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.

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To assess the efficacy and safety of 2 dose levels of NTRA-2112 on intestinal malabsorption in preterm infants as compared to placebo.The sub-study aims to determine whether NTRA-2112 in own mother's milk, donor human milk or preterm formula...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON46903

Source
ToetsingOnline

Brief title
A Study to Assess the Efficacy and Safety of NTRA-2112 in Preterm Infants.

Condition

- Other condition
- Malabsorption conditions

Synonym
intestinal malabsorption in preterm infants

Health condition

prematuratie

Research involving
Human

Sponsors and support

Primary sponsor: Nutrinia Ltd
Source(s) of monetary or material Support: farmaceutisch bedrijf

Intervention

Keyword: enteral feeding, gastrointestinal malabsorption, oral insulin formulation, preterm infants

Outcome measures

Primary outcome

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.

Sub-study sugar absorption test:

lactase activitity en intestinal permeability

Secondary outcome

Key secondary endpoint:

Number of days to discharge from the hospital or readiness-for-discharge 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:

1. Growth velocity (g/kg/day)

2. Change in Z-score at 6, 8 and 10 days from initiation of treatment

3. Gain in body weight during the treatment and follow-up periods

4. Number and percentage of infants reaching full enteral feeding within 6, 8, and 10 days from initiation of treatment.

5. Total number of days receiving parenteral nutrition

6. Number of days to 120Kcal/kg/day

7. Number of days to wean-off PN

Exploratory secondary endpoints:

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

2. Gain in length during the treatment period and follow up period (long term follow-up period)

3. Gain in head circumference during the treatment period and follow up period (long term follow-up period)

4. Percent enteral feedings from total nutrition

5. Percent parenteral nutrition from total nutrition

Study description

Background summary

The study will evaluate the efficacy and safety of 2 dose levels of NTRA-2112 on intestinal malabsorption in preterm infants as compared to placebo.

NTRA-2112 is a powder of insulin formulation for reconstitution in 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 milk and colostrum.

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 the ability of preterm infants to achieve full enteral (EN) feeding (>=150 ml/kg/day) for 3 consecutive days.

In a local sub-study (AMC and Isala) a sugar absorption test will be performed to evaluate the effect of NTRA-2112 on lactase activity and intestinal permeability.

Study objective

To assess the efficacy and safety of 2 dose levels of NTRA-2112 on intestinal malabsorption in preterm infants as compared to placebo.

The sub-study aims to determine whether NTRA-2112 in own mother's milk, donor human milk or preterm formula for 28 days results in higher lactase activity and lower intestinal permeability compared to placebo.

Study design

A Multi-center, Double-blind, Randomized, Three-Arm, Parallel-Group, Placebo Controlled Study.

Intervention

Following dubbel-blind randomization will be treated for 28 days or until hospital discharge, if discharge before Day 28, with 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, subjects will undergo daily evaluation of AE, concomitant medication, daily nutrition, general growth, gastric residuals and development progression. Subjects will be evaluated at discharge day and follow up visits will be performed after completion of treatment at 3 , 12 and 24 months corrected age.

The children participating in the sub-study at AMC and Isala will have three times (Day 4, 7 and 14) a sugar absorption test. The urine will be captured by gauzes in the diaper. Before the urine is collected ,a little extra nutrients (lactulose and mannitol) will be will be administered within 30 minutes after feeding

Study burden and risks

Except for the risks already mentioned in E9 no ther risks are foreseen. The additional burden comparded to standard of care is minimal.

Contacts

Public
Nutrinia Ltd

6 Ha-Khilazon Street NA
Ramat-Gan 5252270
IL
Scientific
Nutrinia Ltd

6 Ha-Khilazon Street NA
Ramat-Gan 5252270
IL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

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-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.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-10-2016
Enrollment:	200
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NTRA-2112
Generic name:	oral insulin formulation

Ethics review

Approved WMO

Date:	15-12-2015

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-05-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-05-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-05-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-08-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-12-2017

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-002624-28-NL
ClinicalTrials.gov	NCT02510560
CCMO	NL53106.018.15