A Multi-Center, Randomized, Double-Blind, Three-Arm, Parallel-Group Trial to Assess the Efficacy and Safety of NTRA-9620 in Infants with Short Bowel Syndrome (SBS) Following Surgical Resection

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The primary objective is to evaluate the efficacy and safety of NTRA-9620 compared with placebo when added to standard of care (SOC) in pediatric subjects (aged 28 weeks post-menstrual age to 52 weeks chronological age) with SBS within 4 months from...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Malabsorption conditions
Study type	Interventional

Summary

ID

NL-OMON45489

Source
ToetsingOnline

Brief title
GIFT-02

Condition

- Malabsorption conditions

Synonym
SBS, short bowel disease

Research involving

Human

Sponsors and support

Primary sponsor: Nutrinia Ltd
Source(s) of monetary or material Support: Sponsor company: Nutrinia Ltd.

Intervention

Keyword: intestinal malabsoption, SBS, Short Bowel Syndrome, surgical resection of the intestine.

Outcome measures

Primary outcome

The primary endpoints are the percent changes in %PN (PC_PN0-t) from baseline

based on caloric intake to 12 weeks and again to 24 weeks. Each endpoint is

calculated as:

*PC_PN*_(0-t)=100×(*%PN*_Baseline-*%PN*_t)/*%PN*_Baseline

where:

t = 12 or 24weeks.

%PN = % Parenteral Nutrition (feeding) calculated as parenteral calories

divided by calculated total caloric requirements (the Schofield equation).

Each *PC_PN*_(0-t) observation will be computed as an average over a

single week.

Thus, for example, PC_PN at 12 weeks will be the average of PC_PN over

days 78 to 84.

PC _PN at 24 weeks will be the average of PC_PN over days 162 to 168.

The study will have shown benefit if either PC_PN0-12 or PC_PN0-24 in the

treated group is statistically significantly superior to placebo.

Secondary outcome

Key Secondary Endpoint

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

Other Secondary Endpoints

a) Time to wean off parenteral nutrition

b) Number of patients reaching readiness to wean off at 12 and 24 weeks from baseline.

c) Time to 50% PN/IV reduction from baseline in %PN based on total calories.

d) Time to 50% PN/IV reduction from baseline in %PN based on volume.

e) Number of patients reaching 50% PN/IV reduction from baseline in %PN based on total calories at 12 and 24 weeks.

f) Number of patients reaching 50% PN/IV reduction from baseline in %PN based on volume at 12 and 24 weeks.

g) Percent change from baseline in %PN/IV based on total calories.

h) Percent change from baseline in %PN/IV based on volume.

i) Percent change from baseline in PN/IV fluid volume during treatment period.

j) Change in Z-scores (Fenton) from baseline during the treatment period

k) Percent change from baseline in %EN based on total calories.

l) Percent change from baseline in %EN based on total volume.

m) Change from baseline in liver enzymes (ALT, GGT, and total and direct bilirubin).

n) Change from baseline in plasma citrulline levels.

o) Change from baseline in body weight during the treatment period.

p) Weekly average of hours on prescribed PN/IV during the last month of

treatment.

q) General safety variables including episodes of significant feeding

intolerance

compared to placebo.

Study description

Background summary

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

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

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

NTRA-9620 is an oral formulation of insulin for local GI therapy without systemic insulin exposure aimed at increasing intestinal adaption.
Evidence supports the fact that intestinal adaptation is enhanced and sustained when growth factors are provided immediately following intestinal loss (3).
This adaptation is likely to be further augmented when growth factors are administered during early development, the most critical period of gut growth.
The dual effects of NTRA-9620 to enhance both adaptation and enteral tolerance at this vital time are major strengths of the product concept.

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

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

Study objective

The primary objective is to evaluate the efficacy and safety of NTRA-9620 compared with placebo when added to standard of care (SOC) in pediatric

subjects (aged 28 weeks post-menstrual age to 52 weeks chronological age) with SBS within 4 months from surgical resection who are on parenteral nutrition (PN) support.

Study design

This multi-center, randomized, double-blind, three-arm, parallel-group trial is designed to assess the efficacy and safety of two doses (8 IU/kg/day and 4 IU/kg/day) of NTRA-9620 or matching placebo at two time points (12 and 24 weeks post randomization) administered to infants less than 52 weeks chronological age with SBS (following surgical resection). The study will be conducted in approximately 40 clinical trial sites worldwide. Subjects will continue on SOC nutrition after the 24 week intervention period. A final study visit will be conducted at Week 28, 4 weeks after the end of dosing. All subjects will be further followed for long-term safety through Week 104; these safety data will be reported as an addendum to the final clinical study report

Intervention

All three groups will receive NTRA-9620 or matching placebo four times per day for 24 weeks.
Group 1: NTRA-9620 2 IU/kg for each dose (8 IU/kg per day).
Group 2: NTRA-9620 1 IU/kg for each dose (4 IU/kg per day).
Group 3: Matching placebo for each dose.

Study burden and risks

Except for the risks mentioned in E9, no other risks are foreseen. The additional burden compared to the standard of care is minimal.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

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

Exclusion criteria

Subjects meeting any of the following criteria at study entry will be excluded:
1) Subject has undergone any bowel lengthening procedure.
2) Subject has a malabsorption disorder such as:
* Congenital etiology (such as microvilli inclusion disease, tufting enteropathy)
* Untreated Hirchsprung*s disease
3) Significant motility disorder such as:
* Pseudo obstruction

* Severe gastroschisis defined as: primary reason for PN support is due to persistent feeding intolerance of less than 20 ml/kg/day EN intake or signs and symptoms (i.e., abdominal distention, vomiting) requiring prokinetic agents.
4) Any known inherited abnormality (e.g., Fanconi syndrome,) that is not related to SBS.
5) Prior bowel resection due to isolated spontaneous intestinal perforation.
6) < 10 cm of remaining small bowel left with no colon.
7) Uncontrolled systemic infection, acute gastroenteritis, pneumonia, cardiovascular or other abnormality including EKG findings that in the opinion of the investigator makes the infant unstable and at significant risk of not completing the first 12 weeks of the study.
8) Subjects with known hyperinsulinemia .
9) Subjects with unexplained or recurrent hypoglycemia with blood glucose * 50 mg/dL within 48 hours of treatment initiation.
10) Subjects with severe anemia of Hemoglobin less than 60 g/L and requiring transfusion within 48 hours of treatment initiation to avoid a life threatening event.
11) Subjects who require pancreatic enzyme replacement therapy.
12) Subject is currently receiving oral or injectable insulin for any reason.
13) Participation in another interventional clinical study within the past 30 days that may interfere with the results of this study.
14) History or current use of growth factors or glutamine.
15) In the opinion of the investigator, the subject has any other medical condition that would make participation in this study either unsafe or would compromise the potential benefit of insulin treatment

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	15

Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	NTRA-9620
Generic name:	human insulin

Ethics review

Approved WMO Date:	14-02-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-07-2017
Application type:	First submission
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	EUCTR2015-000181-60-NL
ClinicalTrials.gov	NCT02865122
CCMO	NL60431.018.17