consented to include their child in the trial and, if capable of doing so, have signed and personally dated the ICF, the witness should also sign and personally date the ICF. By signing the ICF, the witness attests that the information in the ICF was accurately explained to, and apparently understood by, the subject's parent(s) or legal guardian(s) and that Informed Consent was freely given by the subject's parent(s) or legal guardian(s).

Prior to participation in the trial, the subject's parent(s) or legal guardian(s) will receive a copy of the signed and dated written ICF. During participation in the trial, the subject's parent(s) or legal guardian(s) will receive a copy of any signed and dated revised consent forms, and a copy of any amendments to the written information provided to subject's parent(s) or legal guardian(s).

The ICF may be signed by the subject's parent(s) or legal guardian(s) prior to the bowel resection and up to 30 days prior to initiation of dosing in the trial.

The investigator should document in the source data that the Informed Consent Form was signed prior to subject's participation in the study and according to the International Conference on Harmonization (ICH) guidelines, as described above.

4.1.2. Medical History and Demographics

The subject's medical history will be fully documented at screening to ensure compliance with study eligibility criteria. Medical history information must include, but not be limited to, past and present medical conditions, concomitant non-drug treatments and hypersensitivity to drugs. Any event that occurs before study drug dosing will be recorded as medical history.

4.1.3. Maternal Data

At screening, data on the infant's mother will be collected including age, medical history of any congenital abnormalities and complications during gestation or delivery.

4.1.4. Physical Examination

The investigator will conduct a complete physical examination at screening and on Day 84 (Week 12), Day 168 (Week 24), and Day 196 (Week 28). A limited problem-oriented physical examination will be performed on each visit between Week 12 (Day 84) and Week 24 (Day 168): Days 98, 112, 126, 140, and 154, if needed.

4.1.5. Weight and Body Length

Subjects' weight and body length will be measured at screening, baseline, and randomization. Weight and body length will be measured weekly at each study evaluation (at the in-patient institution) or visit if the subject has been discharged from the site from screening through Day 196 (Week 28). Long-term safety evaluations post primary study completion will also include measurement of subjects' weight and body length on Day 364 (Week 52) and Day 728 (Week 104).

4.1.6. Head Circumference

The subject's head circumference will be measured at screening, randomization and at each weekly study evaluation (at the institution) or visit, if discharged, through Day 196 (Week 28). Long-term safety evaluations will also be conducted after study completion on Day 364 (Week 52) and Day 728 (Week 104).

4.1.7. Vital Signs

The subject's vital signs will be measured at screening, baseline, and randomization in order to ensure compliance with study inclusion criteria. Vital signs will also be measured at each study evaluation (at institution), or visit if discharged, from screening to Day 196 (Week 28).

Vital sign measurements will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature.

4.1.8. Electrocardiogram (EKG)

The subject's EKG will be performed at screening in order to ensure compliance with study inclusion criteria. The EKG is to be performed on at least a triplicate of heartbeats for all measurements and will be recorded at a speed of 25 mm/sec and an amplitude of 10 mm/mV.

Computerized EKG analysis will include: heart rate, R-R interval, sinus rhythm, PR interval, QRS axis, and QRS duration. QT interval and QTcF will be calculated manually according to the Fridericia formula.

4.1.9. Clinical Laboratory Tests

Clinical laboratory tests will be conducted at screening in order to ensure compliance with study inclusion criteria. Additional tests will be conducted on different study visits according to the schedule as written in the sections below. The maximum volume of collected blood would not exceed 3 mL/Kg over 24 hours and up to 50 mL total volume over 8 weeks. All laboratory test results required by this protocol will be recorded in the EDC for evaluation of any change over time during treatment. The investigators will assess every out-of-range laboratory value and deem each as either clinically significant or not clinically significant. Values that represent a change from baseline in subject's medical status according to the laboratory normal ranges and considered as clinically significant will be adequately documented as an adverse event (AE) as described in Section 7.1.1.

4.1.9.1. Blood Count

Hematology tests will be conducted at screening in order to ensure compliance with study inclusion criteria. Additional hematology testing will be conducted on study visit Week 12 (Day 84) and Week 24 (Day 168)/Early Termination. Repeat testing at follow-up visit Week 28 (Day 196) will be performed only if abnormal clinically significant values are obtained at the Week 24 (Day 168) visit.

Hematology tests will include: white blood cells (WBC), red blood cells (RBC), hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelets, and mean platelet volume (MPV).

Testing includes RBC morphology and reticulocyte count.

4.1.9.2. Serum Chemistry

Testing of blood chemistry values will be conducted at screening in order to ensure compliance with study inclusion criteria. Additional serum chemistry testing will be weekly when patients are in the hospital and at study visits when patients are in a home care setting. Repeat testing at follow-up visit Week 28 (Day 196) will only be performed if abnormal clinically significant values are obtained at Week 24 (Day 168) visit. Serum chemistry will include serum alkaline phosphatase, triglyceride, ALT, AST, GGT, glucose, calcium, phosphorus, chloride, sodium, potassium, BUN, creatinine, total and direct bilirubin, albumin, total protein, amylase, bicarbonate/carbon dioxide (CO_2), uric acid, and lactate dehydrogenase (LDH).

4.1.9.3. Urinalysis

Urinalysis will be conducted at screening. Additional testing will be conducted on study visit Week 12 (Day 84) and Week 24 (Day 168)/Early Termination. Repeat testing at follow-up visit Week 28 (Day 196) will only be performed if abnormal clinically significant values are obtained at the Week 24 (Day 168) visit.

Urinalysis will include: nitrite, Na, K, Ca, P, Protein, RBC, WBC, blood, glucose, ketone bodies, bilirubin (conjugated), urobilinogen, urine specific gravity, osmolarity, and pH.

4.1.9.4. Plasma Citrulline

Testing of plasma citrulline value will be conducted at baseline in order to establish a baseline level. Additional testing will be conducted on study visit Week 12 (Day 84) and Week 24 (Day 168)/Early Termination.

4.1.9.5. Blood Glucose Levels

Blood glucose monitoring will be performed pre-dose at randomization (Day 0) and on Days 1, 2, and 3, and twice a week for the rest of the treatment period while hospitalized. If subjects are discharged home the test would be done on each visit once a week. In addition, any abnormality in blood glucose levels that would be captured outside of these tests, would also be reported. This is a part of standard monitoring conducted on this population.

4.1.9.6. Anti-Insulin Antibodies

Blood will be drawn to test for the presence of anti-insulin antibodies at baseline. Additional anti-insulin antibody testing will be conducted on study visit Week 12 (Day 84) and Week 28 (Day 196).

4.1.10. Episodes of Significant Feeding Intolerance

Episodes of significant feeding intolerance will be collected throughout the study period at baseline, randomization, initial treatment period (Days 1, 2 and 3), at each weekly study evaluation (at the institution) or visit, if discharged, through Week 12, and Week 24.

Significant feeding intolerance is defined as:

- The need to hold enteral feeds for 24 hours.

Reasons or requirements to hold feedings may include, but are not limited to, the following:

- Increased stool output (compared to the previous 24 hours or leading to perianal excoriation)

- Increased vomiting (associated with residuals of previous feeds, bilious vomiting, increase of volume of regurgitation or number of events of emesis compared to the previous 24 hours).
- Abdominal distention (leading to abdominal pain with respiratory compromise)

4.1.11. Concomitant Medication

All concomitant medication given within 30 days prior to study entry will be documented. Dietary supplements, prescription drug, and non-prescription drugs will be listed at screening, at baseline, randomization, and at each visit through the Week 28 (Day 196) assessment. After week 28, only clinically significant medications that are used to treat potential adverse effects of NTRA-9620 will be recorded at 52 and 104 weeks. The investigator will assess the clinical significance of the medication use. Each entry will include the treatment's start date, medication/treatment name (generic), indication for use, dosing regimen (dose and frequency of use), route of administration, and stop date (if applicable) or ongoing. Study subjects will be routinely assessed for changes in the administration of concomitant medication during the trial.

Subjects may not receive the following medications while on study:

- Systemic insulin administration unless an acute life-threatening event occurs.
- Other investigational drugs or growth factors and glutamine.
- Pancreatic enzymes (replacement therapy).

Cholestyramine, if given, should be administered 2 hours apart from study medication because of its potential to absorb insulin.

Any concomitant medication and its potential to interfere with the study medication will be discussed with the investigator.

4.1.12. Long-Term Follow-Up Visits

Follow-up evaluations will be conducted at 52 and 104 weeks after initiation of treatment. Each follow-up visit during the safety follow-up period will include body weight, body length, head circumference, parenteral nutrition intake, enteral nutrition intake, re-hospitalizations and adverse events.

In this patient population, SOC visits are routine and may occur before the scheduled study visits on weeks 52 and 104. Thus, any available clinical data on body weight, body length, head circumference, parenteral nutrition intake, enteral nutrition intake, re-hospitalizations and adverse events will be documented and entered in the Unscheduled Visit form and entered into the eCRF. These data will include neurodevelopmental Bayley's score cognitive, language and motor domains at 2Y corrected age (details of neurodevelopment assessment are included in Appendix D). If such a routine Standard of Care visit is not conducted or complete data is not collected as part of these visits, these will not be considered missing data.

In the interim, scheduled telephone calls will be made to the patient and the family every three months after week 28.

4.1.13. Adverse Events (AEs)

The information obtained during study visits, physical examinations, vital signs measurements, blood testing, and by any other means will be evaluated in light of baseline medical data and thus provide the basis for identification and grading of AEs.

The AEs reported during the trial will be graded (see Section 7.1), documented, and assessed in light of their clinical significance and relation to investigational product. In addition, the following information regarding the AE must be obtained and recorded in subject's source document and Case Report Form (CRF): AE description, start date, end date (if applicable) or ongoing, severity, seriousness, investigator's assessment of the relationship of the AE to study drug, outcome (i.e., resolved, resolved with sequelae, ongoing, death due to this AE, death due to other events, unknown) and action taken (e.g., concomitant medication). Information regarding occurrence of AE monitoring will be captured throughout the study, from Day 7 (initiation of dosing) 28 days after the final primary study visit at Week 28 (Day 196). AEs considered treatment related by the Investigator will be documented after the primary study completion on Week 52 (Day 364) and Week 104 (Day 728) to assess any potentially related adverse outcomes of treatment and re-hospitalizations. Pre-treatment emergent events will not be considered as AEs, but will be recorded as medical history.

Prior to this current trial, four clinical trials including three in preterm infants and one in SBS infant subjects have been performed with oral administration of insulin. No treatment-related adverse events have been reported and no systemic absorption of insulin has been detected.

4.1.14. Evaluation of Response

4.1.14.1. Parenteral Nutrition (PN) Intake

PN intake will be obtained at screening, baseline, randomization, and at each study visit (as described in Appendix B). In case of an acute medical event during the study period the patient will be clinically stable before study visit occurs. The total volume and the caloric value of parenteral nutrition administered will be recorded in each study visit. The daily total amount of PN/IV, and number of hours per day on PN/IV will be entered into the CRF. For patients discharged home a diary will be provided to confirm prescribed PN and EN intake.

4.1.14.2. Enteral Nutrition (EN) Intake

EN intake will be obtained at screening, baseline, randomization, and at each study visit (as described in Appendix B). In case of an acute medical event during the study period the patient will be clinically stable before study visit occurs. The total volume and the caloric value of enteral nutrition administered will be recorded in each study visit. The daily total amount of EN

and caloric content will be entered into the CRF. For patients discharged home a diary will be provided to confirm prescribed EN and PN intake.

Solids intake information will be collected at the site level and reported by the investigator as part of enteral intake in the CRF.

Negligible amounts of breast milk/formula/solids intake that are only provided for stimulation of suck and swallow coordination and not used as part of the calculations for providing adequate caloric needs for growth will not be calculated as part for daily enteral intake.

4.2. STUDY VISITS

4.2.1. Screening Procedures

All information collected and documented during screening procedures will be reviewed to ensure that the subject satisfies eligibility requirements as described by the study inclusion and exclusion criteria. This information will be fully documented in the subject's file.

The Screening Visit will be performed at a minimum 7 days prior to the Baseline Visit. Study screening procedures will include the following:

- Informed Consent - Section 4.1.1
- Medical History and Demographics - Section 4.1.2
- Maternal Data - Section 4.1.3
- Physical Examination - Section 4.1.4
- Weight and Body Length - Section 4.1.5
- Head Circumference - Section 4.1.6
- Vital Signs - Section 4.1.7
- EKG - Section 4.1.8
- Clinical Laboratory Tests - Section 4.1.9 (as applicable within Section 4.1.9)
- Concomitant Medication Listing - Section 4.1.11
- PN/IV and EN Intake - Sections 4.1.14.1 and 4.1.14.2

4.2.2. Baseline

All information collected and documented during baseline procedures will be reviewed to ensure eligibility in reference to study inclusion and exclusion criteria, and fully documented in the subject's file.

The interval between the signing of the consent (Screening Visit) and the Baseline Visit is considered the baseline period. It is defined as a minimum of 14 days prior to the

Randomization Visit. During this period, data will be collected on PN/IV and EN use that will be used for calculating the baseline %PN and to confirm eligibility. All assessments will be performed and recorded for each day of baseline, except for plasma citrulline and anti-insulin antibodies that will be conducted and recorded on the last day of baseline, 0-1 day prior to the randomization visit. Baseline procedures will include the following:

- Weight and Body Length - Section 4.1.54.1.5
- Vital Signs - Section 4.1.7
- Plasma Citrulline - Section 4.1.9.4
- Anti-insulin Antibodies - Section 4.1.9.6
- Episodes of significant feeding intolerance - Section 4.1.10
- Concomitant Medication Listing - Section 4.1.11
- PN/IV and EN Intake - Sections 4.1.14.1 and 4.1.14.2

4.2.3. Randomization

Once qualified for the study, subjects will be randomized in a 1:1:1 ratio to 2 IU/kg of NTRA-9620 or to 1 IU/kg of NTRA-9620 or matching placebo. Randomization should take place as close as possible to treatment initiation and not more than 24 hours before the first dose of study drug. Randomization, which will be done centrally, will be stratified by length of small intestine ($L < 50\%$ or $50\% \leq L \leq 70\%$, L is the length remaining compared to expected length for gestational age (13)) and presence or absence of an ileocecal valve.

The study has recruitment goals aimed at randomizing at least 30 subjects with < 50% remaining length of small intestine for gestational age and at least 30 subjects born prematurely. During the course of the study, Nutrinia or its designees will monitor recruitment of subjects with < 50% remaining bowel and of premature infants. If the goal of 30 subjects with < 50% remaining bowel is unlikely to be achieved, Nutrinia will consult appropriate Regulatory Authorities and may increase the sample size of the trial to ensure enrolling at least 30 subjects with < 50% bowel remaining.

The randomization and baseline visits are expected to occur at the same visit. However, in some instances the logistical complications at the investigative site may require these visits to be up to 24 hours apart. All information collected and documented during the randomization visit will be reviewed prior to randomizing the subjects to ensure the subject meets study inclusion and exclusion criteria. The information will be fully documented in the subject's file.

The following data will be collected at the randomization visit:

- Weight and body length - Section 4.1.5
- Head circumference - Section 4.1.6
- Vital signs - Section 4.1.7
- Blood glucose level - Section 4.1.9.5
- Episodes of significant feeding intolerance - Section 4.1.10
- Concomitant medication Listing - Section 4.1.11
- PN/IV and EN intake - Sections 4.1.14.1 and 4.1.14.2

4.2.4. Study Treatment

NTRA-9620 is an insulin-based drug product intended to enhance bowel adaptation, promote EN, and reduce dependence on PN/IV. NTRA-9620 consists of maltodextrin (MD) and recombinant human insulin in powder form for reconstitution.

Subjects will receive SOC PN/IV and enteral feedings containing either dose of NTRA-9620 or matching placebo. NTRA-9620 will be dosed to target an insulin dose of 4 IU/kg/day or 8 IU/kg/day for 24 weeks. NTRA-9620 and matching placebo can be reconstituted in normal (0.9%) or half normal (0.45%) saline (NaCl) and can be administered concomitantly with SOC infant formula, donor breast milk, or mother's milk used for enteral feeds. During hospitalization, NTRA-9620 or matching placebo will be dosed 4 times a day as bolus administration spaced as equally over 24 hours as possible (ideally at every six hours, but no less than 3 hours between any two doses). In home care setting, subjects will receive NTRA-9620 or matching placebo four times a day (ideally at every six hours, but no less than 3 hours between any two doses).

4.2.5. Subject Site Visits

Subject site visits will be performed as follows:

- For study Days 1 to 84, the study day window will be ± 2 day.
- For study Days 98 to 168, the study day window will be ± 7 days.
- For study days after Day 196, the study day window will be ± 14 days.
- Subject site visits will include procedures as described in Appendix B: Schedule of Study Procedures.
- For site visit that results in study discontinuation, see termination visit in Section 4.2.6.

4.2.6. Visit and Early Discontinuation from Study Medication Visit

If a subject prematurely discontinues study medication, all reasonable measures will be taken to perform an Early Discontinuation from Study Medication Visit (Week 28 visit). This visit should include all procedures listed in the schedule of events Follow Up (Final Primary Study Visit) for Week 28 (Day 196). These procedures are necessary to complete subjects' records: physical examination, weight, body length, head circumference, vital signs, clinical laboratory test (only if clinically significant values were obtained at the Day 196, or if terminated earlier), anti-insulin antibodies, plasma citrulline (only if terminated before Day 168), parenteral nutrition intake, enteral nutrition intake, concomitant medication, adverse event, and updating of subject contact information.

All reasonable efforts will be made to perform a termination visit (Week 28) in patients who discontinue early.

4.2.7. Termination Visit and Early Discontinuation from Long-Term Follow-up Visits

If a subject prematurely discontinues from the long-term follow-up portion of the study, all reasonable measures will be taken to perform an Early Discontinuation Visit. This visit should include all procedures listed in the Follow Up and updating of subject contact information.

4.2.8. Unscheduled Visit

Unscheduled visits will be performed upon the investigator's discretion, upon Sponsor request to redo tests with unusual results, or to complete missing results. These visits may also occur upon subject's parent or guardian request. Unscheduled visits will include any study procedure deemed necessary.

During the long term follow-up period after the intervention period and Week 28 visit, this patient population is expected to continue routine Standard of Care visits that may be conducted at approximately three month intervals. If these routine Standard of Care visits are conducted the following data will be collected: body weight, body length, head circumference, parenteral nutrition intake, enteral nutrition intake, re-hospitalizations and adverse events. These data will be entered into the eCRF as Unscheduled Visits. If a routine Standard of Care visit is not conducted or complete data are not collected as part of these visits, these will not be considered missing data. These data will include neurodevelopmental Bayley's score cognitive, language and motor domains at 2Y corrected age.

5. SAFETY CONSIDERATIONS AND GUIDANCE FOR INVESTIGATORS

Adherence to protocol monitoring procedures along with the following safety guidance will aid and promote subject safety.

5.1. SAFETY MEASUREMENTS

Nutrinia has performed four trials, three in preterm infants and one in SBS infants, with oral administration of insulin. In these trials no treatment-related adverse event has been reported and no systemic absorption of insulin was detected. The NTRA-9620 formulation has been extensively studied in two clinical studies with pre-term infants (26-33 week gestational age) and in one clinical study with term infants (34-42 week gestational age). Table 1 summarizes the non-drug related AEs and SAEs observed in the previous clinical trials.

Table 1: Adverse Events Observed in Previous Nutrinia Clinical Studies of Oral Insulin in Premature Infants

According to the study investigator, none of the recorded adverse events was related to the investigational product or trial.

Phase I Efficacy Trial (n = 8)

Adverse Events	No. of subjects with an event (n = 8)
Green gastric residue + residue of 20-50% of the prior meal, 3 meals in a row	1
Bradycardia	1
Hypertension	1
Apnea	1

Phase I Safety Trial (n = 11)

Adverse Events	No. of subjects with an event (n = 11)
Seborrhea dermatitis	1
Rhinitis	3
Rosseolla infantum	1
Upper respiratory tract infection	1
Cough	1
Soft stool	1
Conjunctivitis	1
Viral infection	2
Mild stridor	1
Otitis media mild	1
Fine macular rash on face and abdomen	1

Adverse Events	No. of subjects with an event (n = 11)
Fever	1
Viral rash	1

Phase II Efficacy Trial (n = 33)

Adverse Events	No. of Subjects affected	Number of AE defined as Serious Adverse Events (SAE)
Coffee ground	1	0
Supraventricular tachycardia	1	0
Gastro enteritis	2	1
Hernia Inguinal	4	0
Low hemoglobin	1	0
Sepsis due to staphylococcus epidermidis	1	0
Sepsis gram positive colli	1	0
Sepsis	4	2
Acute otitis media	1	0
Upper respiratory tract infection	2	0
Respiratory distress	1	0
Rt. Upper Lobe pneumonia	1	1
Neutropenia	1	0
Hypothyroidism	2	1
Gastroesophageal reflux	1	1
Diaper dermatitis	1	0
Skin irritation	1	0
Ulceration of strawberry hemangioma	1	0
Apnea	2	1
Fever	1	1
Mild conjunctivitis	1	0

5.2. PREMATURE DISCONTINUATION FROM STUDY MEDICATION

Subjects will be discontinued from the study medication after evaluation by the investigator and sponsor's medical monitor in any of the following cases:

- Any CTCAE Grade 3 or 4 adverse event (see Section 7) that the investigator considers related to study medication and not attributable to the underlying disease or considered common events listed in Appendix C.
- Systemic hypersensitivity reaction related to study medication.
- Non-compliance of the subject's parent(s) or legal guardian(s) with study procedures
- Other reasons regarded as warranting subject's discontinuation from study medication.
- Premature study termination as described in Section 5.3.

Parent(s) or legal guardian(s) who voluntarily have their child discontinue the study medication will be questioned to determine whether an AE contributed to the decision to discontinue study medication.

Subjects who are withdrawn from treatment because of an adverse event will be followed and treated by the investigator until the abnormal parameter/condition or symptom has resolved or stabilized or the investigator deems further observations or examinations no longer required as medically indicated.

The investigator will make reasonable attempts to provide a reason for a subject's being withdrawn from study medication. The reason for the subject's withdrawal from study medication will be described in the subject's source documents and CRF

Subjects who prematurely discontinue will have an Early Discontinuation for Study Medication Visit as described in Section 4.2.6□ . Subjects who discontinue study medication early should return four (4) weeks after study medication discontinuation to receive follow-up visits.

5.3. PREMATURE DISCONTINUATION FROM STUDY

Participation in the study is strictly voluntary. In accordance with the current revision of the Declaration of Helsinki, parent(s) or legal guardian(s) of subjects have the right to withdraw their child from the study at any time, for any reason, specified or unspecified, and without prejudice to any future medical care by the physician or the institution. If the parent(s) or legal guardian(s) of subjects choose to withdraw their child, the investigator and the Sponsor must be informed immediately.

The subject will be withdrawn from the study if the parent(s) or legal guardian (s) withdraws consent.

The investigator will make reasonable attempts to provide a reason for withdrawal of subjects from the study. The reason for the subject's withdrawal from the study will be specified in the subject's source documents and CRF. When a parent or guardian asks to withdraw consent, the investigator should confirm that the parent/guardian understands the difference between withdrawal of study medication and withdrawal from the study. If the parent/guardian is willing to withdraw the subject from study medication but remain in the study, then the investigator should follow procedures in Section 4.2.6.

5.4. PREMATURE STUDY TERMINATION

The study subjects are expected to experience many adverse events, including severe adverse events related to premature birth, invasive surgery, their medical/surgical complications or other underlying conditions including but not limited to the short bowel condition. Therefore, all safety concerns potentially leading to study termination will be referred to the Data Safety Monitoring Board (DSMB), which is responsible for a formal assessment of the safety of the study. This Board will propose the appropriate course of action to the Sponsor.

Individual Events:

Any of the following individual events would be referred by the study Medical Monitor to the DSMB chairman for review, who may decide that the events warrant a full DSMB review. The DSMB will review these events unblinded to fully evaluate the potential risk to subjects in this trial. Given this is a blinded trial, the DSMB review is required to consider if the events, both serious and related non-serious events, are occurring more frequently in the active arms and to judge whether there is a meaningful likelihood that these events are drug-related. The DSMB may recommend to the Sponsor to stop the study, or any portion of it, at any time for safety reasons on the basis of their review. Individual events that may trigger a DSMB review based on individual cases:

- Two or more cases of Grade 3 or greater allergic reactions or anaphylaxis, that the investigator deems as possibly related to study medication;
- Any case of autoimmune disease associated with neutralizing antibodies to insulin and where other related causes, such as Type I diabetes, are ruled out;
- Two or more cases of persistent Grade 3 or greater hypoglycemia that is non-responsive to treatment within 72-hours and reoccurs after temporary discontinuation of study medication and re-challenged.
- Two or more subjects who develop liver enzyme increases of greater than 10 times the ULN that is attributed to study medication and the investigator does not consider related to the underlying disease process or administration of parenteral nutrition.

Further, the Medical Monitor will be responsible for review of all reported SAEs in an ongoing manner. Any SAE that is deemed potentially related to study medication, or of particular concern by the Medical Monitor, will also be sent to the DSMB Chairman for review within

15 days. The DSMB Chairmen may decide to bring any individual SAE event that may be related and of concern to the full DSMB for review.

Collective Events:

The Medical Monitor and DSMB will review aggregate safety data in an ongoing manner, at DSMB meetings which will be held approximately each 4 months throughout the trial. The Medical Monitor will remain blinded to treatment assignment for cumulative data at all times, but may refer any safety concerns based on review of safety data to the DSMB for further evaluation. The DSMB will receive unblinded safety data summaries from an independent statistician that is assigned to prepare the unblended study reports for all subjects at each DSMB meeting. Reviews of cumulative safety data will be conducted every four (4) months during the trial conduct during scheduled DSMB meetings. The DSMB statistician will compare the event rates for AEs between the groups and the probability that the groups differ in the frequency of events. If there are differences in Grade 3 or higher adverse events that differ materially between active and control and that may be attributable to study medication based on the mechanism of action of the drug, the DSMB has the option to recommend that the Sponsor stop the study, or modify the protocol for safety reasons.

The study may also be prematurely terminated for administrative reasons, ethical considerations, at the request of local regulatory agencies, or for any other reason the Sponsor deems appropriate.

5.5. DEVIATION FROM STUDY PROTOCOL

The investigator shall not deviate from the study protocol without first obtaining written approval from the Sponsor, or its official designee, and from the local IRB/IEC according to local regulations.

In the event of medical emergencies, the investigator shall use appropriate medical judgment and will remove the subject from any immediate hazard. Then, within 24 hours for related SAEs and within 48 hours for unrelated SAEs, the investigator shall notify the Sponsor or its official designee and, if applicable, the local IRB/IEC of the type of emergency and course of action taken.

Any other changes to or deviations from the protocol will be made as an amendment to the protocol and must be approved by the Sponsor or its official designee and the local IRB/IEC before they can be implemented. Accordingly, the Sponsor will not assume responsibility or liability for any unauthorized deviation from or change to the protocol.

6. INVESTIGATIONAL PRODUCT SPECIFICATIONS

NTRA-9620 drug product is manufactured in accordance with current Good Manufacturing Practices (cGMPs).

6.1. FORMULATION, PACKAGING, AND LABELING OF NTRA-9620

NTRA-9620 (4 IU/g, 8 IU/g), which contains recombinant human insulin as the active ingredient, is intended for oral administration to infants with SBS.

NTRA-9620 consists of maltodextrin, 0.45% sodium chloride, and human insulin (rDNA origin).

To maintain double blinding, for the lower dose (4 IU/kg/day) stick packs will have powder concentration of 4 IU/g while for the high dose (8 IU/kg/day) stick packs will have powder concentration of 8 IU/g.

NTRA-9620 and matching placebo will be supplied in 1gram stick packs as a powder for reconstitution for oral administration. The stick packs will be provided in box cartons. NTRA-9620 or Placebo will be labeled with at least the minimum information listed below:

NTRA-9620 or Placebo
Equivalent to 4 IU Insulin or 8 IU Insulin or Placebo in 1 stick pack for oral solution
Dose according to study protocol instructions
Store at room temperature (15-25ºC/59-77ºF)
Caution: New Drug – Limited for Clinical Trial Use Only

6.2. STORAGE AND STABILITY OF NTRA-9620

The NTRA-9620 packets will be stored at room temperature (15-25°C ± 2°C/59-77°F ± 4°F). Storage space will be separate, designated, and adequately labeled as containing investigational product.

A stability program of NTRA-9620 is ongoing. The Sponsor will manage site inventory according to accumulating stability data and through the IVRS system.

6.2.1. Dosage

NTRA-9620 (oral insulin) and matching placebo will be provided in stick packs of one gram for reconstitution.

6.2.2. Administration and Instructions for Use

Each individual stick pack must be kept and handled at room temperature prior to reconstitution.

Subjects will receive SOC parenteral nutrition and enteral feedings containing either dose of NTRA-9620 or matching placebo. NTRA-9620 or matching placebo will be dosed to target an insulin dose of 8 IU/kg/day or 4 IU/kg/day for 24 weeks. NTRA-9620 and matching placebo can be reconstituted in normal (0.9%) or half normal (0.45%) saline (NaCl) and can be administered concomitantly with SOC infant formula, donor breast milk or own mother's milk used for enteral

feeds. During hospitalization, assigned treatment will be dosed 4 times a day as bolus administration spaced as equally over 24 hours as possible (ideally at every six (6) hours, but no less than three (3) hours between any two doses). In home care, subjects will receive assigned treatment four times a day (ideally at every six (6) hours, but no less than three (3) hours between any two doses). Additional instructions will be provided in the Instruction for Use document.

The SOC with NTRA-9620 or matching placebo will be manually shaken before consumption.

- Group 1: NTRA-9620 will be administered 4 times a day each at a dose of 2 IU/kg (8 IU/kg/day)
- Group 2: NTRA-9620 will be administered 4 times a day each at a dose of 1 IU/kg (4 IU/kg/day)
- Group 3: Matching placebo will be administered 4 times a day

6.3. ACCOUNTABILITY OF NTRA-9620

NTRA-9620 will be supplied in stick packs, in quantities as needed to comply with the treatment of site subjects according to the study protocol.

The initial study drug supply will be shipped after site activation (i.e., after the Sponsor has received all required regulatory documentation and a contract has been executed). The initial study drug shipment will include a specified number (baseline quantity) of study drug kits for each treatment arm. However, since both doses of NTRA-9620 and the matching placebo are packaged and labeled in a blinded manner, the study sites will not be able to distinguish among the three (3) different study drug types and will treat all study drug kits in the same manner.

Subsequent study drug shipments will be made when the inventory level for any study drug type (NTRA-9620 low dose, NTRA-9620 high dose, or matching placebo) reaches its alert quantity. In this case, the electronic randomization and drug supply system generates a shipment request in order to bring the site's inventory of all study drug types to their baseline quantity.

Shipment, storage, and inventory documentation will be updated regularly and kept in the investigation files at the site to allow inspection and trace of the supplied product.

Used investigational product: Used/opened stick packs will be destroyed.

All unused stick packs must be returned to the Sponsor after accountability records have been confirmed by the study monitor. Accountability of the study medication must include reconciliation of any unused stick packs not returned.

7. SAFETY MONITORING AND ADVERSE EVENTS

7.1. ADVERSE EVENTS

Data regarding treatment-emergent AEs will be collected. Treatment-emergent AEs are events that are not present at baseline or, if present at baseline, have worsened in severity or frequency.

If applicable to this study population, the descriptions and grading scales found in the Common Terminology Criteria for Adverse Events (CTCAE) v 4.03 will be used for AE reporting. For events where the specific definitions for grading in CTCAE does not apply to this study population, general grading criteria described in CTCAE will be used and investigator judgment on severity will determine the grade of the event. See Appendix C for link to a copy of CTCAE v 4.03.

7.1.1. Definition of Adverse Events

Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a subject administered a pharmaceutical product (either test product or control product); an AE does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product or other protocol-imposed intervention, regardless of attribution, i.e., whether or not related to that investigational (medicinal) product. An AE may include intercurrent illnesses or injuries that represent an exacerbation (increase in frequency, severity, or specificity) of pre-existing conditions (e.g., worsening of asthma). A laboratory abnormality will be reported on the "Adverse Event" case report form only if the investigators considered it clinically significant, or if it is associated with clinical sequelae or requires therapeutic intervention.

Adverse Drug Reaction (ADR)

Any AE for which there is a reasonable possibility that the study drug caused the adverse event, means there is evidence to suggest a causal relationship between the study drug and the adverse event, or that a causal relationship between a study drug and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. The relationship may be ruled as unlikely, possibly or probably related to study drug – see definitions below.

Unexpected AE

An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

A pre-treatment emergent event will not be considered an AE, but will be recorded as medical history.

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of symptoms relating to a diagnosis. AEs will be graded according to the CTCAE v 4.03 (Appendix C). For events where the specific definitions for grading in CTCAE does not apply to this study population, general grading criteria described in CTCAE will be used and investigator judgment on severity will determine the grade of the event.

AEs monitoring will be captured throughout the study, from Day 0 (initiation of dosing) until final primary study visit at Week 28 (Day 196). Long-term safety evaluations will also be conducted post primary study completion on Week 52 (Days 364) and Week 104 (Day 728) to assess any potentially related adverse outcomes of treatment.

If an unrelated AE remains unresolved after Week 28, at the Investigator's discretion, the subject may be followed until Week 104, or until resolution of the event. The investigators must follow a related AE and any unrelated/related SAE until resolution even if the time extends beyond the study-reporting period. Resolution is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic; it is not a discharge date from the hospital.

The investigator will assess AEs for severity, for relationship to the study drug, and as to whether the event meets one or more of the definitions of an SAE.

The investigator will determine the relationship of an AE to the study drug and will record it on the source documents and AE CRF, using the categories defined below.

Causality Category	**Description**
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations. For the purpose of this protocol, the term unlikely will be considered not related to study medication and an "Adverse Event".
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear. For the purpose of this protocol, an event that has possible relationship to study medication will be defined as a "Suspected Adverse Drug Reaction".
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal. For the purpose of this protocol, an event that has probable relationship to study medication will be defined as an "Adverse Drug Reaction".

In order to classify adverse events and diseases, the sponsor or its designee will assign preferred terms to the original terms entered on the CRF, using the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be graded on a 5-point scale (mild, moderate, severe, life-threatening, and death) and reported as indicated on the CRF. Intensity of adverse event is defined as follows:

Table 2: Severity Assessment Terminology for Reporting Adverse Events

CTCAE Grade	Common Term	Description
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
4	Life-threatening	Life-threatening consequences; urgent intervention indicated
5	Death	Outcome of AE was death

AEs that are not described on the CTCAE v 4.03 will be graded according to the scale defined in Table 2.

7.2. SERIOUS ADVERSE EVENTS

According to the ICH Guidelines for Good Clinical Practice (GCP) (E6), an SAE is any untoward medical occurrence during the course of a clinical investigation that is characterized by one or more of the following:

- Results in death
- Is life-threatening
- Requires in-subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Important medical events

7.2.1. SAE Reporting

All SAEs must be promptly reported to the Sponsor by the Investigator, study coordinator, other designated study personnel, or clinical research associate within 24 hours of notification of the SAE for related SAEs and within 48 hours for unrelated SAEs. To report such events, the

Investigator must complete an SAE form and send it within 24 hours by email or fax with relevant information.

Within the 48 hours following the initial report, the Investigator must provide further information on the SAE. This should include a copy of the completed SAE form, and any other information that will assist the understanding of the event. Significant new information on ongoing SAEs will be provided promptly as a follow-up.

The Investigator also must report all SAEs promptly to the appropriate IRB/IEC as required by the IRB/IEC.

Contact Information for SAE Reporting

SAE Reporting will be sent to:

PREMIER Research Pharmacovigilance (PREMIER PV):

US/Canada Cases: fax +215-972-8765 OR e-mail "**GlobalPV-US@premier-research.com**"

EU/ROW Cases: fax +421 2 6820 3713 OR e-mail "**PVDS-ROW@premier-research.com**

Medical Monitor Contact: Sarina Tanimoto, MD, PhD	
Office/Cellular	+1-858-227-3008/+1-858-774-8716
Email	Sarina@pacificlinkconsulting.com

7.2.2. Recording of Serious Adverse Events

All SAE information must be recorded on the SAE form provided by the Sponsor. Additional follow-up information (e.g., test results, autopsy report, discharge summary, and CRF pages for AEs, concomitant medications, study drug administration, and medical history) must be obtained to supplement the SAE report form. A copy of all initial and follow-up reports must be filed with the subject's CRF.

8. STATISTICAL CONSIDERATIONS

8.1. OVERVIEW

The aim of this study is to evaluate the safety and efficacy of NTRA-9620 relative to matching placebo on intestinal failure due to SBS. Safety will be assessed by AEs while primary efficacy will be assessed by change in parenteral feeding.

This section briefly describes the analyses planned for the trial. A full statistical analysis plan (SAP), to be written while the study is still blind, will describe the methods in detail. Should the SAP and this protocol not be in complete agreement, the methodology in the SAP will prevail.

8.1.1. Interim Check of Variance Assumption

This multicenter trial will allow inclusion of a large population of infants from preterm to one year, SBS of varying etiologies, bowel length of varying sizes, presence or absence of ileocecal valve, and varying feeding regimes (e.g., formula only, full or partial own mother's milk). We know of no similar study that has been conducted in such a wide-ranging population - a population that is expected to have especially high variation with respect to prognosis and therefore to study outcome. Our best estimate of within-group variation, which is critical for accurately computing study power, is based on a small pilot study in a related, but not identical, indication. Consequently, we will assess the assumptions used for calculating power by computing the common pooled standard deviation of percent change in %PN when 75 subjects have completed 12 weeks in the study. Should the calculated standard deviation be at least 22% (i.e., 10% greater than the 20% assumed in the protocol), sample size may be adjusted upward accordingly. A statistician blinded to group assignment will compute this interim standard deviation. That statistician will not be involved in any other aspect of the trial. The sponsor will decide whether to increase the sample size during the trial; the decision will be based on the estimated variance but without any knowledge of the interim effect size.

8.1.2. Statistical Tests of Co-Primary and Key Secondary Endpoints

Co-Primary Endpoint (means)

The two endpoints (12 weeks and 24 weeks) will each be analyzed using an analysis of covariance model with $PC\_PN_{0\text{-}12}$ and $PC\_PN_{0\text{-}24}$ serving as the dependent variable for each respective analysis. Treatment group and the randomization stratification variables will serve as factors and the baseline %PN value will serve as a covariate in each analysis. In each analysis, the higher dose group will be compared to placebo group first. The high-dose comparison will be tested at the 0.025 two-sided significance level at each timepoint. If the high-dose comparison at a particular timepoint is significant at $p < 0.025$, then the low-dose comparison with placebo (at the same timepoint) will be tested at the 0.025 level.

For this endpoint, the Type I error rate will be controlled at 0.05 by using a Bonferroni correction for the two timepoints and a step-down procedure to compare each dose group (high dose first, then low dose) with placebo.

Co-Primary Endpoint (responders)

The continuous responder analysis will be displayed graphically where the *x*-axis displays the percent reduction in %PN and the *y*-axis shows the proportion of infants who meet each response threshold (from 0 to 100%). The continuous responder curves for each dose vs. placebo will be compared using the Mann Whitney U test based on the 12 week data and another graph and analysis will make the similar comparison at 24 weeks. Each test will be carried out at the 1-sided $p<0.10$ significance level.

The trial will have shown benefit if any group comparison stated above is shown to be superior to placebo on both of the co-primary endpoints at the same time (12 or 24 weeks, or both), each at the stated significance level.

Key Secondary Endpoint

The key secondary endpoint will be analyzed using a stratified log-rank test with factors for treatment group and the randomization stratification variables. Separate analyses will be carried out for each dose group.

The Statistical Analysis Plan will describe in detail the methods to be used for the primary and key secondary endpoints. The methods will be designed to ensure protection of the Type I error rate across the primary and key secondary endpoints.

8.1.3. Treatment of Subjects Lost to Follow-up

Several subjects in this trial may undergo significant interventions during the trial and some may die. Specifically, about 10% of subjects are not expected to reach the 12-week time point for reasons such as death, risk of or actual necrotizing enterocolitis (NEC), or other complications. An additional 10% of subjects are not expected to reach the 24 week time point for similar reasons. Partial data collected from such infants are informative for comparing the treatment arms. For subjects who do not provide any data during the 10-day period for the week 12 or week 24 time point, the endpoint will be imputed using multiple imputation, replacing each missing value with a set of plausible values that represent the uncertainty about the correct value to impute. The multiple imputed datasets will then be analyzed by standard statistical procedures for complete data and combining the results from these analyses. Multiple imputation does not attempt to estimate each missing value through simulated values, but rather to present a random sample of the missing values.

Multiple imputation involves three steps:

1. the missing values are filled in *m* times to generate *m* complete data sets,
2. the *m* complete datasets are analyzed using standard statistical procedures,
3. the results from the *m* analyses are combined (using a roll-up estimator) for statistical inference.

The SAP will present full details of the methodology.

8.2. ANALYSIS SETS

8.2.1. Safety Analysis Set

The safety analysis set will consist of all subjects for whom the study treatment, whether placebo or NTRA-9620, was initiated.

8.2.2. Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomized subjects. Subjects will be analyzed by randomized treatment.

Blind review will be used to assess which interventions undergone during the trial are likely to affect outcome. As noted in the preceding section, major interventions are expected to be independent of treatment.

8.2.3. Modified Intent-to-Treat Set

The Modified Intent-to-Treat (mITT) set will consist of all randomized subjects who received at least one dose of NTRA-9620 or placebo, and who have baseline and at least one post-baseline measurement on the primary endpoint (for primary endpoint testing) or the key secondary endpoints (for key secondary endpoint testing). Subjects will be analyzed by randomized treatment.

Blind review will be used to assess which interventions undergone during the trial are likely to affect outcome. As noted in the preceding section, major interventions are expected to be independent of treatment.

8.2.4. Per-Protocol Analysis Set

The per-protocol (PP) analysis set will be the subset of FAS subjects with no major protocol violation likely to affect outcome prior to the time point at which a confirmatory endpoint is tested. Blind review will be used to assess which interventions undergone during the trial are likely to affect outcome. Subjects with these major interventions will be included in the PP up to the point of intervention.

Analysis of PP sets need to be performed in a way that adjusts for the selection bias inherent in PP sets. The SAP will describe these analyses.

8.3. STUDY ENDPOINTS

This section presents the safety and efficacy endpoints in this trial. The primary endpoints are computed as percent change from baseline to 12 weeks and to 24 weeks, where the change is based on the average of the daily values obtained during the specified week. The difference between the relevant week and baseline is calculated such that the expected outcomes are positive (i.e., since greater %PN at baseline is expected, the primary endpoint is computed by subtracting the 12-week or 24 week measurement from baseline).

8.3.1. Safety Endpoints

Safety endpoints are SAEs and AEs occurring at any time during the trial or follow-up.

8.3.2. Co-Primary Efficacy Endpoints

The first co-primary endpoints in this trial is percent change in %PN ($PC\_PN_{0\text{-}t}$) from baseline[13] based on caloric intake to 12 weeks and again to 24 weeks. The 12 and 24 week endpoints are calculated as:

$$PC\_PN_{0-t} = 100 * \frac{\%PN_{Baseline} - \%PN_t}{\%PN_{Baseline}}$$

Where

- t = 12 or 24 weeks
- %PN = % Parenteral Nutrition (feeding) will be calculated as parenteral calories divided by total caloric requirements (the Schofield equation (1)).
- $PC\_PN_{0\text{-}t}$ observations will be computed as an average over a single week.

Thus, PC_PN at 12 weeks will be the average of PC_PN over Days 78 to 84.
PC_PN at 24 weeks will be the average of PC_PN over days 162 to 168.

The use of the Schofield equation would be solely in the analysis of the study and would not be used at bedside during the actual trial.

The second co-primary endpoints are responder endpoints, calculated as continuous responder comparisons at 12 weeks and again at 24 weeks. Each test will be carried out at the 1-sided $p<0.10$ significance level.

8.3.3. Key Secondary Endpoint

The trial has the following key secondary endpoint:

Time to reduction of PN to less than 10% of the total caloric intake on each of 14 consecutive days.

8.3.4. Other Secondary Endpoints

The study has the following additional secondary endpoints:

a) Time to wean off [14] parenteral nutrition
b) Number of patients achieving readiness to wean off [15] at 12 and 24 weeks from baseline
c) Time to 50% PN/IV reduction from baseline in %PN based on total calories.
d) Time to 50% PN/IV reduction from baseline in %PN based on volume.

[13] Baseline: prior to treatment. Baseline measurement period should be at least 7 days.
[14] Wean off defined as complete cessation of parenteral nutrition and achieving full enteral autonomy for two weeks.
[15] Reduction to PN of less than 10% of the total caloric intake for two weeks.

e) Number of patients reaching 50% PN/IV reduction from baseline in %PN based on total calories at 12 and 24 weeks
f) Number of patients reaching 50% PN/IV reduction from baseline in %PN based on volume at 12 and 24 weeks.
g) Percent change from baseline in %PN/IV based on total calories.
h) Percent change from baseline in %PN/IV based on volume.
i) Percent change from baseline in PN/IV fluid volume during treatment period.
j) Change in Z-scores (Fenton) from baseline during the treatment period.
k) Percent change from baseline in %EN based on total calories.
l) Percent change from baseline in %EN based on total volume.
m) Change from baseline in liver enzymes (ALT, GGT, and total and direct bilirubin).
n) Change from baseline in plasma citrulline levels.
o) Change from baseline in body weight during the treatment period.
p) Weekly average of hours on prescribed PN/IV during the last month of treatment.
q) General safety variables including episodes of significant feeding intolerance compared to placebo

8.4. SAMPLE SIZE

The sample size is based on testing the superiority of the high dose of NTRA-9620 compared to placebo on the primary endpoints of percent change in %PN from baseline to time "t" (PC_PN0-t) where "t" = 12 and 24 weeks. On the basis of historical data, the assumed reduction in PC_PN0-t is 30% and 42% in placebo and NTRA- 9620, respectively, at both 12 and 24 weeks. A common within-group standard deviation of 20% has been assumed for both arms.

Given the above specifications, and based on the use of a two-sided, two-sample comparison of means at the alpha = 0.025 level of significance, a sample of 45 subjects per group would provide approximately 80% power to demonstrate superiority. Since some subjects may not complete the entire trial, an additional 10% of subjects will be enrolled per arm (50 subjects per arm) to account for this potential loss. Thus, the proposed sample size is 150 subjects.

8.5. STATISTICAL ANALYSIS

8.5.1. Overview

Safety and Full Analysis Set (FAS) will be conducted on the safety analysis set. Primary and key secondary efficacy testing will be done using the FAS and the mITT sets. Efficacy testing, including primary and key secondary endpoints, may also be performed on the PP set.

The data will be summarized by group and overall. For continuous data, tables will present means, standard deviations, medians, minima, maxima, appropriate percentiles, and number of

subjects. For categorical data, tables will show counts and percentages. "Time-to-event" data will be summarized using the Kaplan-Meier method. Data listings by subject will be provided.

Statistical analyses will generally be performed using the SAS® system. The effects of noncompliance, dropouts, and possible covariates such as gestational age, birth weight and gender will be assessed as sensitivity analyses.

8.5.2. Subject Disposition

Subject disposition will be tabulated; the number of subjects enrolled, exposed, prematurely terminated from study drug, prematurely terminated from study, and completed will be summarized by treatment group and overall. A list of dropouts will be prepared including reason for, and time of, discontinuation.

8.5.3. Demographic and Baseline Characteristics

Subjects in each treatment arm will be characterized using tables, figures, and descriptive statistics for demographic and baseline clinical variables. Treatment groups will be compared to evaluate the balance achieved by randomization. Observed differences between the groups, should there be any, will be interpreted for their clinical significance and their potential use as covariates in sensitivity analyses of the analysis of efficacy endpoints.

8.5.4. Safety Analysis

The safety analyses will be descriptive and narrative in nature, with SAEs and AEs coded using MedDRA and tabulated by body system, preferred term, treatment group, severity and relation to procedure. Descriptive statistics will be provided by treatment group as appropriate.

8.5.5. Primary Efficacy Analysis

8.5.5.1. Co-Primary Endpoints

The first two primary endpoints (12 weeks and 24 weeks) will each be analyzed using an analysis of covariance model with $PC\_PN_{0\text{-}12}$ and $PC\_PN_{0\text{-}24}$ serving as the dependent variable for each respective analysis. Treatment group and the randomisation stratification variables will serve as factors and the baseline %PN value will serve as a covariate in each analysis. In each analysis, the higher dose group will be compared to placebo group first. The high-dose comparison will be tested at the 0.025 two-sided significance level at each timepoint. If the high-dose comparison at a particular timepoint is significant at $p < 0.025$, then the low-dose comparison with placebo (at the same timepoint) will be tested at the 0.025 level.

The second co-primary endpoints are responder endpoints, calculated as continuous responder comparisons at 12 weeks and again at 24 weeks. Each test will be carried out at the 1-sided $p<0.10$ significance level.

The trial will have shown benefit if any group comparison stated above is shown to be superior to placebo, at the same time (12 or 24 weeks, or both), each at the stated significance level.

8.5.5.2. Key Secondary Endpoint

The key secondary endpoint will be analyzed using a stratified log-rank test with factors for treatment group and the randomization stratification variables.

8.5.5.3. Other Secondary Endpoints

The SAP will describe the analyses planned for the other secondary endpoints.

8.5.6. Sensitivity Analyses

The SAP will describe the sensitivity analyses planned for the primary and key secondary endpoints.

8.5.7. Treatment of Missing Values

The SAP will describe the planned approaches for missing primary and key secondary endpoints.

8.5.8. Analyses of Follow-up Data

In this 24-week study, primary efficacy is measured at 12 and 24 weeks. Data lock will occur after all subjects have completed 24 weeks in the trial, before which the SAP will have been finalized and signed. The final statistical report will include outcomes up to and including 24 weeks.

8.5.9. Interim Analysis

As described in Section 8.1.1, a blind review of the data will be performed during the study in order to estimate the variance.

A Data Safety Monitoring Board (Section 10.3) will review the ongoing data to ensure safety of the subjects.

No formal interim analysis of efficacy will be performed.

9. DATA COLLECTION, STUDY MONITORING, AND DATA DISCLOSURE

9.1. DATA COLLECTION AND REPORTING

The Investigator will maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (i.e., Electronic Data Capture (EDC) system) when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a site number, subject number and initials. An electronic CRF will be completed for each subject who is assigned a study number and for whom a study-approved ICF is signed and dated. For all entries into the EDC that are not source electronic data, the data entries must be supported by original source documentation (e.g., laboratory reports, medical records) maintained at the investigational site. If a correction is required for an EDC, the time and date stamps track the person entering or updating EDC data and create an electronic audit trail.

The Investigator will make safety assessments (AEs, vital signs, results from physical examinations, and laboratory tests) on an ongoing basis. The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator.

If a subject is lost to follow-up, (i.e., fails to return for scheduled visits) every reasonable effort must be made to contact the subject's parent or guardian in order to determine why the subject failed to return. All actions taken in this regard will be documented and dated in the CRF.

The investigator is required to electronically sign the EDC at appropriate times. The investigator's signature on the CRF serves to certify that the data collected for each subject is accurate, complete and legible. A copy of the CRF will remain at the study site at the completion of the study.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

9.2. STUDY MONITORING

The Sponsor's designees will monitor all aspects of the study carefully with respect to cGCPs and SOPs for compliance with applicable government regulations. The investigator is responsible for providing all study records, including eCRFs, source documents, medical history, etc., for review and inspection by the clinical monitor.

EDC (CRFs) will be periodically monitored and source verified against corresponding source documentation (e.g., office and clinical laboratory records) for each subject. Clinical monitors will evaluate periodically the progress of the study, including the verification of appropriate consent form procedures, review of drug accountability and study drug preparation procedures, adherence to dosing procedures, the investigator's adherence to the protocol, maintenance of records and reports, review of source documents for accuracy, completeness, and legibility, and review of study regulatory documents, including, but not limited to: study agreement, study insurance, study approval letters by the IRB/IEC and the Regulatory Authority, site staff CV and

financial statements, study forms, protocol signature page, etc. In addition, the monitor shall review completed electronic case report form (eCRF) and study documentation for accuracy and completeness, and protocol compliance. The monitor should assure that data captured in the eCRF is fully supported by the source documents. Clinical monitors will also ensure that all protocol requirements, applicable Food and Drug Administration (FDA) regulations (CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP - E6), other requirements, and Investigator's obligations are being fulfilled.

By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

Apart from assuming responsibility for the communication between the investigator and the Sponsor, the clinical monitor duties include:

- On-site visits; and
- Review of study documents and results.

On-site monitoring visits include pre-study/qualification visits, initiation visits, interim monitoring visits and, a close-out visit at the end of the study. At the close of the study, the monitor will be required to make a final on-site visit to assure that all study data has been properly completed.

Reports of on-site visits shall be made by the monitor and should include, as applicable, resolution of concerns and queries, completion of appropriate follow-up activities, completion of assigned tasks, and corrective actions. Monitoring visits Follow-up letters will be sent to the site for filing and adherence.

All data generated in the current clinical investigation will be managed according to relevant guidelines (e.g., GCP, 21 CFR Part 11).

9.3. CONFIDENTIALITY, DATA DISCLOSURE, AND PUBLICATION

Subject medical information obtained as a result of this study is considered confidential. Disclosure to third parties other than those noted below is prohibited. All reports and communications relating to subjects and their parent(s) or guardians(s) in this study will identify all persons only by their initials and number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, the Sponsor, the Sponsor-assigned clinical monitor (or designee), and the IRB/IEC.

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by a coded number to maintain subject confidentiality. All records will be maintained in lockable file cabinets. All computer entry and networking programs will be identifiable only by coded numbers. Clinical information will not be released without written permission from the subject's parent or guardian, except as necessary for monitoring by the IRB, the FDA, or representatives of the study Sponsor.

Any information, inventions, or discoveries (whether patentable or not), innovations, suggestions, ideas, and reports, made or developed by an investigator as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions, as the Sponsor deems necessary or appropriate, to obtain patents in the Sponsor's name covering any of the foregoing.

The results of this study will be published under the direction of the Sponsor. Results will not be published without prior review and approval by the Sponsor.

10. PROTECTION OF HUMAN SUBJECTS

10.1. DECLARATION OF HELSINKI

Both the Investigator and the Sponsor will ensure that the study is conducted in agreement with the Declaration of Helsinki, ICH-GCP, and the local laws and regulation.

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a subject's name to a subject identification number will be stored separately in another locked file cabinet. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996).

10.2. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

The Investigator agrees to provide the IRB/IEC with all appropriate material, including a copy of the ICF. The study will not be initiated until the Investigator obtains written approval of the research plan and the ICF from the appropriate IRB/IEC and copies of these documents are received by the Sponsor. Appropriate reports on the progress of this study will be made by the Investigator to the IRB/IEC and Sponsor in accordance with applicable government regulations and in agreement with the policies established by the Sponsor. The Sponsor ensures that the IRB/IEC complies with the requirements set forth in 21 Code of Federal Regulations (CFR) Part 56.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the subject or when the change involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved will be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse events occurring during the study in accordance with the standard operating procedures and policies of the IRB/IEC; new information that may affect adversely the safety of the subjects of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

10.3. DATA SAFETY MONITORING BOARD (DSMB)

A DSMB will be convened for this protocol to ensure the safety of subjects enrolled. The details of the DSMB activities, including review of the safety data, will be outlined in a specific charter approved by the DSMB members, Medical Monitor, and Sponsor.

10.4. INFORMED CONSENT

See Section 4.1.1.

10.5. INVESTIGATOR'S RESPONSIBILITIES

By signing the Investigator Agreement, the investigator agrees to the following:

Seek IRB/IEC and Regulatory Authority (RA) approval (when needed) for the study protocol, Informed Consent Form (ICF), any other written information provided to subjects and advertising material any follow any request made by the IRB/IEC or RA. Written approval of the protocol and ICF and any advertising material must be obtained from the IRB/IEC and if applicable the corresponding RA prior to any subject enrollment.

Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.

Personally conduct or supervise the study (or investigation).

Ensure that the requirements relating to obtaining informed consent and IRB/IEC review and approval meet federal guidelines, as stated in 21 CFR, Parts 50 and 56.

Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with 21 CFR Part 312.64.

Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

Maintain adequate and accurate records in accordance with 21 CFR Part 312.62 and to make those records available for inspection with the Sponsor (or designee).

Ensure that an IRB/IEC that complies with the requirements of 21 CFR Part 56 will be responsible for initial and continuing review and approval of the clinical study.

Promptly report to the IRB/IEC and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).

Seek IRB/IEC approval before any changes are made in the research study, except when necessary to eliminate hazards to the subjects.

Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in 21 CFR Part 312, Good Clinical Practice (ICH-GCP E6) and the ethical principles that have their origin in the Declaration of Helsinki.

10.6. LIABILITY AND INSURANCE CONDITIONS

Nutrinia Ltd. holds a clinical trial liability insurance policy. A copy of the policy summary will be filed in the investigator's site file.

11. REFERENCES

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Appendix A: Feeding Protocol

General

Study entry threshold: Subject can tolerate at least 10 mL/kg/day of enteral nutrition and not less than 70% of parenteral nutrition for at least 7 days at time of enrollment.

Enteral nutrition: Infant Formula (soy-based not recommended per SOC consensus), donor breast milk, and own mother's milk will be allowed in the study.

Protocol

1. Feeds of at least 10 mL/kg/day after evidence of bowel function are confirmed
2. Based on clinical status advance enteral feeds as tolerated and consider PN/IV reduction Suggested criteria for assessment:
    a. Growth at least maintained through Z score stable on a weekly basis (Fenton).
    b. Enterostomy or fecal losses ≤ 50 mL/kg/day and weight gain.
    c. Tolerating feeds (no hold of feeds lasting 24 hours).
    d. If criteria a-c are met, patient may advance enteral feeds by:
        1. In- patients- daily
        2. Out-patients- weekly
        3. Enteral advancement would be 5-10 ml/kg/day
    e. If increase in feeds is tolerated and patient is clinically ready, patient should undergo PN reduction by 5-15% of PN/IV
    f. If advance in feeds not tolerated reassess enteral feeding and PN regimen

Stop PN/IV protocol

Subjects with < 10% caloric intake from PN/IV for two weeks will be considered clinically for complete weaning off as they are not receiving any meaningful calories for maintaining growth from PN, based on recommended caloric goals per age [16].

IV fluids that are not providing meaningful calories and are used for maintaining central line patency are still permitted even when weaned off PN/IV.

Reinitiating PN/IV protocol

[16] ESPEN and AAP Energy Needs guidelines

Evaluate the clinical status including weight after 1-2 weeks to determine if PN/IV should be re-started.

Appendix B: Schedule of Study Procedures

Study Procedure	Screening	Baseline	Randomization	Initial Treatment Period	Initial Treatment Period	Week 12 Assessment	Continued Treatment Period	Week 24 Assessment	Week 28 Follow-Up (Final Primary Study Visit)[a,b]	Follow-up (Routine SOC)[c]	Week 52 Safety Follow-Up	Follow-up (Routine SOC)[c]	Week 104 Safety Follow-Up (Final Visit of Long-Term Follow-Up Period)[a]	Follow-up (Routine SOC)[c]
Study Day	**Day -14 to -1**	**Day -7 to 0**	**Day 0**	**Days 1,2,3**	**Days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77**	**Day 84**	**Days 98, 112, 126, 140, 154**	**Day 168**	**Day 196**		**Day 364**		**Day 728**	
Visit Window				**± 2 days**	**± 2 days**	**±2 days**	**±7 days**	**±7 days**	**±7 days**		**±14 days**		**±28 days**	
Signed informed consent	X													
Medical history[d] and Demographics	X													
Inclusion/Exclusion Criteria	X	X	X											
Maternal Data[e]	X													
Physical exam	X					X	X[f]	X	X					
Weight, Body Length	X	X	X		X	X	X	X	X		X		X	
Head Circumference	X		X		X	X	X	X	X		X		X	
Vital signs[g]	X	X	X		X	X	X	X	X					
EKG[h]	X													
Hematology[i], chemistry[j], urinalysis[k]	X					X		X	X[l]					
Plasma Citrulline		X				X		X	X[m]					
Blood Glucose levels[n]			X	X	X	X								
Anti-Insulin Antibodies		X				X			X					
Concomitant medication assessment	X----------→										X[o]		X[o]	

Study Procedure	Screening	Baseline	Randomization	Initial Treatment Period	Initial Treatment Period	Week 12 Assessment	Continued Treatment Period	Week 24 Assessment	Week 28 Follow-Up (Final Primary Study Visit)[a,b]	Follow-up (Routine SOC)[c]	Week 52 Safety Follow-Up	Follow-up (Routine SOC)[c]	Week 104 Safety Follow-Up (Final Visit of Long-Term Follow-Up Period)[a]	Follow-up (Routine SOC)[c]
Study Day	Day -14 to -1	Day -7 to 0	Day 0	Days 1,2,3	Days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77	Day 84	Days 98, 112, 126, 140, 154	Day 168	Day 196		Day 364		Day 728	
Visit Window				± 2 days	± 2 days	±2 days	±7 days	±7 days	±7 days		±14 days		±28 days	
Adverse event assessment [p]					X----------→									
Randomization			X											
Parenteral Nutrition Intake [q]	X	X	X		X	X	X	X	X	X	X	X	X	
Enteral Nutrition Intake [r]	X	X	X		X	X	X	X	X	X	X	X	X	
Episodes of significant feeding intolerance		X	X	X	X	X	X	X						
Investigational Product Dosing			X----------→											

a. The final study day for purposes of the trial statistical analysis and Clinical Study Report (CSR) is Day 196. Subjects will be further followed long-term for safety to evaluate growth and nutritional intake as well as potential related adverse events through Day 728.

b. If a subject prematurely discontinues study medication, all reasonable measures will be taken to perform an Early Discontinuation from Study Medication Visit (Week 28 visit). This visit should include all procedures listed in the schedule of events Follow Up (Final Primary Study Visit) for Week 28 (Day 196). These procedures are necessary to complete subjects' records: physical examination, weight, body length, head circumference, vital signs, clinical laboratory test (only if clinically significant values were obtained at the Day 196, or if terminated earlier), anti-insulin antibodies, plasma citrulline (only if terminated before Day 168), gastric residuals (only if terminated before Day 84 and if part of SOC), parenteral nutrition intake, enteral nutrition intake, concomitant medication, adverse event, and updating of subject contact information.

c. If routine Standard of Care Visits are conducted this data, if collected will be entered as an unscheduled visit. The data to be included, if collected, is body weight, body length, head circumference, parenteral nutrition intake, enteral nutrition intake, re-hospitalizations and adverse events, If these routine SOC visits are not conducted with these procedures, these will not be considered missing visits. These data will include neurodevelopmental Bayley's score cognitive, language and motor domains at 2Y corrected age. After Week 28 (Day 196), a follow up phone call every 3 months as part of long-term follow up.

d. A complete physical examination at screening and on Day 84 (Week 12), Day 168 (Week 24), and Day 196 (Week 28). A limited problem-oriented physical examination will be performed on each visit between Week 12 (Day 84) and Week 24 (Day 168): Days 98, 112, 126, 140, and 154, if needed.

e. Any event that occurs before study drug dosing will be recorded as medical history, including but not limited to present medical conditions, concomitant non-drug treatments and hypersensitivity to drugs.

f. Infant's mother will be collected including age, medical history of any congenital abnormalities and complications during gestation or delivery.

g. Measurements will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature.

h. EKG is to be performed on at least a triplicate of heartbeats for all measurements and will be recorded at a speed of 25 mm/sec and an amplitude of 10 mm/mV. Computerized EKG analysis will include: heart rate, R-R interval, sinus rhythm, PR interval, QRS axis, and QRS duration. QT interval and QTcF will be calculated manually according to the Fridericia formula.

i. Hematology tests will include: white blood cells (WBC), red blood cells (RBC), hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelets, and mean platelet volume (MPV). Testing includes RBC morphology and reticulocyte count.

j. Serum chemistry will include serum alkaline phosphatase, triglyceride, ALT, AST, GGT, glucose, calcium, phosphorus, chloride, sodium, potassium, BUN, creatinine, total and direct bilirubin, albumin, total protein, amylase, bicarbonate/carbon dioxide (CO_2), uric acid, and lactate dehydrogenase (LDH). Additional serum chemistry testing will be weekly when patients are in the hospital and at study visits when patients are in a home care setting. Repeat testing at follow-up visit Week 28 (Day 196) will only be performed if abnormal clinically significant values are obtained at Week 24 (Day 168) visit.

k. Urinalysis will include: nitrite, Na, K, Ca, P, Protein, RBC, WBC, blood, glucose, ketone bodies, bilirubin (conjugated), urobilinogen, urine specific gravity, osmolarity, and pH

l. Safety laboratory evaluations (hematology, chemistry, urinalysis, coagulation profile) will be repeated at the follow-up visit only if abnormal clinically significant values were obtained at the Week 24 (Day 168) visit.
m. Sample will only be taken if terminated prior to Day 168.
n. Blood glucose monitoring will be performed pre-dose on Day 0 and on Days 1, 2 and 3, and twice a week for the rest of the treatment period while hospitalized. If subjects are discharged home the test would be done on each visit once a week. In addition, any abnormality in blood glucose levels that would be captured outside of these tests, would also be reported. This is a part of standard monitoring conducted on this population.
o. All concomitant medication given within 30 days prior to the time of consent through the Week 28 assessment. After week 28, only clinically significant medications that are used to treat potential adverse effects of NTRA-9620 will be recorded.
p. AE monitoring will be conducted throughout the study from Day 0 (initiation of dosing) until 28 days after the final primary study visit at Week 28 (Day 196). AEs considered to be treatment related by the Investigator will be documented at the post primary study completion on Week 52 (Days 364) and Week 104 (Day 728) to assess any potentially related adverse outcomes of treatment. Pre-treatment emergent events will be recorded on the medical history.
q. The total amount of parenteral nutrition administered for each feeding will be recorded in each study visit. The volume and caloric value of parenteral feeding will be entered into each study visit.
r. The total amount of enteral nutrition administered for each feeding during the day will be recorded. The volume and caloric value of enteral feeding will be entered into each study visit.

Appendix C: Common Terminology Criteria for Adverse Events

Version 4.03
Publication Date: 14 June 2010

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Appendix D: 2Y Corrected Age Neurodevelopmental Assessment

1. Major morbidities and evaluation of medical history
    - Cerebral palsy
    - Retinopathy of prematurity (ROP) that requires intervention
    - Deafness
    - Use of hearing aid
    - Use of glasses
    - Blindness

2. Bayley Scale of Infant and Toddler Development, third edition:
    - Cognitive domain composite score
    - Language domain composite score
    - Motor domain composite score
    - Social-emotional domain composite score
    - Adaptive behavior domain composite score

3. Neurodevelopment Disability Composite
    - Composite score of less than 70 or < 85 on any of the cognitive, language or motor domains of Bayley scale of infant and toddler development, third edition

4. Child Behavior Checklist total problem score

Appendix E: Expected conditions seen in neonatal SBS

Short bowel syndrome (SBS) is defined as the spectrum of malabsorption that occurs after resection of a major portion of the small intestine for congenital or acquired lesions. It is also defined as the need for prolonged parenteral nutrition secondary to intestinal failure after bowel resection. These patients suffer a multitude of complications secondary to long-term hospitalization and prolonged parenteral nutrition (Wales, 2005).

These complications can be broken down to the categories below; GI related complications, post-surgical complications, catheter-related complications, infections, expected laboratory abnormalities, kidney complications and TPN related issues.

All the complications below can be considered expected and common in neonatal SBS.

<u>GI-related complications</u>

- Stoma
  - Prolapse
  - Bleeding
  - Obstruction / stricture
  - Retraction
  - Polyps
- G-tube
  - site infections
  - malfunction
  - breakage
  - blockage
- Liver disease
  - Intestinal Failure Associated Liver Disease
  - PN Associated Liver Disease
  - Prematurity Associated Liver Disease
  - Coagulopathy
  - Cholestasis
- Nutritional deficiencies
  - Micronutrients and vitamin deficiencies
- Gall bladder
  - Colelithiasis
  - Biliary sludge
- Diarrhea
- Abdominal distention
- Nausea
- Vomiting
- Regurgitation / reflux
- Constipation
- Dehydration

Post- surgical complications
- Bowel obstruction
- Adhesion and stricture
- Bleeding
- Anastomotic ulcer
- Bowel perforation
- Intra-abdominal abscess

Catheter related complications
- Central line and catheter-related issues
    - site infections
    - malfunction
    - breakage
    - blockage

Infections
- central line infections
- sites infections
- upper-respiratory infections
- GI infections
- Fever
- Sepsis
- Bacterial overgrowth

Expected laboratory abnormalities
- Hypoglycemia related to sepsis, TPN weaning, advanced liver disease, prematurity
- Hyperglycaemia related to sepsis, TPN
- Anemia secondary to prematurity, nutrition, blood draws
- Blood electrolyte abnormalities i.e Calcium, Magnesium, Phosphorus
- Blood nutrition abnormalities i.e low albumin, low protein

Kidney complications
- Renal insufficiency
- Nephrocalcinosis
- Kidney stones / nephrolithiasis

TPN-related issues
- Fluid overload
- Hypoglycemia related to TPN weaning
- Hyperglycaemia related to TPN, glucose
- Liver disease
- Elevated amylase and lipase secondary to lipids
- Line infections

Prematurity complications

In addition, many SBS infants are premature infants, who suffer from additional complications that are common and expected in the population. These include:

- **Cardiac complications.** The most common heart problems premature babies experience are patent ductus arteriosus (PDA) and low blood pressure (hypotension). PDA is a persistent opening between two major blood vessels leading from the heart. While this heart defect often closes on its own, left untreated it can cause too much blood to flow through the heart and cause heart failure as well as other complications. Low blood pressure may require adjustments in intravenous fluids, medicines and sometimes blood transfusions.
- **Neuro problems.** The earlier a baby is born, the greater the risk of bleeding in the brain, known as an intraventricular hemorrhage. Most hemorrhages are mild and resolve with little short-term impact. But some babies may have larger brain bleeding which causes permanent brain injury.
- **Temperature control problems.** Premature babies can lose body heat rapidly; they don't have the stored body fat of a full-term infant and they can't generate enough heat to counteract what's lost through the surface of their bodies. If body temperature dips too low, hypothermia can result. Hypothermia in a preemie can lead to breathing problems and low blood sugar levels. In addition, a preemie may use up all of the energy gained from feedings just to stay warm, not to grow bigger. That's why smaller preemies require additional heat from a warmer or an incubator until they're larger and able to maintain body temperature without assistance.
- **Metabolism problems.** Premature babies often have problems with their metabolism. Some preemies may develop an abnormally low level of blood sugar (hypoglycemia). This can happen because preemies typically have smaller stores of glycogen (stored glucose) than do full-term babies and because preemies' immature livers have trouble converting stored glycogen into glucose.
- **Immune system problems.** An underdeveloped immune system, common in premature babies, can lead to infection. Infection in a premature baby can quickly spread to the bloodstream causing sepsis, a life-threatening complication.

Long term complications

- **Cerebral palsy.** Cerebral palsy is a disorder of movement, muscle tone or posture that can be caused by infection, inadequate blood flow or injury to a preemie's developing brain either during pregnancy or while the baby is still young and immature.
- **Impaired cognitive skills.** Premature babies are more likely to lag behind their full-term counterparts on various developmental milestones. Upon school age, a child who was born prematurely might be more likely to have learning disabilities.
- **Vision problems.** Premature infants may develop retinopathy of prematurity, a disease that occurs when blood vessels swell and overgrow in the light-sensitive layer of nerves at the back of the eye (retina). Sometimes the abnormal retinal vessels gradually scar the retina, pulling it out of position. When the retina is pulled away from the back of the eye, it's called retinal detachment, a condition that, if undetected, can impair vision and cause blindness.

- **Hearing problems.** Premature babies are at increased risk of some degree of hearing loss. All babies will have their hearing checked before going home.

- **Dental problems.** Preemies who have been critically ill are at increased risk of developing dental problems, such as delayed tooth eruption, tooth discoloration and improperly aligned teeth.

- **Behavioral and psychological problems.** Children who experienced premature birth may be more likely than full-term infants to have certain behavioral or psychological problems, such as attention-deficit/hyperactivity disorder (ADHD). However, more recent research suggests that — at least for late preterm babies — the risk of ADHD may be the same as it is for children who were born at full term.

- **Chronic health issues.** Premature babies are more likely to have chronic health issues — some of which may require hospital care — than are full-term infants. Infections, asthma and feeding problems are more likely to develop or persist. Premature infants are also at increased risk of sudden infant death syndrome (SIDS).