NCT02510560

Clinical Trial Protocol: FIT-04

Study Title:	**A Multi-center, Double-blind, Randomized, Three-Arm, Parallel-Group, Placebo Controlled Study to Assess the Efficacy and Safety of NTRA-2112 on Intestinal Malabsorption in Preterm Infants**
Protocol Number:	**FIT-04**
Protocol Version	**7**
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EudraCT Number	**2014-002624-28**
Sponsor:	**Nutrinia Ltd** **6 Ha-Khilazon Street** **Ramat-Gan, 5252270** **Israel**

CONFIDENTIAL

PROTOCOL SIGNATURE PAGE

Protocol Number: FIT-04 Protocol

[redacted]

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

Protocol Title: A Multi-center, Double-blind, Randomized, Three-Arm, Parallel group, Placebo Controlled Study to Assess the Efficacy and Safety of NTRA-2112 on Intestinal Malabsorption in Preterm Infants

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 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 Informed Consent Form is obtained on behalf of each subject prior to initiation of any study procedures.

I will promptly report (within 24 hours for any related SAEs and any SAE resulted in death, and within 48 hours for unrelated SAEs other than death) any Serious Adverse Event that occurs during the course of the study in accordance with the procedures described in Section 11 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 (no later than within one week after notification).

_____	_____	_____
Investigator's name	Investigator's Signature	Date

Site Name: _____

Site Address: _____

_____

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1. KEY TRIAL CONTACTS

Chief investigator	Prof. Hans Van Goudoever AMC Meibergdreef 9, 1105 AZ Amsterdam Zuid-Oost, Netherlands
Sponsor	[redacted]
Pharmacovigilance	[redacted]
Medical Monitor	[redacted]

2. SYNOPSIS

TITLE	A Multi-center, Double-blind, Randomized, Three-Arm, Parallel-Group, Placebo Controlled Study to Assess the Efficacy and Safety of NTRA-2112 on Intestinal Malabsorption in Preterm Infants

STUDY DESIGN	The study will evaluate the efficacy and safety of 2 dose levels of NTRA2112 on intestinal malabsorption in preterm infants as compared to placebo. NTRA-2112 is a powder of insulin formulation for reconstitution in breast milk, infant formula, normal and half-normal saline administered concomitantly with preterm infant's formula, donor breast milk, or own mother's breast milk for local gastrointestinal (GI) therapy. For both dose levels, the final obtained insulin concentration in the infant's nutrition is within physiological levels present in human breast colostrum milk and amniotic fluid during pregnancy. The study will enroll preterm infants weighing at least 500g born between 26 and up to 32 weeks of pregnancy who meet the inclusion and exclusion criteria. The effect on intestinal malabsorption will be evaluated by comparing the ability of preterm infants to achieve full enteral (EN) feeding for 3 consecutive days. Infants will be treated for 28 days or until hospital discharge, the earliest. Patients would receive NTRA-2112 Treatment A to obtain 400 µU/ml – equivalent dose of insulin or NTRA-2112 Treatment B to obtain 2000 µU/ml dose of insulin or placebo as calculated according to planned daily enteral intake. During the treatment period, infants will undergo daily evaluation of AEs, concomitant medication, nutrition, general growth, gastric residuals, and development progression. Infants will be evaluated at day of discharge. Follow-up visits will be performed at 3 months, 12 months and 24 months corrected age. Infants will be permitted infant formula, donor breast milk (DBM) and own mother's milk (OMM).
PRIMARY OBJECTIVE	To assess the efficacy of 2 doses of NTRA-2112 as compared to placebo on intestinal malabsorption in preterm infants as measured by the time to full enteral feeding*. *Defined as time to reach 3 consecutive days of EN feeding ≥150 ml/kg/day

SECONDARY OBJECTIVES	**Key secondary objective:** To assess the effect of 2 doses of NTRA-2112 compared to placebo on number of days to achieve discharge from hospital or readiness for discharge from hospital, whichever comes first. Readiness for discharge from the hospital is defined as achieving all of the below: • Infant weight ≥1800g • Stable body temperature* • Capable of oral intake (reached full enteral feeding and not dependent on PN) **Other secondary objectives:** To compare 2 doses of NTRA-2112 to placebo with respect to the following: 1. Growth parameters 2. Number and percentage of infants reaching full enteral feeding within 6, 8, and 10 days from initiation of treatment 3. Mean enteral feeding (ml/kg) on days 6, 8 and 10 from initiation of treatment **Exploratory secondary objective:** To compare 2 doses of NTRA-2112 to placebo with respect to the number of days to end gastric residuals over 2ml/measurement. *No external support needed
SAFETY OBJECTIVES	To compare the safety of 2 doses of NTRA-2112 to placebo in preterm infants.
STUDY DESIGN	Multi-center, double-blind, randomized, three-arm, parallel-group, placebo-controlled.
STUDY ARMS	**Treatment A:** NTRA-2112 TREATMENT A, 0.04 IU/g to obtain 400 µU/ml daily enteral intake administered with preterm infants' nutrition **Treatment B:** NTRA-2112 TREATMENT B, 0.2 IU/g to obtain 2000 µU/ml daily enteral intake administered with preterm infants' nutrition **Treatment C:** Placebo oral formulation administered with preterm infants' nutrition
DURATION OF TREATMENT	Up to 28 treatment days or discharge from the hospital, whichever occurs first.
DURATION OF FOLLOW-UP	24 months corrected age. Duration would be dependent on the gestational age at birth of the infant.
STUDY POPULATION	Pre-term infants 26-32 weeks gestation and birth weight ≥ 500g, up to day 5 of life

INCLUSION CRITERIA	1. Male or female pre-term infant 26 and up to 32 weeks gestation (32 weeks + 0 day maximum). Gestational age matching (±2 weeks) between maternal dates and/or early antenatal ultrasound * 2. Birth weight ≥ 500g 3. Singleton or twin birth 4. Postnatal age up through and including Day 5 (up to 120 hours post birth) 5. Fraction of inspired oxygen ≤ 0.60 at enrolment 6. Subjects must demonstrate cardiovascular stability at time of enrolment and would be considered unstable if they require >40% oxygen with blood pressure support and the need for umbilical artery cauterization 7. Infant is able to tolerate enteral feed 8. Infant is expected to wean off parenteral nutrition (PN) at the primary hospital 9. Informed consent form signed by parents or legal guardian 10. In the Investigator's opinion, the infant is able to comply with the study procedures and sufficiently stable to partake in the trial to completion * If both exist and difference > 2 weeks, based on early antenatal ultrasound
EXCLUSION CRITERIA	1. Complete enteral feeding 2. Major congenital malformation (e.g., infants with genetic, metabolic, and/or endocrine disorder diagnosed before enrolment) 3. High index of suspicion of infection before enrolment** 4. Intra-uterine growth retardation (IUGR) defined as either weight for gestational age less than the third percentile or less than the 10th percentile with Doppler abnormalities in utero ***. 5. Confirmed necrotizing enterocolitis (NEC) 6. Maternal diabetes (Type I/II or gestational) requiring insulin during pregnancy or in mothers past medical history. 7. Hyperinsulinemia requiring glucose administration of more than 12mg/kg/min at randomization. 8. Any systemic insulin administration at randomization. 9. Nothing per os (NPO) for any reason at study entry. 10. Heart and chest compression or any resuscitation drugs given to the infant during delivery 11. Subjects at risk for significant GI complications such as twin-totwin transfusion syndrome (TTTS) or monochorionic monoamniotic twins. 12. Participation in another interventional clinical study that may interfere with the results of this trial **Defined as positive blood culture, Leukocytosis >30,000 and Leukopenia <4,000. ***According to Fenton preterm growth chart (see Appendix D). If no Doppler in utero is available for infants with IUGR between third and 10'th percentile of Fenton preterm growth charts, infant is eligible to participate in the study.

SAMPLE SIZE	The study will be comprised of approximately 150 infants per group or 450 infants in all. Each infant will be assigned one of the two doses of the study medication (NTRA-2112) or placebo. If both members of a pair of twins are eligible for the study, both twins will receive the same randomization assignment, but only the first born of the two twins will be part of the analysed cohort for primary efficacy analysis. Assuming up to 30% of the cohort are twin pairs, up to approximately 530 infants are expected to be treated.
PRIMARY ENDPOINT	Numbers of days to achieve full enteral feeding, defined as the ability of the preterm infant to achieve enteral feeding at least 150 ml/kg/day for 3 consecutive days.
SECONDARY ENDPOINTS	**Key secondary endpoint:** Number of days to discharge from the hospital or readiness-fordischarge from hospital, whichever occurs first Readiness-for-discharge is defined as meeting **all** the following criteria: 1. Infant weight ≥ 1800g 2. Stable body temperature 3. Capable of oral feeding (reached full enteral feeding and not dependent on PN) **Additional secondary endpoints:** 4. Growth velocity (g/kg/day) 5. Change in Z-score at 6, 8 and 10 days from initiation of treatment 6. Gain in body weight during the treatment and follow-up periods 7. Number and percentage of infants reaching full enteral feeding within 6, 8, and 10 days from initiation of treatment. 8. Total number of days receiving parenteral nutrition 9. Number of days to 120Kcal/kg/day

	10. Number of days to wean-off PN[1] **Exploratory secondary endpoints:** 11. Number of days to end gastric residuals over 2 ml/measurement according to the feeding protocol (Appendix A). 12. Gain in length during the treatment period and follow up period (long term follow-up period) 13. Gain in head circumference during the treatment period and follow up period (long term follow-up period) 14. Percent enteral feedings from total nutrition 15. Percent parenteral nutrition from total nutrition

[1] Wean off PN is defined as complete cessation of PN support.

PROCEDURES	The study physician will follow a recommended feeding protocol (Appendix A). The final feeding scheme is subject to the physician's clinical evaluation. **Screening procedures** After the parent or guardian signs the Informed Consent Form (ICF), all inclusion/exclusion criteria will be checked for eligibility. A complete medical history and physical examination will be performed. Within 24 hours of the screening procedures, eligible infants will be randomly assigned to one of the three treatment groups. **Treatment procedure** During the treatment period, the infants will receive study medication with their enteral feeding (own mother's milk (OMM), donor breast milk (DBM), or infant formula) until discharge from the hospital or up to 28 days, whichever occurs first. The infant will not be treated more than 28 days. During the 28-day treatment period, the investigator will evaluate the infant for discharge or readiness for discharge from hospital, whichever occurs first. The powder will be administered preferably with all daily enteral feedings, but at least four times each day at enteral feedings.Commencement of the treatment period for infants who are fed solely on OMM should not begin within the first 72 hours post birth. **Follow up period:** The infants will return to the clinical site for a follow-up visit at 3 months, 12 months, and 24 months corrected age.
SAFETY EVALUATION	Baseline safety assessment will be performed during the screening period and throughout the study (see Table 1): 1. Physical examination (PE) 2. Blood chemistry and haematology 3. Vital signs During the treatment period, adverse events (AEs), PE, and vital signs will be assessed and recorded in the source documentation and electronic case report form (eCRF). These would include episodes of NEC, sepsis, meningitis, hypoglycemia and death. Monitoring of glucose levels will be performed during the treatment period.
NUMBER OF CENTERS	Approximately up to 40 sites worldwide (European countries, United States of America, Israel, and possibly other countries).

3. DEFINITIONS

Cardiovascular stability	Normal pulse, blood pressure, and breath; clinically not significant cardiovascular status as determined by the PI
Day (24 hours)	From 00:00/12:00am until 23:59/11:59pm
Enteral feeding (EN)	A method of nutrition delivery where fluid is given directly into the gastrointestinal tract.
Full enteral feeding	The infant consumes at least 150 ml/Kg/day of enteral feeding for 3 consecutive days.
Full term pregnancy (for calculating corrected age)	40 weeks gestation should be considered a full term pregnancy.
Gastric residual	Any leftover nutrition in the stomach that was not digested or absorbed by the body. In hospitals where it is captured as standard of care, when the infant is treated with an orogastric tube, before every meal the nurse checks if any residuals were not absorbed and left in the stomach from the prior meal.
Gestational diabetes	Diagnosis glucose values for gestational diabetes according to WHO: Oral glucose tolerance test (OGTT) 75 g • Fasting: 126 mg/dl • Two hours: 140 mg/dl
High index of suspicion for infection	Occurrence of one or more of the following conditions: (1) Positive blood culture; (2) Leukocytosis > 30,000 (when accompanied by a negative culture result); (3) Leukopenia < 4,000
Hyperglycemia	Blood glucose level above 150 mg/dl
Hypoglycemia	Blood glucose level below 40 mg/dl
Intra-uterine growth retardation (IUGR)	Weight for gestational age less than p3 or less than p10 with Doppler abnormalities in utero.
Necrotizing Enterocolitis (NEC)	NEC is characterized by the sudden onset of gastrointestinal distress that may include symptoms such as vomiting, abdominal distention, bloody stools, or dilated loops of bowel that leads to cessation of enteral feedings.
Parenteral nutrition (PN)	Nutrition provided intravenously.
Total parenteral nutrition (TPN)	TPN is a way of supplying all the nutritional needs of the body by bypassing the digestive system and dripping nutrient solution directly into a central vein.
Trophic feeding	Feeding of small quantities.

4. ABBREVIATIONS

ADL	Activities of Daily Living
AE	Adverse event
AR	Adverse reaction
BPD	Bronchopulmonary dysplasia
BW	Birth weight
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CRO	Contract Research Organisation
CA	Competent Authority
CP	Cerebral Palsy
CT	Clinical trials
CTCAE	Common Terminology Criteria for Adverse Events
DBM	Donor breast milk
DS	Dextrose stick
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EN	Enteral nutrition
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEF	Full Enteral Feeding
GA	Gestational Age
GCP	Good Clinical Practice
GI	Gastrointestinal
HS- PDA	Hemodynamic Significant Patient Ductus Arteriosus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committees
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IUGR	Intra-uterine growth retardation
MedDRA	Medical Dictionary for Regulatory Activities
ND	Not done
NEC	Necrotizing enterocolitis
NFE	Number of days to full enteral feeding
NGT	Nasogastric tube

NICU	Neonatal intensive care unit
NPO	Nothing per os
NRD	Number of days to discharge from the hospital
OGT	Orogastric tube
OGTT	Oral glucose tolerance test
OMM	Own mothers milk
PDA	Patent ductus arteriosus
PE	Physical examination
PI	Principal Investigator
PN	Parenteral nutrition
PP	Per protocol
RDS	Respiratory Distress Syndrome
ROP	Retinopathy of Prematurity
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
TBV	Total Blood Volume
TMF	Trial Master File
TPN	Total parenteral nutrition
TTTS	Twin-to-twin transfusion syndrome
WHO	World Health Organization

5. BACKGROUND AND RATIONALE

5.1. General Introduction

Preterm infants have an under-developed gastrointestinal (GI) tract due to an abrupt disruption of pregnancy. During an essential but short timeframe, preterm infants can compensate for their 3rd trimester lost growth and development, at which time they are at high risk for intestinal malabsorption due to their malfunctioning GI tract and other complications. That leads preterm infants to dependency on prolonged parenteral nutrition support (1-3).

Promoting EN intake at that sensitive time frame leads to GI maturation and reduces dependence on parenteral nutrition (PN) with its associated morbidities and complications. Nutrients consumed enterally are better absorbed, enhancing vital organ development, improving infants' growth and development during the short window of opportunity for compensating lost third trimester growth (3).

Preterm infants who are born 29 to 32 weeks of gestational age find it very difficult to coordinate suckling, swallowing, and breathing regularly. Therefore, they are fed mostly by nasogastric tube (NGT) and as a result of their under-developed GI they are placed on PN for a prolonged period of time to avoid complications and growth retardation. Smaller preemies cannot perform suckling at all. A meta-analysis of 21 articles regarding PN in preterm infants showed that the relevant average gestational age for PN is below 32 weeks. Preemies 33 to 36 weeks can usually feed for themselves (2).

Insulin is one of the biologically active factors in breast milk. During the first days of life, colostrum mother's milk contains higher levels of insulin and other bioactive components than mature maternal milk does. Accumulating evidence indicates that insulin determines important physiological effects on intestinal growth, cell maturation, and enzyme expression in several mammalian species (4, 5).

The perinatal period is critical for human development. The brain of preterm infants, who are born generally with weight of less than 1,500g, is particularly vulnerable to under-nutrition. Enteral nutrition is of major importance for the growth and the development of the GI tract, which depends on the amount and composition of feeds. Thus, the goal in preterm infants is fast transition to EN and enable full enteral feeding as soon as possible (3).

Term infants undergo rapid growth in the third trimester of pregnancy, receiving nutrition through the placenta and swallowed amniotic fluid with no need to expend calories for temperature regulation or gas exchange. Preterm infants miss out on much or all of the third trimester and thus have higher nutritional requirements on a per kilogram basis than term infants. Human milk nourishes the term infant who can tolerate large fluid volumes, whereas preterm infants are less tolerant of high fluid volumes (3).

For these reasons, human milk usually requires fortification for nutritional adequacy in preterm infants. Human milk varies widely in the energy and protein content as well as in other key nutrients. Thus, supplementing human milk is a current practice at NICUs.

A newborn infant's GI tract is naturally exposed to insulin by consuming own mother's milk present mainly in colostrum after birth. Importantly, *in utero* the GI tract is also exposed to insulin levels present in the amniotic fluid consumed by the fetus generating a constant flux of insulin stimulating the GI tract. As of week 26 gestational age, when skin keratinization is achieved (6), the fetus is exposed to the amniotic fluid ingredients such as insulin mainly through the GI tract at ~450 ml of amniotic fluid a day.

Insulin levels in own mother's milk drop from 1,000-2500 µU/ml to a ~ 50-90 µU/ml after the colostrum period (48 hours post-delivery); levels are not significantly influenced by gestational age. Thus, just as human milk is supplemented with proteins and other key nutrients for preterm infants, Nutrinia proposes to supplement human milk with insulin.

Own mother's milk contains nutritional ingredients as well as various peptides such as insulin. Observations on lactating dams and suckling rats have shown that milk-borne insulin is biologically active, and that immature enterocytes have an increased responsiveness to insulin (7). Shehadeh et al. have shown that human milk contains high concentrations of insulin and that insulin is hardly detectable in infant formulas (8, 9).

Insulin stimulates intestinal epithelial cell proliferation, and ileal lactase activity is increased when porcine insulin is added to newborn piglets' feedings (4, 10). Shulman, et al. demonstrated that enteral insulin administration may be of benefit in reducing feeding intolerance in preterm infants (11). Thus, orally administered insulin is expected to demonstrate a beneficial influence on gut development.

The NTRA-2112 powder is mixed with saline, preterm infant's formula, own mother's breast milk or pasteurized breast milk (donor breast milk) for enteral administration. Natural insulin activity level is lost in pasteurized breast milk and absent in formula. The final insulin concentration obtained with NTRA-2112 in the infant's nutrition is physiological and within the range of known local gut exposure to insulin levels in amniotic fluid and own mother's milk.

During the past decade neonatologists have made major efforts to reduce feeding intolerance and time to full enteral nutrition because of the importance of reducing complications and enhancing development of vital organs in preterm infants. Major efforts include the introduction of donor breast milk (DBM) as well as improvement of preterm infant formula composition and other supplementations to mother's milk. NTRA-2112 is aimed at further improving preterm infant progression to enteral autonomy, reducing risks and improving infant development in this crucial window of opportunity.

Preliminary data in preterm infants receiving 4 IU/kg/day insulin enterally from 4 to 28 days of age, suggest that enteral insulin administration increases lactase activity and may be of benefit in reducing feeding intolerance without inducing hypoglycaemia or other adverse effects (11).

The administration of insulin to preterm infants' enteral nutrition proposed in this study will allow assessment of the influence of insulin on gastrointestinal maturation and on blood levels of lipids and glucose.

As described in the following paragraphs, administration of oral insulin to preterm infants, low birth weight infants, humans and animals, at concentrations up to 1,000 times higher than those proposed in this study, demonstrated the safety of oral insulin administration.

Nutrinia conducted a Phase I safety study in 11 low birth weight healthy infants in two centers in Israel (INFOR I). All eleven received NTRA-2112 for 4 months, as in the proposed study, administered within infant nutrition. No treatment related adverse events were observed in any of the 11 infants. The consumption of insulin did not cause hypoglecemia and did not stimulate the production of anti-insulin antibodies.

Nutrinia also conducted an efficacy Phase I study designed as double-blind, randomized, placebocontrolled trial to compare NTRA-2112 to placebo on GI development when added to infants' nutrition (infant formula) (INFOSUP I). The primary evaluation of gastrointestinal maturation was the ability of the preterm infants to achieve full enteral feeding (150ml/kg/day). Other objectives included assessment of whether NTRA-2112 led to reduction in the number of days to discharge from the neonatal ward, measurements of weight gain, and assessment of safety. The insulin concentration administered for 28 days in the study was within the insulin concentration range present in low range maternal colostrum (400 µU/ml) and as proposed for the current study. The study comprised eight preterm infants, gestational age: 26-33 weeks

BW: > 750g were recruited during the study. The gestational age was 27-31 weeks for the control group and 30-31 for the treatment group. Infants in the treatment group reached full enteral feeding earlier, gained more weight during the treatment period than the control group, were discharged on average earlier, and were free of central line nutrition (TPN) earlier.

A Phase II, multi-center, double-blind, randomized controlled clinical trial is currently being finalized in Israel (INFOSUP II). The study's objective was to evaluate further the effect of NTRA-2112 on preterm infants' gastrointestinal maturation. Inclusion criteria included gestational age between 26 and 33 weeks and birth weight ≥ 750g. NTRA-2112 effect on GI development is evaluated by number of days to reach full enteral feeds (150 ml/kg/day). As in the proposed study, NTRA-2112 0.04 IU/g is used to prepare a 400 µU/ml solution of insulin for dosing over a 28-day period. The stock solution is added to standard formula or milk to administer to the infant. The analysed data constitute about 45% (n=33) of the planned sample size. The data set includes twins (10 pairs) and singleton births (6 in the control group and 7 in the treatment group). An interim study analysis demonstrated shorter time to reach full enteral feeding as compared to placebo as well as benefit on other efficacy parameters related to infants' growth. Interim analysis was performed for the group and separately for twins and singletons. Mixed model analysis showed no effect of birth (singleton or multiple) on outcome. No drug related adverse events have been reported in this study.

5.2. Rationale and Justification for the Study

Knowledge of the risks caused by preterm infants' underdeveloped GI tract is described above. Nutrinia developed NTRA-2112 to fulfil the important role of enhancing the preterm infant's capacity for absorption in the GI tract, and reduce intestinal intolerance and malabsorption, therefore reducing dependence on parenteral nutritional support, improving development of vital organs, and reducing catheter-associated bloodstream infections and other associated complications.

A newborn infant's GI tract is naturally exposed to insulin by consuming own mother's milk present mainly in colostrum after birth. Importantly, in utero the GI tract is also exposed to insulin levels present in the amniotic fluid consumed by the fetus generating a constant flux of insulin stimulating the GI tract. As of week 26 gestational age, when skin keratinization is achieved, the fetus is exposed to the amniotic fluid ingredients such as insulin mainly through the GI tract at ~450 ml of amniotic fluid a day (6).

Thus, the choice of therapeutic dose levels for preterm infants should compensate for both intrauterine and extrauterine insulin exposure. Moreover, average colostrum insulin content suffices for stimulation of a term infant's GI for enteral/oral feeding, while the preterm infant GI tissue takes several weeks to compensate for the disruption of pregnancy and critical intrauterine GI development occurring at the last trimester of pregnancy (Investigator's Brochure Section 1.6).

Although human milk is recommended for preterm infants, it does not provide optimal nutrition by itself. The growth and neurodevelopmental needs of the preterm infants are best met by appropriate fortification of enteral nutrition including own mother's milk. Moreover, mothers of preterm infants produce only a few drops of colostrum at each expression for the first 24-48 hours after birth; consequently, OMM is a poor provider of essential nutrients and bioactive proteins (such as insulin).

Roughly three days after delivery, the insulin levels in OMM drop from 1,000-2500 µU/ml to ~50µU/ml. Thus, similar to way human milk is supplemented with proteins and other key nutrients for preterm infants, Nutrinia proposes to supplement human milk with insulin. Infant's formula, DBM, or a mix of these sources needs to be compensated, as natural Insulin activity level is lost in pasteurized breast milk and absent in formula.

Two dose levels will be assessed versus placebo:

* NTRA-2112 Dose level 1[2]: 0.04 IU/g powder formulation (0.5-g stick pack) is reconstituted to achieve 400 µU/ml of planned daily enteral feeds

* NTRA-2112 Dose level 2[3]: 0.2 IU/g powder formulation (0.5-g stick pack) is reconstituted to achieve 2000 µU/ml of planned daily enteral feeds

The choice of the two dose levels is based on safety profiles and evidence of efficacy demonstrated in five independent clinical trials and several non-clinical studies.

The dose levels, were selected within the range of known local gut exposure to insulin levels in amniotic fluid and own mother's milk to compensate for physiological intestinal insulin exposure. Both dose levels have been demonstrated safe in preclinical trials. NTRA-2112 Dose level 1 was assessed in previous clinical studies and was found to be safe and efficacious in the proposed patient population.

Nutrinia and its scientific advisors have conducted clinical trials in preterm infants, small for gestational age infants, and short bowel infants and children with three dose levels (investigator's Brochure Section 4) of orally administered insulin in the course of five separate clinical trials. In these studies, the dose of insulin ranged from 0.01 U/kg/day to 4.0 U/kg/day. These doses correspond to an equivalent dose of 90 to 4,000 µU/ml. As previously described these doses are equivalent or higher than the current target dose of NTRA-2112 which would correspond to an exposure or 400 or 2000 µU/ml. Further supporting the dose selection is the duration of treatment (28 days) in 4 of the 5 studies. The duration in study INFOR 1 was 4 months, while the other clinical trials durations were 28 days. These durations, coupled with the dose described above, support the safe administration of NTRA-2112.

In summary, the accumulated clinical safety and efficacy results in preterm infants dosed with similar and significantly higher orally-administered insulin levels as compared to the current proposed study strongly support further clinical development of NTRA-2112 as a path to reduce intestinal malabsorption in preterm infants.

[2] NTRA-2112 dose level 1 was used in the Phase I & II trials with NTRA-2112 equivalent to 0.04 U/kg/day (based on 1 kg body weight and 100 ml daily enteral nutrition).

[3] equivalent to 0.2 U/kg/day (based on 1 kg body weight and 100 ml daily enteral nutrition)

6. STUDY OBJECTIVES

6.1. Primary Objective

To assess the efficacy of 2 doses of NTRA-2112 as compared to placebo on intestinal malabsorption in preterm infants as measured by the time to full enteral feeding.

Note: days to full enteral feeding will be regarded as the time to 3 consecutive days consumption of at least 150 ml/kg/day enteral feeding.

6.2. Secondary Objectives

Key secondary objective:

To assess the effect of 2 doses of NTRA-2112 compared to placebo on the number of days to achieve discharge from hospital or readiness for discharge, whichever occurs first.

Readiness for discharge from hospital defined as achieving all of the below:

1. Infant weight ≥ 1800g
2. Stable body temperature
3. Capable of oral feeding (reached full enteral feeding and not dependent on PN).

Other secondary objectives:

To compare 2 doses of NTRA-2112 to placebo with respect to the following:

4. Growth parameters (g/kg/day)
5. Change in Z-score at 6, 8 and 10 days from initiation of treatment
6. Gain in body weight during the treatment and follow-up periods
7. Number and percentage of infants reaching full enteral feeding within 6, 8, and 10 days from initiation of treatment
8. Total number of days receiving parenteral nutrition
9. Number of days to 120Kcal/kg/day
10. Number of days to wean-off PN[4]

Exploratory secondary objective:

1. Number of days to end gastric residuals over 2 ml/measurement according to the feeding protocol (Appendix A).

[4] Wean off PN is defined as complete cessation of PN support.

6.3. Safety Objective

To compare 2 doses of NTRA-2112 to placebo in preterm infants.

7. STUDY DESIGN

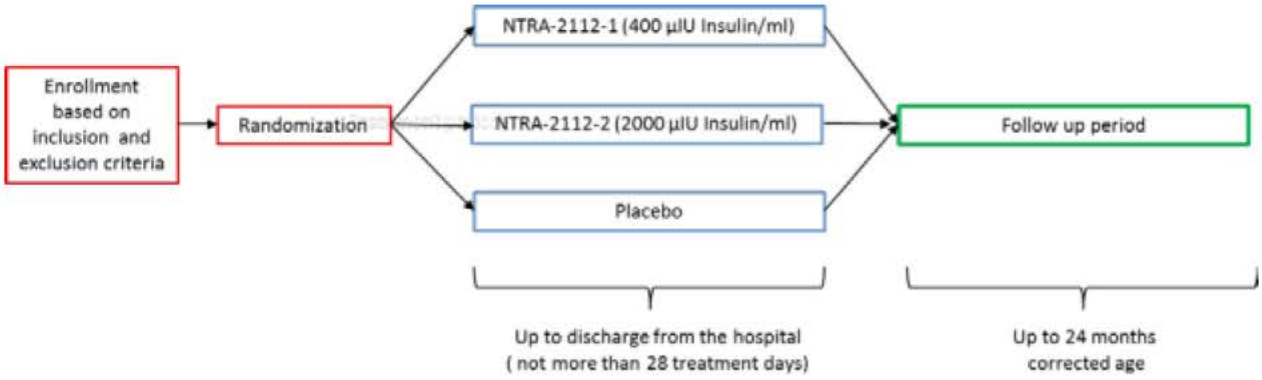
The study is designed as a multi-center, double-blind, randomized, three-arm, parallel-group, placebocontrolled study to assess the efficacy and safety of NTRA-2112.

Infants will be enrolled within 5 days from birth (at least 6 hours post birth and up to 120 hours post birth) and will be treated for 28 days or until hospital discharge (whichever comes first). The study also includes a follow-up period up to 24 months corrected age. Figure 1 and Appendix B includes a detailed study flow diagram.

Full enteral feeding is defined as reaching 3 consecutive days in which the infant consumed at least 150 ml/kg/day of enteral nutrition.

Enrolled infants will be under supervision at a NICU.

Figure 1: Study Flow Diagram



8. STUDY POPULATION

8.1. Study Participants

Infants up to 5 days old (up to 120 hours post birth), born between 26 and up to 32 weeks of pregnancy, weighing at least 500g at birth, and who meet enrolment criteria are eligible for this study. Their parents or legal guardian will be asked to sign an informed consent form (ICF) for the study. Only single or twin births will be eligible, not triplets or higher. Upon parents' signature of the informed consent form, the infants will be screened for eligibility. Once eligibility has been confirmed, the infant will randomly be assigned to one of three treatment groups: low dose or high dose of study medication (treatment A & B) or placebo (treatment C). The study drug (NTRA-2112 or placebo) will be administered with the infant's enteral feeds.

Eligible infants who are enrolled into the study will be assigned a treatment group randomly. Eligible twins will automatically be assigned to the same treatment group.

All enrolled infants, including both members of a pair twins, should undergo all procedures described in this and the following section.

Pre-term infants will be treated at a NICU and will be under constant supervision during the hospitalization period until discharge home.

8.2. Inclusion Criteria

1. Male or female pre-term infants 26 and up to 32 weeks gestation (32 weeks + 0 day maximum).
   Gestational age matching (±2 weeks) between maternal dates and/or early antenatal ultrasound*.
2. Birth weight ≥ 500g.
3. Singleton, or twin birth.
4. Postnatal age up through and including Day 5 (up to 120 hours post birth).
5. Fraction of inspired oxygen ≤ 0.60 at enrolment.
6. Subjects must demonstrate cardiovascular stability at time of enrolment and would be considered unstable if they require >40% oxygen with blood pressure support and the need for umbilical artery cauterization.
7. Infant is able to tolerate enteral feed.
8. Infant is expected to wean off PN at the primary hospital.
9. Informed consent form (ICF) signed by parents or legal guardian.
10. In the Investigator's opinion, the infant is able to comply with the study procedures and sufficiently stable to partake in the trial as required until trial completion. * If both exist and difference > 2 weeks, based on early antenatal ultrasound

8.3. Exclusion Criteria

1. Complete enteral feeding.
2. Major congenital malformation (e.g., Infants with genetic, metabolic, and/or endocrine disorder diagnosed before enrolment).
3. High index of suspicion of infection before enrolment**
4. Intra-uterine growth retardation (IUGR) defined as either weight for gestational age less than the third percentile or less than the 10'th percentile with Doppler abnormalities in utero***.
5. Confirmed necrotizing enterocolitis (NEC).[5]
6. Maternal diabetes (Type I/II or gestational) requiring insulin during pregnancy or in mothers past medical history.
7. Hyperinsulinemia requiring glucose administration of more than 12mg/kg/min at randomization.
8. Any systemic insulin administration at randomization.

[5] NEC is characterized by the sudden onset of gastrointestinal distress that may include symptoms such as vomiting, abdominal distention, bloody stools, or dilated loops of bowel that leads to cessation of enteral feedings.

9. Nothing per os (NPO) for any reason at the study entry.
10. Heart and chest compression or any resuscitation drugs given to the infant during delivery.
11. Subjects at risk for significant GI complications such as twin-to-twin transfusion syndrome (TTTS) or monochorionic monoamniotic twins.

12. Participation in another interventional clinical study that may interfere with the results of this trial

**Defined as positive blood culture, Leukocytosis >30,000 and Leukopenia <4,000.

***According to Fenton preterm growth chart (see Appendix D). If no Doppler in utero is available for infants with IUGR between third and 10'th percentile of Fenton preterm growth charts, infant is eligible to participate in the study.

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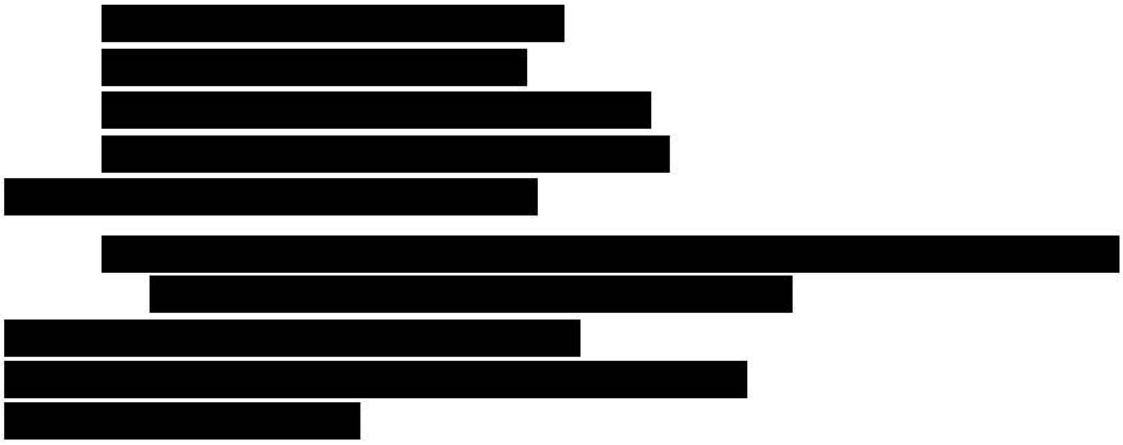

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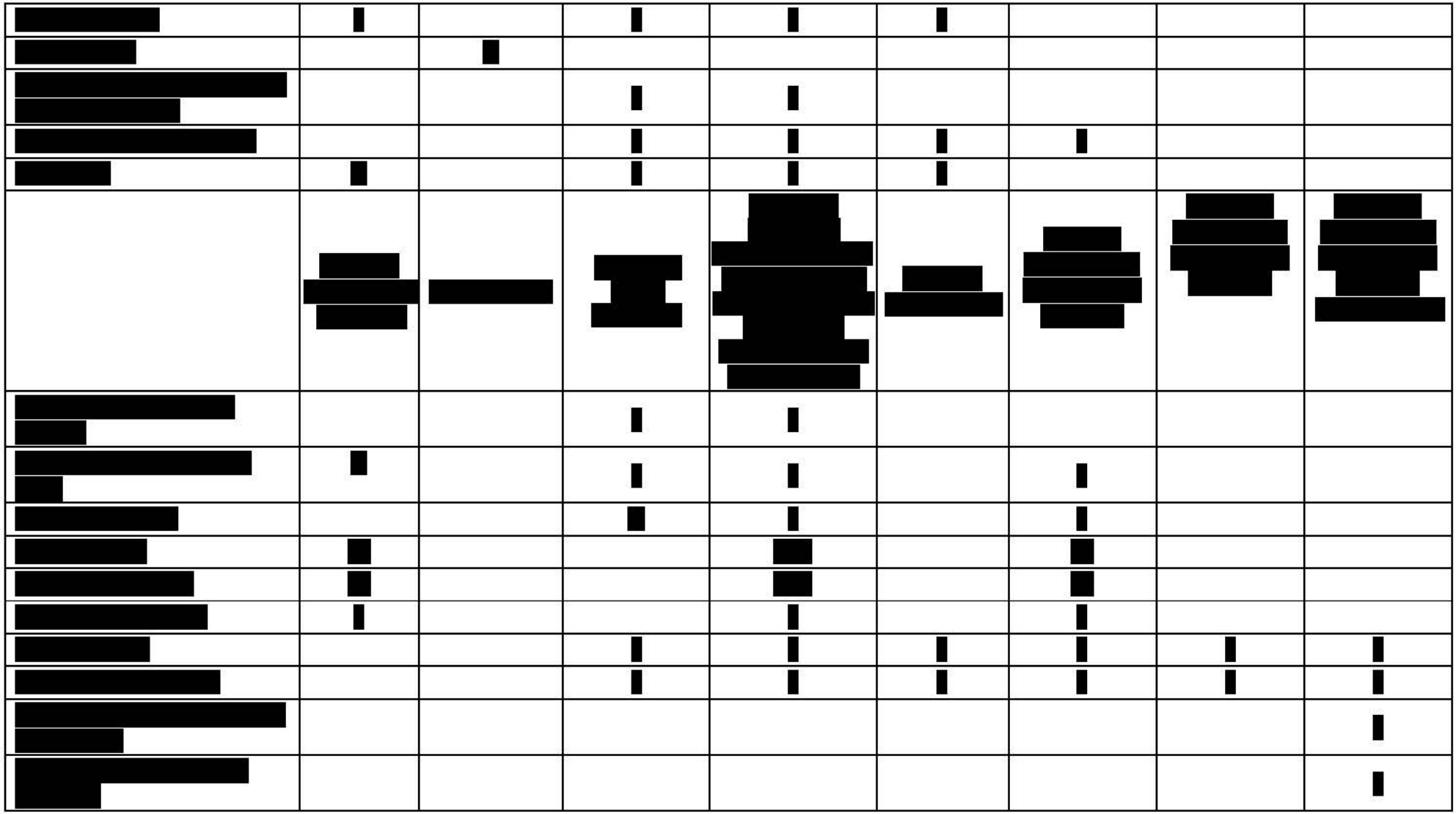

9.5. Discontinuation/Withdrawal of Infants

9.5.1. Discontinuation Criteria

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 11.3) that the investigator considers related to study medication and not attributable to the underlying disease or considered common events listed in Appendix E.
- 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 below in this section.

The parent or guardian has the right to withdraw the infant from the trial at any time. In addition, the Investigator may discontinue an infant from the trial at any time if the Investigator considers it necessary for any reason including:

- Non-compliance of the subject's parent(s) or legal guardian(s) with study procedures as evaluated by the Investigator and/or Sponsor as warranting subject's discontinuation from study medication
- An adverse event requiring discontinuation of the trial medication or resulting in inability to continue to comply with trial procedures
- Other reasons regarded by the Investigator as warranting subject's discontinuation from study medication
- Parental withdrawal of consent
- Major congenital malformation – a genetic, metabolic, or endocrine disorder diagnosed after enrolment that is known to be congenital

The reason for withdrawal will be recorded in the source documentation and the eCRF. Parents and guardians, if willing, will be encouraged to return to the site for safety follow-up visits per the study schedule in the event of withdrawal.

If withdrawal of the infant is due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

- If the event causing the withdrawal occurred within the first 28 days of the study and while consent is still obtained, the infant will stop consuming the study medication; however, the infant will be followed up and the data will be recorded for all remaining study visits up to final study visit at 24 months corrected age.

- AEs considered related to the trial medication as judged by a medically qualified investigator and all SAEs (related and unrelated to trial medication) will be followed until resolution. Resolution is defined as the return to baseline status or stabilization of the condition when investigator deems further observations or examinations no longer required as medically indicated.

- If the event causing the withdrawal occurred between days 28 and the final study visit (follow-up visit), and the event was designated as not product-related, the study withdrawal will be recorded with no additional follow up.

9.5.2. Premature Study Termination

The study subjects are expected to experience many adverse events, including severe adverse events related to premature birth, invasive surgery, or other underlying conditions including potential to develop NEC. NEC is characterized by the sudden onset of gastrointestinal distress that may include symptoms such as vomiting, abdominal distention, bloody stools, or dilated loops of bowel that leads to cessation of enteral feedings. Therefore, all safety concerns potentially leading to study termination will be referred to the Data Monitoring Committee (DMC), 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 DMC chairman for review, who may decide that the events warrant a full DMC review. The DMC will review these events unblinded to fully evaluate the potential risk to subjects in this trial. Given this is a blinded trial, the DMC 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 DMC 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 DMC 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.

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

Collective Events:

The Medical Monitor and DMC will review aggregate safety data in an ongoing manner, at DMC 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 DMC for further evaluation. The DMC will receive unblinded safety data summaries from an independent statistician that is assigned to prepare the unblinded study reports for all subjects at each DMC meeting. The DMC 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 the active arms and/or placebo, and that may be attributable to study medication based on the mechanism of action of the drug, the DMC 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.

10. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

10.1. IMP Description

The study medications include an active formulation designated NTRA-2112 with human insulin in 2 different doses as the active pharmaceutical ingredient and a placebo formulation. The placebo formulation consists of the same inactive ingredients as NTRA-2112.

NTRA-2112 is incorporated into preterm infant's formula, own mother's milk and pasteurized breast milk (donor breast milk) for enteral administration. NTRA-2112 may also be reconstituted with normal (0.9% NaCl) or half normal saline (0.45% NaCl) for enteral administration, as described in the pharmacy manual. Natural insulin activity level is lost in pasteurized breast milk and absent in formula. The final insulin concentration obtained with NTRA-2112 in the infant's nutrition is physiological and within the range present in human breast milk and colostrum.

NTRA-2112

[redacted]

[redacted]

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[redacted]

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Dosage form:

Powder for oral solution added to own mother's milk, pasteurized breast milk, infant's formula.

10.2. Presentation and Storage Conditions

0.5g powder for oral solution in stick packs. The stick packs should be stored at room temperature in a cool and dry place (further instructions are available in the Pharmacy Manual).

10.3. Method of Administration

The NTRA-2112 and placebo powder will be administered for 28 days or until discharge. The product is provided in 0.5g stick packs.

NTRA-2112 TREATMENT A, 0.04 IU/g to obtain 400 µU/ml Insulin; NTRA-2112 TREATMENT B, 0.2 IU/g to obtain 2000 µU/ml insulin; NTRA-2112 mimics the insulin levels in human breast milk and amniotic fluid in-utero. NTRA-2112 may be reconstituted with normal saline as described in the pharmacy manual.

The powder will be administered preferably with all daily enteral feedings, but at least four times each day at enteral feedings according to the study definitions and enteral feeding protocol only (see Appendix A).

10.4. Concomitant Therapy, Restrictions and Rescue Treatment

There are no limitations or restrictions on concomitant therapy.

Rescue medication will be administered according to the Investigator's discretion.

In case of overdose, the glucose level should be monitored carefully for 12 hours and treated according to Investigator's discretion.

10.5. Treatment Compliance

The compliance check will be based on the number of meals to which NTRA-2112 or placebo was added (i.e., actually taken) to the infant's planned daily enteral nutrition. Missed doses should not be replaced or added.

Compliance should be emphasised; however, randomized infants will not be discontinued for lack of compliance.

Full or partial dose interruptions are permitted at the Investigator's discretion; interruptions should last no longer than 3 consecutive days.

10.6. Packaging and Labelling

The IMP (NTRA-2112 and Placebo) is packed in stick packs. Secondary carton packaging is provided with 200 stick packs for each infant, which generally is the sufficient amount of stick packs for the entire treatment period. Each infant will have a designated carton package of study medication. In case of a need, an unscheduled re-supply of additional IMP kit can be assigned to the infant.

All labelling complies with Volume 4. Good Manufacturing Practices, Annex 13. Manufacture of investigational medicinal products, July 2010.

10.7. Storage of Study Medication

Study medication will be stored at room temperature in the pharmacy or in the neonatal intensive care unit, depending on where the institution stores medication and prepared medication for the study infants.

Further instructions are available in the Pharmacy Manual.

10.8. Accountability of the Study Medication

Upon receipt of study drugs, the Investigator (or designee) will conduct an inventory count of the supplies. The Investigator will retain a copy of this inventory at the site and provide a copy to the study monitor. The study monitor may check the inventory of supplies at the study site at any time during the study.

Drug supplies, which the sponsor will provide, must be kept in a secure, limited access storage area under the storage conditions defined by the sponsor (see Pharmacy Manual).

The Investigator, pharmacist and/or investigational drug storage manager will receive the investigational drugs when all country-specific required approvals are in place and all required country-specific essential documents are provided to Nutrinia or its designee.

The Investigator, pharmacist and/or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each infant, and the return to the Sponsor of unused or partially used product. These records will include dates, quantities, batch/serial numbers, re-test ('use by') dates, and the unique kit numbers assigned to the investigational product and

the trial infants' study number. The Investigator, pharmacist and/or investigational drug storage manager will maintain records that document adequately that the infants were provided the doses specified by the protocol, plus kits assigned by randomization system and reconcile all investigational products received from the Sponsor. At the time of return to the Sponsor, the Investigator, pharmacist and/or investigational drug storage manager must verify that all unused or partially used drug supplies have been returned and that no remaining supplies are in the Investigator's possession.

The study monitor is responsible for ensuring that the Investigator (or designee) has correctly documented the dispensing of study drugs on the dispensing log. The study monitor will perform an inventory of study drugs at routine monitoring visits and at the closeout visit to the site.

11. SAFETY MEASURMENTS

Safety will be evaluated daily during the treatment period. An additional safety evaluation will be performed at discharge or end of treatment and at the final study visit (follow-up visit).

11.1. Definitions

Adverse Event (AE)	Any untoward medical occurrence in a clinical investigation of a subject administered a pharmaceutical product (either test product or control product) and that 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

Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity Other 'important medical events' may also be considered serious if they jeopardise the study infant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the infant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question described: • in the case of a product with a marketing authorisation, in the Summary of Product Characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the Investigator's Brochure relating to the trial in question.

11.2. Causality

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

Causality Category	Description
Unlikely	A clinical event, including a laboratory test abnormality, with a temporal relationship to drug administration, that makes a causal relationship improbable, and in which other drugs, chemicals, or the underlying disease provide plausible explanations. For the purpose of this protocol, the term unlikely will be considered not related to study medication and will be termed an "Adverse Event".
Possible	A clinical event, including a laboratory test abnormality, with a reasonable time sequence to administration of the drug, but that 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 a 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 that 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".

11.3. Collecting, Recording and Reporting of Adverse Events and Serious Adverse Events

Treatment-emergent AEs are events that are not present at screening, or if present at screening, have worsened in severity or frequency.

Data regarding all treatment-emergent AEs will be collected in this study and recorded in the source documentation and in the eCRF, whether or not the event is attributed to trial medication. Pre-treatment emergent events will not be considered as AE and will be recorded as medical history.

Adverse event monitoring will be captured throughout the study from Day 1 (initiation of dosing) until the final study visit (follow-up visit).

AEs and SAEs will be evaluated daily during the treatment period. An additional safety evaluation will be performed at discharge or end of treatment and at final study visit (follow-up visit).

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device, and action taken. Follow-up information should be provided as necessary. 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.

AEs will be graded on a 5-point scale (mild, moderate, severe, life-threatening, and death) and reported as indicated in the source documentation and in the eCRF. Severity of such an AE 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 lifethreatening; hospitalization or prolongation of hospitalization indicated;
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 using the scale in Table 2.

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

AEs considered related to the trial medication as judged by a medically qualified investigator and all SAEs (related and unrelated to trial medication) must be followed until resolution. Resolution is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

The Investigator will use clinical judgment to decide whether or not an AE is of sufficient severity to require the study infant's removal from treatment. A participant's parents or legal guardian may also voluntarily withdraw from treatment for what he or she perceives as an intolerable AE. If either of these occurs, the infant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

All SAEs must be 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 any related SAEs and any SAE resulted in death (related or unrelated), and within 48 hours for SAEs unrelated to the investigational product, other than death. To report such events, an SAE form must be completed by the Investigator and/or designee and sent by email or fax with relevant information.

The Investigator or designee must provide further information on the SAE as soon as it is available. 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 should be provided promptly as a follow-up.

The Investigator and/or designee also must report all SAEs promptly to the appropriate Independent ethics committee (IEC) / Institutional Review Board (IRB) as required by the institution.

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[redacted]	[redacted]

All SAE information must be recorded in ink on the SAE form provided by the Sponsor and then printed and signed by the Investigator who completed the SAE form. Additional follow-up information (e.g., test results, autopsy, and discharge summary) 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 source documentation.

An SAE reporting flow chart is provided in Appendix C.

11.4. Safety Monitoring Plan

The Investigator is responsible for the classification of adverse events and together with the Sponsor for the ongoing safety evaluation of the clinical investigation.

The sponsor shall:

- Set up a Data Monitoring Committee - An independent DMC will review safety data and will make recommendations whether to continue or terminate the study. The DMC analyses and operations will be formally separated from the sponsor, the investigators, and the Steering Committee. Details on the composition of the committee, its procedures, and its interactions are provided in a separate DMC Charter.
- Review the investigator's assessment of all adverse events and determine and document in writing their seriousness and relationship to the study medication; in case of disagreement between the sponsor and one or more principal investigator, the sponsor shall communicate both opinions to the IEC/IRB and the national regulatory authorities, if required.
- Report or ensure the reporting to the IEC/IRB by the PIs of all serious adverse events according to timelines specified in Section 11.3.
- Report to regulatory authorities, within the required time period, all serious adverse events, if required by national regulations.
- Inform all PIs in writing of all the serious adverse events at all investigation sites that have been reported to the sponsor, and ensure that the PIs report them to their IEC/IRB, if required by national regulations; this information shall be sent to all PIs within a time frame established based on the perceived risk.
- Ensure that the IEC/IRB and the regulatory authorities are informed of significant new information about the clinical investigation.
- In case of a serious adverse event, determine whether the risk analysis needs to be updated and assess whether corrective or preventive action is required.

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12. SAMPLE SIZE AND STATISTICAL METHODS

12.1. Overview

This trial aims to assess the efficacy and safety of 2 doses of NTRA-2112 as compared to placebo on intestinal malabsorption in preterm infants. The primary efficacy will be assessed by comparing the distributions of days to full enteral feeding (NFE) between active doses and placebo. Safety will be assessed by adverse events and safety measurements.

12.1.1. Design Considerations

This multi-center, double-blind, randomized, placebo-controlled study will compare preterm infants receiving one of 2 doses of NTRA-2112 to those receiving placebo. Infants will be randomized to treatment A or B or C using a 1:1:1 ratio. Randomization will be blocked and stratified by two levels of gestational age:

- 26+0 to 28+6 wks
- 29+0 to 32+0 weeks

The block size will remain blinded to the Sponsor and the Investigators.

This study allows inclusion of both fraternal and identical twins. For ethical reasons, each twin pair (if both are eligible for the study) will be randomized into the same treatment arm. The decision was made after consultation with physicians who assert that parents should not be put in a position in which one of their twins receives placebo while the other receives NTRA-2112. Because of the possible dependency between the outcomes for twins, if both are eligible for the study, the primary analysis will include only the firstborn.[6] If only one twin is eligible, then that twin (whether first- or second-born) will be included in the primary analysis.

While only one of the twins will be included in the trial's full analysis set (FAS), throughout the trial period all eligible twins will receive the treatment to which they were assigned. The safety analyses will include all infants receiving study treatment, whether or not they are members of the FAS. Some additional efficacy analyses will include both participating twins and some will include only the second born of the participating twins.

The planned trial is multi-center; it will be comprised of a large population of infants including twins and those given different types of feeding regimens (i.e., OMM, DBM only, formula, combinations). Nutrinia knows of no similar study that has been conducted in such a wide-ranging population. The best estimate of within-group variation, which is critical for correctly computing study power, is based on Nutrinia's INFOSUP II – Phase II study with a narrower population. For this current trial, it is important to assess the accuracy of our assumption regarding within-group variation because an underestimation of variance has the potential to reduce study power substantially. Consequently, a sample size re-estimation procedure will be used at the time of the interim futility analysis. The sample size may be increased if the standard deviation is at least 5% larger than assumed in the protocol.

The same statistician who will prepare the analysis for the interim futility calculation will compute the average within-group standard deviation; this person will not be involved in any other aspect of the trial. The Statistical Analysis Plan, which will be written prior to the futility analysis, will describe in detail the method for the estimation of standard deviation and the methods to be used to ensure blinding of study statisticians to all information apart from the updated sample size.

This trial has one primary and one key secondary endpoint. The key secondary endpoint will be formally tested only if the data show statistically significant benefit on the primary endpoint. The study is

[6] The non-parametric primary analysis does not enable controlling for dependency between siblings as, for example, the parametric models can.

comparing each of two doses to placebo; a Bonferroni approach will be used to adjust for the two tests of the two doses NTRA-2112.

The key secondary endpoint in this trial is number of days to discharge from the hospital. The decision to discharge a preterm newborn from the hospital is based on standard of care and hospital policies, which may also include social considerations[7]. Thus, the key secondary endpoint refers to actual discharge from the hospital. Infants not reaching NRD (number of days to discharge from the hospital) due to death or complications will, as noted in the preceding paragraph, be excluded from the primary analyses.

12.2. Analysis Sets

12.2.1. Safety Analysis Set

The safety analysis set will consist of all infants in whom any study drug—placebo or NTRA-2112—was initiated. If both members of a pair of twins are participating in the study, the safety analysis set will include both.

12.2.2. Full Analysis Set (Intention-to-treat)

The Full Analysis Set will consist of all randomized singletons and, for twins who both participate in the study, only the first born.

12.2.3. Per-Protocol Analysis Sets

Instead of defining a Per-Protocol (PP) analysis set, modern methods of analysis of PP data that separate the reasons for noncompliance from the effect of study drug will be used as per, for example, Robins (1989)(12).

12.2.4. Safety

Serious adverse events and adverse events occurring at any time during the trial or follow-up will be listed and summarized.

The incidence of (1) NEC and (2) death will be compared between the treatment groups.

Safety assessments will include:

- Length of exposure to study medication
- Physical examination and vital signs
- Blood chemistry and haematology

[7] For example, one of a twin pair may remain in the hospital despite readiness for discharge until his/her sibling is also ready for discharge, so that both can be discharged at the same time.

- Concomitant medications

12.2.5. Primary Efficacy Endpoint

Numbers of days to achieve full enteral feeding (NFE) is defined as:

Number of Days to achieve enteral feeding of at least 150 ml/kg/day for at least 3 consecutive days

12.2.6. Secondary Efficacy Endpoints

Key secondary objective:

To assess the effect of 2 doses of NTRA-2112 compared to placebo on the number of days to achieve discharge from hospital or readiness for discharge, whichever occurs first.

Readiness for discharge from hospital defined as achieving all of the below:

- Infant weight ≥ 1800g
- Stable body temperature
- Capable of oral feeding (reached full enteral feeding and not dependent on PN).

Other secondary objectives:

To compare 2 doses of NTRA-2112 to placebo with respect to the following:

- Growth velocity (g/kg/day)
- Change in Z-score at 6, 8 and 10 days from initiation of treatment
- Gain in body weight during the treatment and follow-up periods
- Number and percentage of infants reaching full enteral feeding within 6, 8, and 10 days from initiation of treatment.
- Total number of days receiving parenteral nutrition
- Number of days to 120Kcal/kg/day
- Number of days to wean-off PN[8] Exploratory secondary objective:

- Number of days to end gastric residuals over 2 ml/measurement according to the feeding protocol (Appendix A)

**Enteral feeding defined as at least 150 ml/kg/day for at least 3 consecutive days.*

<u>Exploratory secondary analyses:</u>

- Number of days to end gastric residuals over 2 ml (per feeding protocol Appendix A)
- Gain in length during the treatment period and follow up period (long term follow-up period)

[8] Wean off PN is defined as complete cessation of PN support.

- Gain in head circumference during the treatment period and follow up period (long term followup period)
- Percent enteral feedings from total nutrition

- Percent parenteral nutrition from total nutrition

12.3. Sample Size Considerations

Presentation of sample size is based on the hypothesis that NFE in either treatment group is shorter than in the placebo group. Based on limited historical data (phase 2), the conservative mean is 8.0 days for the placebo group and 6.6 days for each of the 2 active dose groups. This assumes a standard deviation of 3.5 days for each group.

The analysis will be based on a nonparametric test. The NFEs for each infant in the FAS will be ranked from shortest time (the best outcome) to longest time. Infants who do not achieve EN because they experience NEC will be assigned the next set of ranks; all the infants experiencing NEC will be ranked in terms of their time to NEC (the earlier the worse) and will be assigned ranks one greater than the rank of the longest time to achieve NFEs. All infants who die will be assigned the next set of ranks, again with the earliest deaths assigned the worst rank. Thus, each infant who has achieved EN or who has died or suffered NEC will have an observed rank.

Study Infants will be randomized by center and by gestational age group. The statistical analysis will stratify the infants by gestational age group and region (United States and Europe), but not by center. Because the analysis will be based on ranks, a Van Elteren test will be used to compare NTRA-2112 to placebo. To calculate sample size, an independent groups t-test for 85% power to account for the reduced power of the non-parametric test was used (i.e., expect that a t-test with 85% power to have at least 80% when the Van Elteren test is applied). A 2.5% significance level to account for 2 dose comparisons to placebo was used. These calculations give N = 136 infants per group. To account for the reduction in power caused by potential missing data, the sample size was increased to 150 per group or a total sample size of 450.

Note: The sample size provided in this section relates only to those *infants included in the FAS*; however, the total number of infants treated with NTRA or placebo may be as high as 530, depending on how many of the infants in the study are pairs of twins. As described above, the FAS will include only the first born infant in a participating pair of twins. The second born sibling will be included in safety analyses and some supplementary efficacy analyses.

12.4. Statistical Analysis

This section briefly describes the statistical analysis planned for the study. A full Statistical Analysis Plan (SAP), to be written prior to the futility analysis, will describe the methodology in detail. Should the methods in SAP differ from methods in this section, the methods in the SAP will take precedence.

Statistical methodology will be consistent with ICH and other regulatory guidelines as well as general principles of rigorous statistics.

12.4.1. Overview

Data listings by infant will be provided.

The data will be summarized in tables listing the mean, standard deviation median, 25th and 75th percentiles, minimum, maximum for continuous data, or in tables presenting counts and percentages. Tables will be presented by study arm and overall. "Time-to" data will be described by survival curves.

All statistical analyses will be performed and data appendixes will be created using the SAS® system or other validated software.

12.4.2. Disposition of Study Infants

Disposition of study infants will be reported for the FAS and the safety analysis set. Tables will present the number of infants enrolled, exposed, prematurely terminated, and completed will be summarized by treatment group and overall. A list of dropouts will show the reason for and time of discontinuation.

12.4.3. Baseline Comparability

Demographic and baseline clinical variables will be presented for infants in each treatment arms using tables and figures along with descriptive statistics. Treatment groups will be compared to evaluate the balance achieved by randomisation. 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 efficacy endpoints.

12.4.4. Safety

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 IMP. Descriptive statistics will be provided by treatment group as appropriate.

12.4.5. Primary Efficacy Endpoint

The FAS will be used to test the primary efficacy endpoint.

The primary efficacy analyses (one for each dose) will test the following null and alternative hypotheses:

H_0: The distribution of the number of days to full enteral feeding is the same in the treated and the placebo groups.

H_1: The distribution of the number of days to full enteral feeding differs in the treated and the placebo groups.

The ranks for any missing values will be calculated using multiple imputation; the SAP will describe the methods in detail.

The Van Elteren Test will be used for the primary efficacy analysis with data stratified by two Gestational age (GA) strata and two regions (North America and Europe). For each dose, the test will be performed with a Bonferroni correction, which will maintain the overall two-sided Type I error rate at 0.05.

The study will have shown benefit of NTRA-2112 if the null hypothesis for either tested dose is rejected and NFE is shorter for NTRA-2112 than for placebo.

12.4.6. Key Secondary Endpoint

The FAS will be used to test the key secondary efficacy endpoint.

The key secondary endpoint will be tested only if the primary efficacy analysis shows superiority. For each dose that shows superiority for the primary efficacy endpoint, the following hypothesis will be tested:

H_0: The distribution of the number of days to NRD is the same in the treated and the placebo groups.

H_1: The distribution of the number of days to NRD differs in the treated and the placebo groups.

where NRD = number of days to discharge from the hospital.

The ranks for any missing values will be calculated using multiple imputation; the SAP will describe the methods in detail.

Testing of the key secondary endpoint will be by the Van Elteren test, stratified by region (North America and Europe) with a threshold for statistical significance of $P<0.025$.

The data will have shown benefit on the key secondary outcome for either dose for which the null hypothesis is rejected and the NRD is shorter for NTRA-2112 than for placebo.

12.4.7. Other Secondary Endpoints

The other secondary endpoints will be tested in the FAS. For each of these other endpoints, the two-sided Type I error rate will be 0.025 for each dose. Statistical testing of these other secondary endpoints will be considered exploratory and will not control for Type I error rate. The SAP will describe the methods used for these endpoints including the approaches planned for missing data. Long term follow-up data at 12 and 24 months will be summarised descriptively. Full details will be given in the SAP.

12.4.8. Analyses of Predictor Variables

Effect of covariates: The effect on the primary and key secondary outcomes of the following variables will be assessed:

- GA
- Birth weight

- Gender
- Ethnicity
- Enteral feedings type
    1. Own mother's milk only to full enteral feeding
    2. Donor breast milk only to full enteral feeding
    3. Infant formula only to full enteral feeding
    4. Own mother's milk and formula, in any combination of proportions, to full enteral feeding
    5. Donor breast milk and formula, in any combination of proportions, to full enteral feeding The methodology will be described in the SAP.

12.4.9. Sensitivity Analysis: Missing Values

[redacted]

The following sensitivity analyses will be conducted on the primary and key secondary endpoints to explore the effect of these missing values:

- **Worst reasonable case analysis**: Infants in an NTRA-2112 group with a missing rank will be assigned the median rank in the placebo group and infants in the placebo group with a missing rank will be assigned the median rank in the combined NTRA-2112.
- **Best reasonable case analysis**: Infants in an NTRA-2112 group with a missing rank will be assigned the median rank in the respective NTRA-2112 group and infants in the placebo group with a missing rank will be assigned the median rank in the placebo group.
- **Tipping point analysis**: Infants in any group with a missing rank will be assigned varying ranks to find the point at which the results reverse from favoring one treatment group to the other.
- **Survival ("time-to-event") analysis**: a log rank test will be performed to compare time-to-FEF. In this analysis, infants who experience NEC will be assigned censoring times of 29 days and infants who die will be assigned censoring times of 30 days. Any other infants who withdraw from the study early will be considered censored at the day of their last participation in the study (unless they have already achieved FEF in which case they will not be censored.

12.4.10. Sensitivity Analysis: The second born Twin

Several analyses will be performed to include the second born twin.

One analysis will repeat test the primary and key secondary endpoints replacing the first born twin by the second born twin.

Another approach will be a hierarchical mixed model that includes both twins in a way that accounts for the possible correlation between them. The SAP will describe in detail the method to be used, including the approach to handle deaths and cases of NEC.

12.4.11. Sensitivity Analysis: The PP Set

Many physicians are interested in the effect of an intervention on patients who actually take the drug. The typical approach is to analyze the data in a so-called PP set of data. These analyses are prone to serious bias. Nutrinia plans to use modern methods of analysis of PP data that disentangle the reasons for noncompliance from the effect of study drug.(12). The SAP will describe these analyses.

12.4.12. Interim Futility Analysis

The study will include an interim futility analysis as defined in the SAP. For the futility analysis, the conditional power of showing statistically significant evidence of benefit on the primary endpoint will be calculated for each dose group. If the conditional power is less than 20% in either dose, continuing to enter infants in that dose group will be considered statistically futile.

An independent statistician will perform the futility analysis. This statistician will not be involved in the preparation of the statistical analysis plan or in other aspects of the trial. The statistical analysis performed during the futility interim look will be presented as defined in the SAP to an independent Data Monitoring Committee (DMC), which will review the results and make a recommendation regarding continuing the study, stopping the study, or discontinuing recruitment into one dose group. The DMC will base its recommendation on trial continuation on the totality of evidence available to it, rather than only on the statistical futility criterion. Because the only reason to recommend stopping the study, or stopping one dose, is futility (or safety) and not efficacy, this analysis does not compromise the Type I error rate.

The Sponsor will be blinded to all efficacy and safety data. Only the final DMC recommendation will be provided to the Sponsor.

13. DATA MANAGEMENT

13.1. Source Data

Source documents are the documents where data are first recorded, and from which participants' eCRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the eCRF), clinical and office charts, laboratory and pharmacy records, diaries, radiographs, and correspondence.

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. The Investigator will make all 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.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific eCRF when the information corresponding to that visit is available. For all entries into the eCRF 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 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 eCRF and source record.

All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

13.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits, and inspections.

13.3. Data Recording and Record Keeping

An eCRF will be completed for each subject who is assigned a study number and signs and dates the studyapproved ICF. All trial data will be entered on eCRF, which is software for capturing and managing clinical trial data. The software supports Good Clinical Practice (GCP). It has an intuitive interface for enrolment, clinical data capture, validation, and query management. The software uses tools for data cleaning, clinical data management, site monitoring, and for overall system oversight, auditing, and reporting. The study infants will be identified by a unique trial specific number and/or code in all databases. The name and any other identifying detail will NOT be included in any trial data electronic file. The investigator or a designee will be logging into the system and entering the data directly at the site. The entries made in the eCRF will be monitored by a Clinical Research Associate (CRA) for completeness and accuracy. Edit checks/rules will be configured for identifying discrepancies. These discrepancies will be resolved by investigators or designee after logging into the system. If a correction is required for an eCRF data, the time and date stamps track the person entering or updating eCRF data and create an electronic audit trail.

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

14. STUDY MONITORING

The trial will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations, and standard operating procedures.

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

eCRF 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 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 visit 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).

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Declaration of Helsinki

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and the applicable regulatory requirements.

15.2. ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

15.3. Approvals, Information on Study Infants, and Consent Form

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments. Prior to an infant's participation in the trial, written informed consent must be obtained for each infant (by both parents and accepted legal representatives) according to ICH GCP and the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory, and the informed consent form and any additional infant information form must be retained by the investigator as part of the trial records. A signed copy of the informed consent form and any additional infant information must be given to each infant's parents or the infant's legally accepted representative.

The parents must be informed that his/her personal trial-related data will be used by Nutrinia in accordance with the local data protection law. The level of disclosure must also be explained to the parents.

15.4. Data Quality Assurance

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

15.5. Participant 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.

15.6. Expenses and Benefits

No complications are anticipated from feeding the infant with the study insulin-enriched oral nutrition. No evidence or scientific findings of long-term negative effects stemming from feeding preterm infants with the insulin-enriched nutrition have been noted. This is also true when administering higher concentrations of insulin than the quantity proposed in this trial. Nonetheless, the possibility of long-term effects on the creation of insulin antibodies or the prevention of diabetes cannot be ruled out. A study infant may experience a slight but insignificant drop in the blood sugar level.

Should the trial show that insulin indeed speeds up the maturation of the digestive tract, a study infant treated with NTRA-2112 may reach full nutrition sooner than would have occurred had the infant not been in the trial. This would reduce the risks to preterm infants and may provide better growth and development. In addition, the infant will contribute to study a new medication that may help thousands of pre-term infants born each year and suffer from complications due to immature digestive system Nutrinia is responsible for managing the financing for the study. Nutrinia has signed a contract with the facilities where they will perform the trial with the study doctor. The participation of the infant in the study will not involve any costs and the infant's parent or guardian will not have to pay for the study drugs.

16. RETENTION OF STUDY DOCUMENTS

The PI should retain records for all study infants, including eCRFs, all source documentation (containing evidence of study eligibility, history and physical findings, laboratory data, results of consultations, etc.) as well as IRB/IEC records and other regulatory documentation in a secure storage facility. The records should be accessible for inspection and copying by authorized authorities.

Essential documents must be retained for a minimum of 2 years after the final marketing approval in an ICH region or at least 2 years have elapsed since the discontinuation of clinical development of the investigational product. In addition, all medical records of the infant and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

17. FINANCE AND INSURANCE

17.1. Funding

Financing of this study will be outlined in a separate document.

17.2. Insurance

Insurance of this study will be outlined in a separate document.

The terms and conditions of the insurance cover are made available to the investigator and the parents through documentation in the Investigator Site File.

18. PUBLICATION POLICY

The investigator contract describes the rights of the investigator and of the sponsor with regard to publication of the results of this trial. As a general rule, no trial results should be published prior to finalization of the Clinical Trial Report to regulatory authorities.

The Principal Investigator will prepare a complete review of the study and abstracts for professional meetings. Published data must not compromise the objectives of the study or the confidentiality of the infants enrolled.

19. REFERENCES

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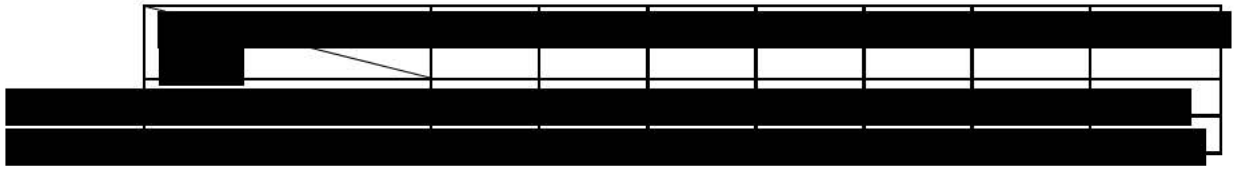

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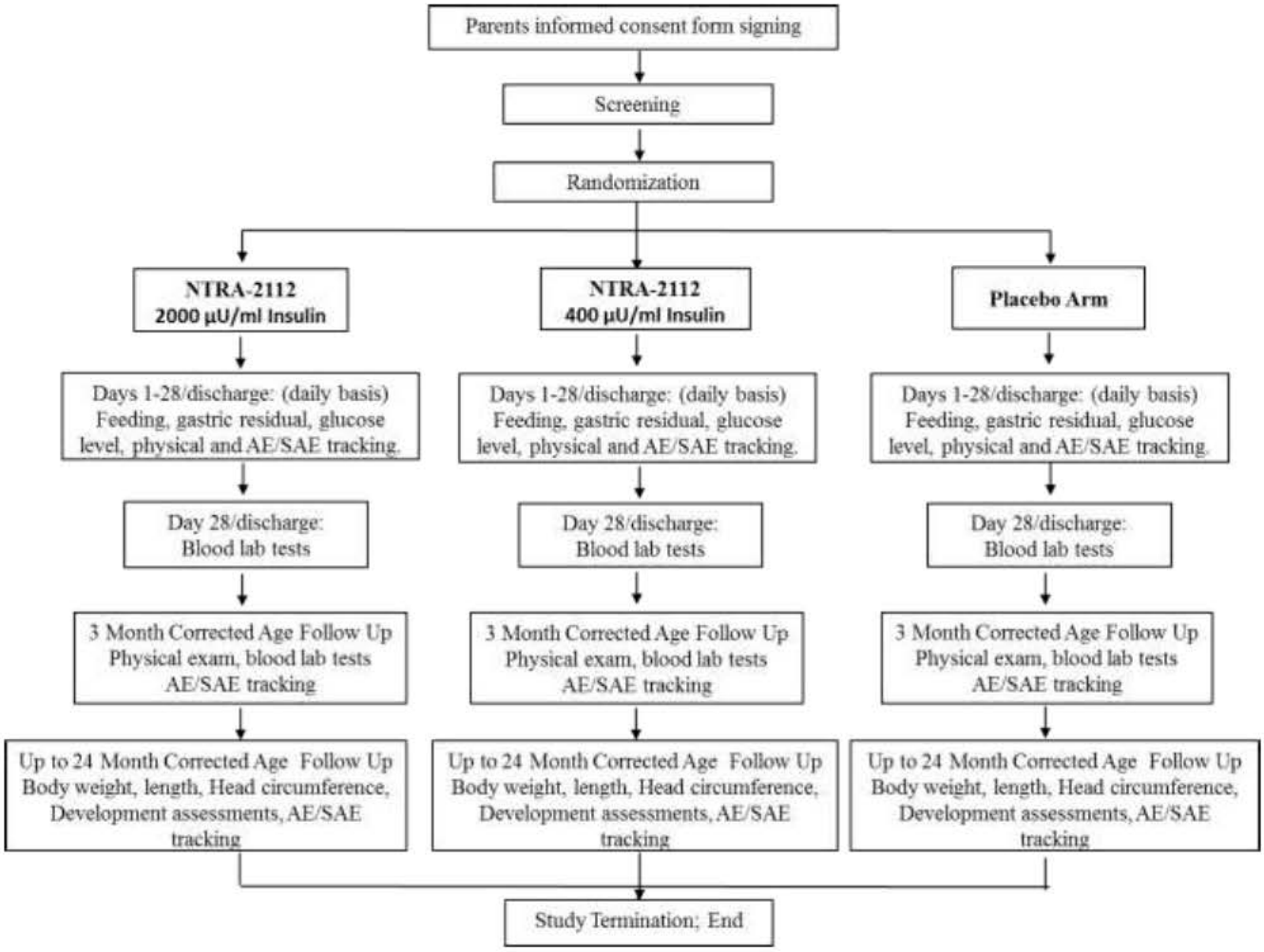
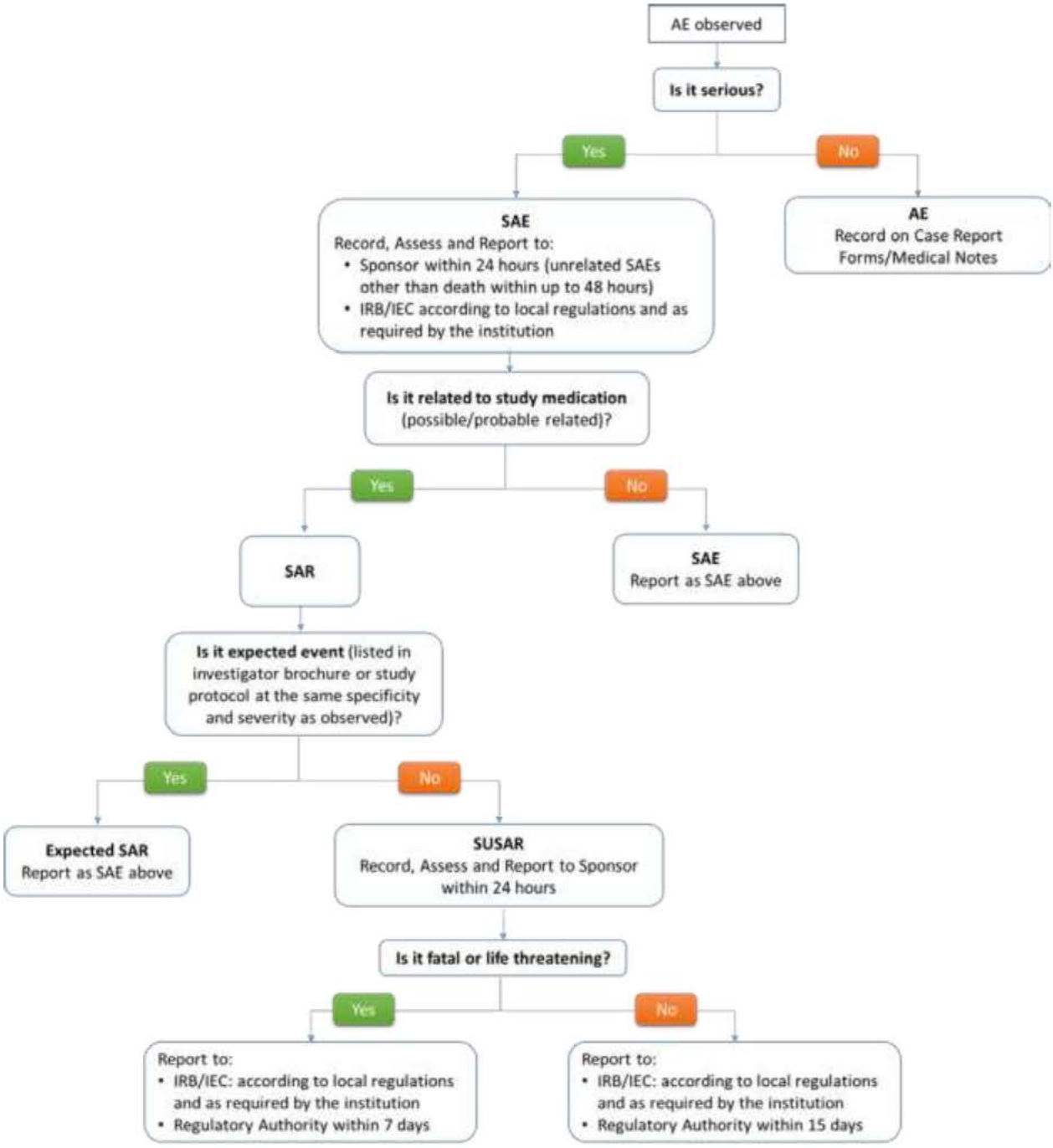
Appendix B: Study Flow Diagram



Appendix C: SAE Reporting Flow Chart



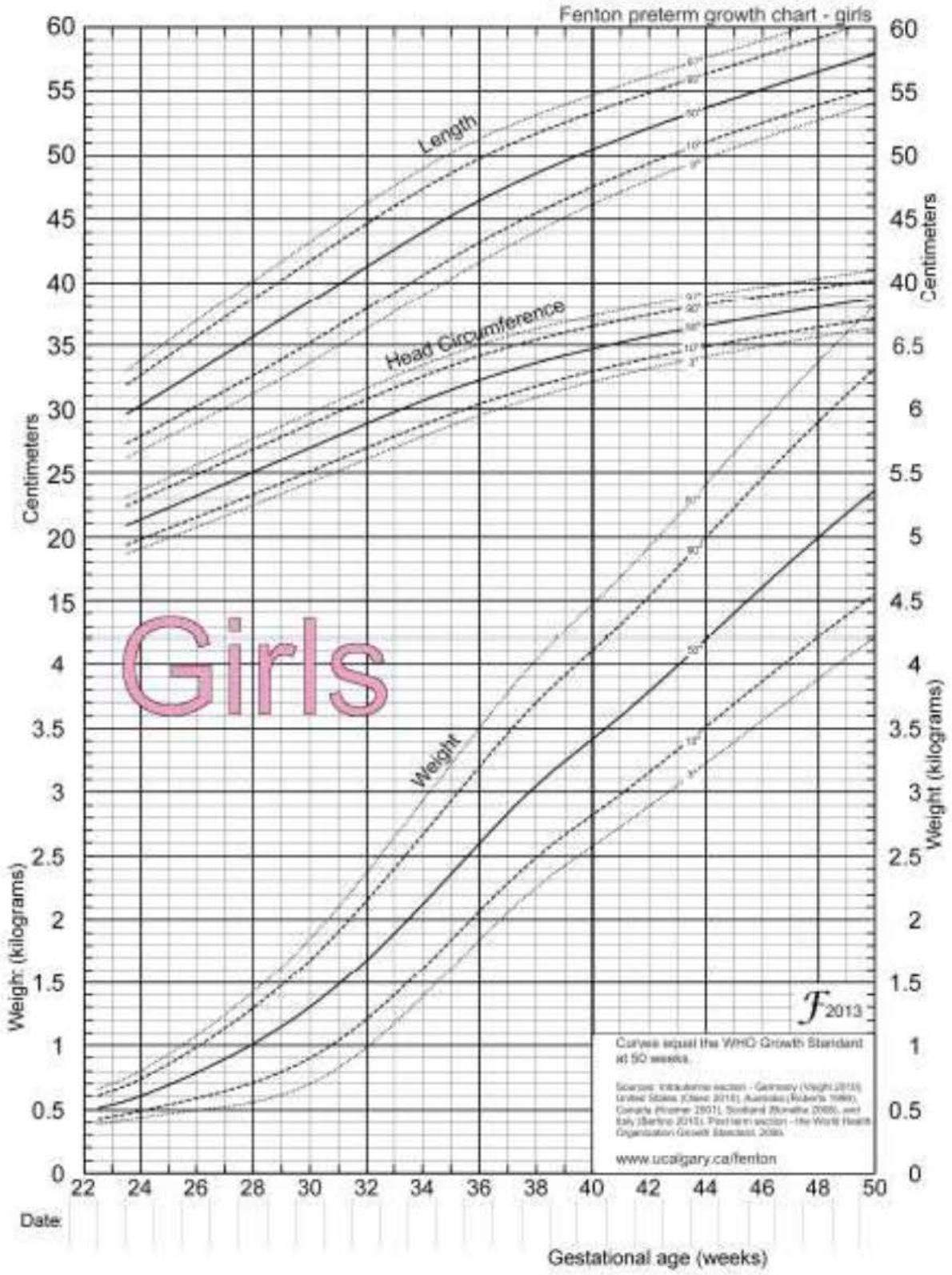
AE: Adverse event

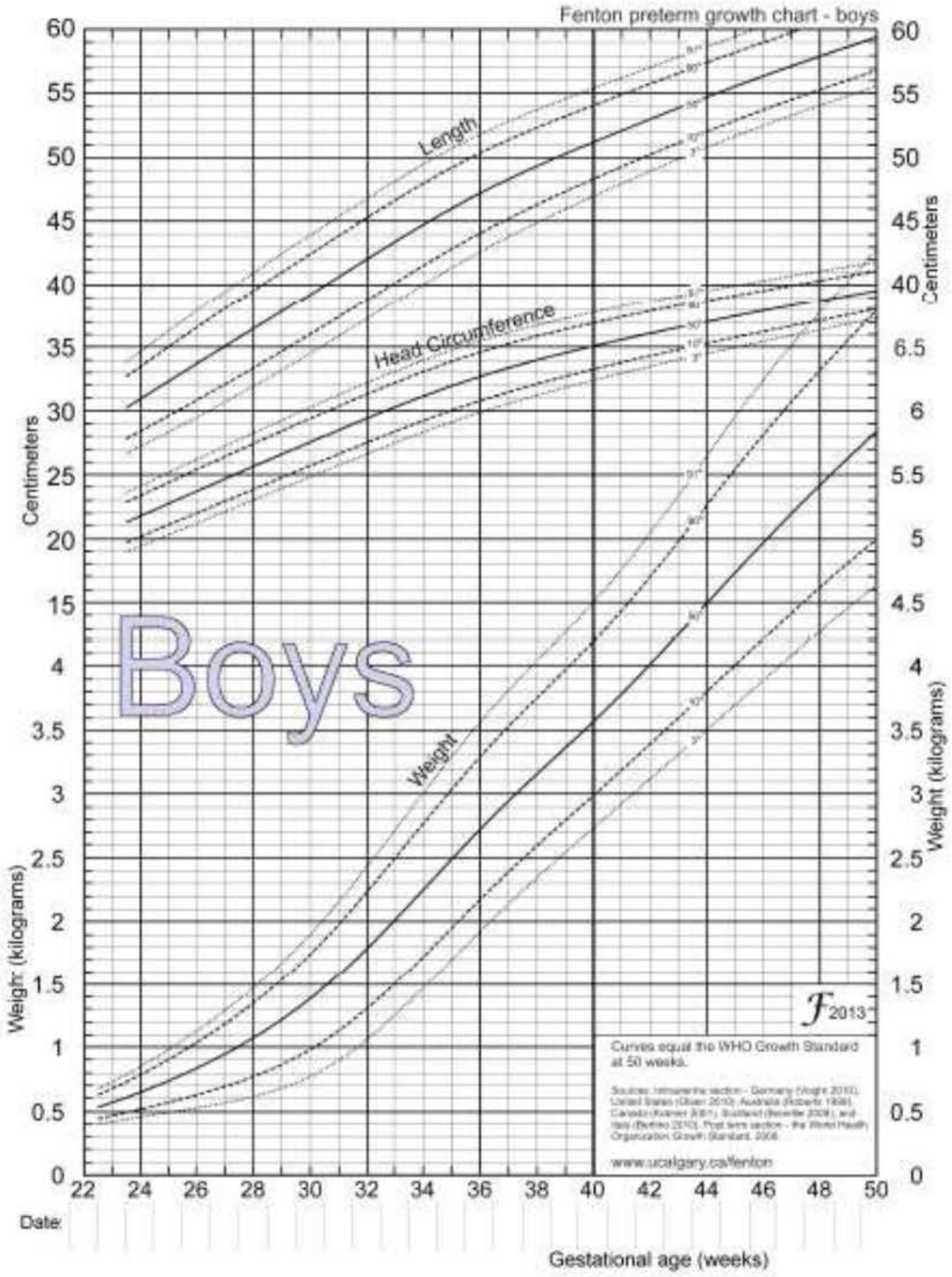
SAE: Serious adverse event

SAR: Serious adverse reaction

SUSAR: Suspected unexpected serious adverse event

Appendix D: Fenton Preterm Growth Chart




Fenton preterm growth chart - boys
Length
Head Circumference
Weight
Boys
Centimeters
Weight (kilograms)
Gestational age (weeks)
Date:
Curves equal the WHO Growth Standard at 50 weeks.
www.ucalgary.ca/fenton
2013

Appendix E: Expected Complications Related to Premature Birth

While not all premature babies experience complications, being born too early can cause short-term and long-term health problems for preemies. Generally, the earlier a baby is born, the higher the risk of complications. Birth weight plays an important role, too.

Some problems may be apparent at birth, while others may not develop until later.

Short-term complications

In the first weeks, the complications of premature birth may include:

- **Breathing problems.** A premature baby may have trouble breathing due to an immature respiratory system. If the baby's lungs lack surfactant — a substance that allows the lungs to expand — he or she may develop respiratory distress syndrome because the lungs can't expand and contract normally.

  Preemies may also develop chronic lung disease known as bronchopulmonary dysplasia. In addition, some preemies experience prolonged pauses in their breathing, known as apnea.

- **Heart problems.** 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.

- **Brain 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.

  Larger brain bleeds may lead to fluid accumulation in the brain (hydrocephalus) over a number of weeks. Some babies who develop hydrocephalus will require an operation to relieve the fluid accumulation.

- **Temperature control problems.** Premature babies can lose body heat rapidly; they do nott have the stored body fat of a full-term infant and they cannot 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 is why smaller preemies require additional heat from a warmer or an incubator until they are larger and able to maintain body temperature without assistance.

- **Gastrointestinal problems.** Preemies are more likely to have immature gastrointestinal systems, leaving them predisposed to complications such as necrotizing enterocolitis (NEC). This potentially serious condition, in which the cells lining the bowel wall are injured, can occur in premature babies after they start feeding. Premature babies who receive only breast milk have a much lower risk of developing NEC.

- **Blood problems.** Preemies are at risk of blood problems such as anemia and infant jaundice. Anemia is a common condition in which the body does not have enough red blood cells. While all newborns experience

a slow drop in red blood cell count during the first months of life, the decrease may be greater in preemies, especially if the baby has a lot of blood taken for lab tests.

Infant jaundice is a yellow discoloration in a newborn baby's skin and eyes that occurs because the baby's blood contains an excess of a yellow-colored pigment from the liver or red blood cells (bilirubin).

- **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 lifethreatening complication.

Long-term complications

In the long term, premature birth may lead to these 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 is 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 attentiondeficit/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).

Appendix F: Example for TBV volume

TBV is considered based on the following table:

Subjects Weight (Kg)	Total Blood Volume (mL)	Maximum in 24 hours (3 mL/kg)	Maximum in 30 day period (5% of TBV)
1	100	3	5
2	200	6	10
3	240	9	12
4	320	12	16
5	400	15	20
6	480	18	24
7	560	21	28
8	640	24	32
9	720	27	36
10	800	30	40
11-15	880-1200	33-45	44-60
16-20	1280-1600	48-60	64-80