A randomised, controlled, double-blind, parallel group, multi-country study to investigate the effects of an infant formula containing partially hydrolysed proteins on growth, safety, and tolerance in healthy term infants

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To investigate the effects of a partially hydrolysed protein based infant formula (pHPformula) in healthy term infants until 17 weeks of age on growth, blood parameters, safety,and gastro intestinal tolerance compared to standard infant formula....

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

Summary

ID

NL-OMON45527

Source
ToetsingOnline

Brief title
TENUTO

Condition

- Other condition

Synonym
Weight gain

Health condition

Growth, Weight gain

Research involving
Human

Sponsors and support

Primary sponsor: Nutricia Research
Source(s) of monetary or material Support: Nutricia Research BV

Intervention

Keyword: growth, healthy infants, infant formula, weight gain

Outcome measures

Primary outcome

The primary outcome parameter in this study is weight gain in grams per day

from baseline until 17 weeks of age.

Secondary outcome

Gain from baseline until 17 weeks of age of

* Recumbent length (mm/day)

* Head circumference (mm/day)

* Mid-upper arm circumference (mm/day)

Z-scores of anthropometric parameters at 17 weeks of age:

* Weight-for-age

* Weight-for-length

* Length-for-age

* Body Mass Index (BMI)-for-age

* Head circumference-for-age

* Mid-upper arm circumference-for-age as of 13 weeks of age

Blood parameters assessed at 17 weeks of age:

* Albumin

* Serum mineral markers: calcium, phosphorus, iron and magnesium

* Blood Urea Nitrogen

These parameters will only be measured in blood of infants, whose parents gave additional

consent to draw blood.

Safety parameters from baseline until 17 weeks of age as measured by:

* Number, type and severity of (Serious) Adverse events and possible relatedness to study

product

* Use of (co-)medication

Gastrointestinal tolerance parameters from baseline until 17 weeks of age including:

* Occurrence and severity of gastrointestinal symptoms:

- regurgitation (return of the milk into the mouth without force)

- vomiting (return of the milk into the mouth with force)

* Stool frequency

* Stool consistency

* Occurrence of diarrhoea

* Occurrence of constipation

Study description

Background summary

It is universally accepted that the optimal nutrition for a newborn infant is breast milk. Consequently, exclusive breastfeeding is the preferred mode of feeding for all term new born infants and the World Health Organisation therefore recommends exclusive breastfeeding for at least 6 months. Breast milk provides a complete supply of nutrients to support growth and development in early life. Breast milk contains bioactive components that beneficially affect intestinal health, gut microbial colonization and immune maturation.

When a mother is unable to breastfeed her infant, or chooses not to breastfeed, an infant formula following the composition of mature breast milk is recognized as the best alternative. Research to improve the quality of infant milk formulas is aimed at mimicking the composition of breast milk, but above all at achieving the functional effects that are observed in breastfed infants. One of the important functional effects of breast milk is prevention of allergies. Breastfeeding is considered to be one of the main pillars in allergy prevention. Consequently in the last decades, to get as close as possible to this functional benefit of breast milk, development of infant nutrition to prevent allergies has been a major field of interest with an important role for hydrolysed proteins. In a (partially) hydrolysed protein formula, the cow*s milk protein is enzymatically hydrolysed (fragmented) with the goal to reduce protein size and as such allergenicity of the proteins.

Current international evidence-based guidelines, recommend formula with such partially hydrolysed proteins for infants at risk of allergy, defined by family history, for the first 4-6 months if breastfeeding is insufficient or not possible. It is considered a good option for these infants, because the small milk protein fragments are more likely to be recognized as harmless by the immune system.
However, recently this preventive effect on developing allergies has been challenged in a meta-analysis. This indicates that the effect of partially

hydrolysed formula on the development of allergic disease
needs better understanding on intervention period, target population and outcome parameter to
determine whether the modest effects of hydrolysed formula on the incidence of allergic manifestations
can be confirmed.

Apart from the fact that it is necessary to gain more insight in the effect of hydrolysed proteins on
allergy risk reduction, it is also necessary to ensure healthy growth and nutritional value. In particular
because large variations exist in the composition of hydrolysed formula in the source of macro-nutrients
and (protein) levels. In addition, hydrolysed formula may impact the food intake compared to intact
formula possibly due to sensory taste and the large amount of free amino acid of which some may
influence satiety. So far, studies demonstrated no evidence for long-term effect on growth or body
composition of hydrolysed formulas in healthy infants without family allergic history. On the
other hand, the GINI study gives indication of a slower BMI development in healthy infants with family
allergic history who received extensively hydrolysed casein formula during first year of life compared to
infants on extensively and partially hydrolysed whey based formula, cows* milk formula or breast milk.

Whether hydrolysed formulas in the Nutricia portfolio have an effect on growth, either with extensively
hydrolysed or partially hydrolysed proteins, was studied for example by comparing different levels of
hydrolysed proteins (Giraffe: internal report) and by investigating the effect of adding synbiotics to
extensively hydrolysed proteins. Both studies indicated that the products were safe, well tolerated
and support an adequate growth in infants fed (extensively) hydrolysed formula compared to the WHO
growth standards. However, a head-to-head comparison of the effect of partially hydrolysed proteins
versus intact proteins and breastfeeding on growth and safety parameters was not performed.

The primary aim of this study therefore is to evaluate the safety and nutritional adequacy of a hydrolysed
protein formula compared to an intact protein formula and to breastfeeding as a reference on growth

until 17 weeks of age.

Study objective

To investigate the effects of a partially hydrolysed protein based infant formula (pHP
formula) in healthy term infants until 17 weeks of age on growth, blood parameters, safety,
and gastro intestinal tolerance compared to standard infant formula.

Primary:
The primary objective of this study is to investigate equivalence of weight gain per day from baseline until the age of 17 weeks in infants receiving partially hydrolysed proteins (test
product) compared to infants receiving intact proteins (control product).

Secondary:
The secondary objectives of this study are:
- To investigate equivalence of weight gain per day in infants receiving formula containing
partially hydrolysed proteins compared to infants receiving breast milk from baseline until the
age of 17 weeks;
-To investigate equivalence of other growth parameters (recumbent length, head circumference, mid upper arm circumference) in infants receiving formula containing partially
hydrolysed proteins compared to infants receiving formula containing intact proteins or infants
receiving breast milk from baseline until the age of 17 weeks;
- To investigate equivalence of other growth z-scores parameters (weight-for-age, weight-for length, length-for-age, BMI-for-age,head circumference-for-age, mid upper arm circumference) in infants receiving formula containing partially hydrolysed proteins compared to infants
receiving formula containing intact proteins or infants receiving breast milk at the age of 17 weeks;
- To investigate the effect on blood parameters in infants receiving formula containing partially
hydrolysed proteins compared to infants receiving formula containing intact proteins or infants
receiving breast milk at the age of 17 weeks;
- To assess the effect on safety in infants receiving partially hydrolysed proteins compared to
infants receiving formula containing intact proteins or infants receiving breast milk from
baseline until the age of 17 weeks;
- To assess the effect on gastrointestinal tolerance in infants receiving formula containing

partially hydrolysed proteins compared to infants receiving formula containing intact proteins or
infants receiving breast milk from baseline until the age of 17 weeks.

Study design

This is a randomised, controlled, double blind, parallel group, multi-country, Phase IIb study.
The study consists of 2 infant formula arms i.e.:
- Test product: Partially hydrolysed 100 percent whey protein based infant formula
containing scGOS/lcFOS.
-Control product: Intact cow*s milk protein based infant formula (whey:casein ratio of
60:40) containing scGOS/lcFOS.
In addition, a breastfeeding arm is added to be used as a reference arm.

Intervention

After parent(s)/legal guardian(s) have agreed to and signed informed consent, infants may enrol in the study. Infants, whose mother has the intention to breastfeed her infant until the infants* age of 17 weeks, may be enrolled in the breastfeeding reference arm. Infants, whose mother has the intention to exclusively formula feed her infant as of 14 days of age at the latest, may be randomised to one of the infant formula arms. Infants will enrol in the study as soon as they pass the eligibility check.

At a maximum age of 14 days all infants will have a screening/randomisation visit (Visit 1), followed by four follow up visits when the infant is 4 (Visit 2), 8 (Visit 3), 13 (Visit 4) and 17 weeks of age (Visit 5). At the infants* age of 19 weeks the Investigator performs a phone call (PC) to parents of all participating infants to follow up e.g. on safety and outstanding issues, adverse events or transition to commercial product.

During the seven days before Visit 2, 3, 4 and 5, parent(s)/caretaker(s) of all infants are requested to fill out an eDiary on daily basis. The eDiary collects data on the intake of study products or breastfeeding, the infants* defecation pattern and aspects of gastro intestinal tolerance. Parent(s)/legal guardian(s) or caretaker(s) will receive automatic reminders from the eDiary system to fill out the diary.

Infants eligible for the infant formula arms
As soon as an infant is exclusively formula fed the screening/randomisation visit (Visit 1) takes place. At that time point, the infant will have a maximum age of 14 days. After eligibility assessment, eligible infants will be randomised in a double-blinded manner to receive either the test product or the

control product until the age of 17 weeks. This means that the infant receives the test or control product for a minimum duration of 15 weeks to a maximum duration of 17 weeks, depending on the age at randomisation. At Visit 1, the Investigator collects also baseline data
on demographics, medical and social information, and anthropometrics. In addition, the Investigator provides the study product, gives instructions to the parents on how to use the eDiary and plans the next study visit.

At each of the following visits, the Investigator collects data on anthropometrics, study product intake, compliance with the study protocol, information on (Serious) Adverse Events, and information of use of medication and nutritional supplements. To support collection of data for the eCRF on intake of study product, the Investigator may use the data filled out by the parents in the eDiary the week before each study visit as a tool for the discussion. Likewise, data on gastro intestinal tolerance in the eDiary may be used to support the assessment of e.g. adverse events related to gastro intestinal tolerance during the visits.
At visit 5, in addition to follow-up assessments the Investigator will draw a venous blood sample (1.4mL) for assessment of plasma proteins and mineral status parameters, of infants whose parent(s)/legal guardian(s) provide informed consent for a blood sample on a voluntary base.

Infants eligible for the breastfeeding reference arm
As soon as parents or legal guardian(s) give informed consent, infants will have an eligibility assessment and enrol, if meeting the in- and exclusion criteria, in the study. The maximum age at enrolment is 14 days of age. These infants follow the same visit schedule and study assessments as
the randomised infants as described above, including completion of the eDiaries and blood sampling (if separate informed consent for taking a blood sample is given). In case parents/ caretakers cannot use eDiaries, data will be collected via paper diaries.

Study burden and risks

Time spent
4/5 extra hospital visits.

Risk of infant formula
Infants who participate in one of the Infant Formula groups receive an infant formula that is already on the market for more than 10 years. Therefore no major risks or disadvantages are expected for participants compared to infants who do not participate in this study. A general risk is that these formulas contain proteins derived from cow*s milk. These proteins can cause allergic reactions in infants who have a cow*s milk, soy oil or fish oil allergy. For infants who appear to have a cow*s milk, soy or fish allergy, participation will be reassessed by the doctor. Both types of formula contain lactose and are therefore not suitable for infants with lactose intolerance.

Infants might have softer stools due to the non-digestible fibres in these formulas compared to breastfed infants or other commercially available infant formula.

Risk of blood sample
After consent, a blood sample of infant can be collected, this will be done by appropriately trained and experienced staff. Prior to the collection of the blood sample, numbing cream may be applied to reduce discomfort. The procedure may be slightly painful to the infant and may cause bruising at the site of the needle puncture. In rare cases, an infection may occur at the puncture site after blood collection.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. Healthy term infants (gestational age * 37 weeks + 0 days and * 41 weeks + 6 days);
2. Infants* age at enrolment * 14 days;
3. Birth weight within normal range for gestational age and sex (10th to 90th percentile according
to the WHO Child Growth Standards * or local growth standards if available);
4. Head circumference at inclusion within normal range for age and sex (within 2 SD curves according to WHO Child Growth Standards * or local growth standards if available);
5. Infant formula arms: infants who are exclusively formula fed by time of randomisation with a
maximum infants* age of 14 days (infants of mothers who choose not to breastfeed or mothers
who cease breastfeeding for any reason before the infant is 14 days of age);
OR
Breastfeeding reference arm: infants who are exclusively breastfed and whose mothers are intending to exclusively breastfeed their infant at least until the infant is 17 weeks of age;
6. Written informed consent from parent(s) and/or legal guardian(s) aged * 18 years.

Exclusion criteria

Infants of pregnant women/mothers:
1. who are currently participating or will participate in any other (clinical) study involving investigational or marketed products during pregnancy and/or lactation;
2. known to have a significant medical condition (including during pregnancy) that might interfere
with the study or known to affect intra-uterine growth (e.g. placenta previa, pre-eclampsia, eclampsia, gestational diabetes requiring insulin or oral medication), as per investigator*s clinical judgement;
Infants of parents:
3. who are incapable to comply with study protocol or Investigator's uncertainty about the willingness or ability of the parents to comply with the protocol requirements;
Infants:
4. who have to be fed with a special diet other than standard (non-hydrolysed) cow*s milk based
infant formula
5. known to have current or previous illnesses/conditions which could interfere with the study or
its outcome parameters, such as gastrointestinal malformations, congenital metabolic disorders, immune deficiency or major surgery, as per investigator*s clinical judgement;
6. with any history of, or current participation in any other study involving investigational or marketed products.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-04-2017
Enrollment:	12
Type:	Anticipated

Ethics review

Approved WMO

Date:	01-09-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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
ClinicalTrials.gov	NCT03062761
CCMO	NL61257.056.17