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# NutriBrain: A controlled study to investigate the effect of a food product on brain development in very early born infants

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| **Submission date**<br>27/09/2017 | **Recruitment status**<br>No longer recruiting | [X] Prospectively registered<br>[X] Protocol<br>[_] Statistical analysis plan<br>[_] Results<br>[_] Individual participant data<br>[X] Record updated in last year |
| **Registration date**<br>10/10/2017 | **Overall study status**<br>Completed | |
| **Last Edited**<br>26/11/2024 | **Condition category**<br>Neonatal Diseases | |

## Plain English summary of protocol

Current plain English summary as of 21/04/2021:
Background and study aims
Very early born infants have an increased risk of problems during development. This could be learning problems, delayed motor development and attention/behavioral problems. During the 2nd and 3rd trimester of pregnancy important growth and development of the brain occurs. Normally development of the brain of a baby occurs in the safe environment of the womb. Therefore very early birth may lead to disturbed growth and development of the brain, which in turn may result in an increased risk of developmental problems. Previous research shows that infection and inflammation play an important role in the occurrence of brain damage and disturbance of normal growth and development of the brain in very early born infants. Additionally it is known that nutrition is very important for normal brain growth and development of very early born infants. The aim of this study is to investigate the effect of a food supplement on the brain development of very early born infants. It is thought that this supplement may lead to fewer infections, less inflammation and improved functioning of the immune system of very early born infants. In turn this may lead to better growth and development of the brain. The food supplement that is being investigated consists of three main components. The first is a probiotic. Probiotics are ‘good’ bacteria, which offer health benefits. Previous research in very early born infants shows that providing probiotics results in fewer deaths and fewer serious bowel infections. The probiotic used in this study will be provided once a day. The second component is a prebiotic. Prebiotics are fibers that cannot be digested which stimulate growth and activity of ‘good’ bacteria in the bowel. Comparable food components can be found in mother’s milk and it is assumed that these components play an important role in the development of a healthy immune system. The third component is a free amino acid which is an important source of energy for bowel cells and immune system cells. Treatment of very early born infants with free amino acids may lead to improved functioning of the bowel and immune system. The prebiotics and free amino acid will together be added to the infant’s feeding (mothers milk or infant formula) which will be provided throughout the day.

Who can participate?
Very early born infants (born between 24 week and 30 weeks of pregnancy)

What does the study involve?
The infants are randomly allocated to be treated with either an active product (the product described above) or a control product (which does not contain active ingredients). The infants enter the study between 48-72 hours after birth. Treatment is provided from 48-72 hours after birth until 36 weeks postmenstrual age (meaning 36 weeks of the expected pregnancy duration) or discharge home, whichever comes first. If the infant is transferred to a regional hospital the treatment continues at that hospital. The infants are then followed for a period of about 2 years. During the treatment period feeding details (intake and tolerance) are collected. In addition, a number of samples are collected. These samples include stool samples, swabs from skin, oral cavity and nasopharynx, and in total six blood samples of 0.5 to 1 ml. The blood samples are only collected during regular blood samples taken as part of standard care. At the expected date of delivery, and in some cases also at 30 weeks of the expected pregnancy duration, a scan of the brain (MRI scan) is performed to measure growth, development and possible injury of the brain. During the first 2 years of the infants' lives, additional swabs from skin, oral cavity and nasopharynx and stool are collected. This is done during regular hospital visits (no additional visits for the study are required). At the visit at 2 years of age the neurodevelopment of the infant will be assessed.

What are the possible benefits and risks of participating?
It is unknown whether treatment with the product (a combination of probiotics, prebiotics and free amino acid) has any benefits for very early born infants. Previous studies showed that treatment of very early born infants with either probiotics or prebiotics or free amino acid is safe. These studies showed that treatment with probiotics may result in fewer deaths and fewer serious bowel infections. Prebiotics play an important role in the development of a healthy immune system and treatment with free amino acid may lead to an improved function of the bowel and immune system. Possible side effects of different components of the product are mild flatulence, mild abdominal pain and loose stools. In very rare cases the probiotic may cause an infection. This is unexpected for this study, but if it occurs it will be treated with antibiotics.

Where is the study run from?
The study will take place at one enrolling hospital and a number of regional hospitals. The infants enter the study at the enrolling hospital: the Wilhelmina Children's Hospital of the University Medical Center Utrecht. Once the infants are stabilized they are transferred to a regional hospital where the study treatment continues. Nutricia Research will be the sponsor for the intervention study phase (from randomisation until and including TEA). The UMC Utrecht will be the sponsor of the follow-up phase of the study (after TEA until 24 months corrected age).

When is the study starting and how long is it expected to run for?
March 2015 to April 2025

Who is funding the study?
This study is funded by the Athena Grant, a collaboration of the University Medical Centre Utrecht, Nutricia Research and 'Utrecht Center for Food and Health – research program specialized nutrition', subsidy from the Dutch Ministry of Economic Affairs, Utrecht Province and the municipality of Utrecht.

Who is the main contact?
1. Prof. Dr Manon Benders, M.Benders@umcutrecht.nl
2. Gerda van Wijhe, register.clinicalresearchnutricia@danone.com / Gerda.vanWijhe@danone.com

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Previous plain English summary:
Background and study aims
Very early born infants have an increased risk of problems during development. This could be learning problems, delayed motor development and attention/behavioral problems. During the 2nd and 3rd trimester of pregnancy important growth and development of the brain occurs. Normally development of the brain of a baby occurs in the safe environment of the womb. Therefore very early birth may lead to disturbed growth and development of the brain, which in turn may result in an increased risk of developmental problems. Previous research shows that infection and inflammation play an important role in the occurrence of brain damage and disturbance of normal growth and development of the brain in very early born infants. Additionally it is known that nutrition is very important for normal brain growth and development of very early born infants. The aim of this study is to investigate the effect of a food supplement on the brain development of very early born infants. It is thought that this supplement may lead to fewer infections, less inflammation and improved functioning of the immune system of very early born infants. In turn this may lead to better growth and development of the brain. The food supplement that is being investigated consists of three main components. The first is a probiotic. Probiotics are 'good' bacteria, which offer health benefits. Previous research in very early born infants shows that providing probiotics results in fewer deaths and fewer serious bowel infections. The probiotic used in this study will be provided once a day. The second component is a prebiotic. Prebiotics are fibers that cannot be digested which stimulate growth and activity of 'good' bacteria in the bowel. Comparable food components can be found in mother's milk and it is assumed that these components play an important role in the development of a healthy immune system. The third component is a free amino acid which is an important source of energy for bowel cells and immune system cells. Treatment of very early born infants with free amino acids may lead to improved functioning of the bowel and immune system. The prebiotics and free amino acid will together be added to the infant's feeding (mothers milk or infant formula) which will be provided throughout the day.

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Very early born infants (born between 24 week and 30 weeks of pregnancy)

What does the study involve?
The infants are randomly allocated to be treated with either an active product (the product described above) or a control product (which does not contain active ingredients). Treatment is provided from 48-72 hours after birth until 36 weeks postmenstrual age (meaning 36 weeks of the expected pregnancy duration). If the infant is transferred to a regional hospital the treatment continues at that hospital. The infants enter the study between 48-72 hours after birth and are treated until 36 weeks (of the expected pregnancy). The infants are then followed for a period of about 2 years. During the treatment period feeding details (intake and tolerance) are collected. In addition, a number of samples are collected. These samples include stool samples, samples of skin cells, samples of mucus membrane from the nose and mouth, and in total six blood samples of 0.5 to 1 ml. The blood samples are only collected during regular blood samples taken as part of standard care. At the expected date of delivery, and in some cases also at 30 weeks of the expected pregnancy duration, a scan of the brain (MRI scan) is performed to measure growth, development and possible injury of the brain. During the first 2 years of the infants' lives, additional samples of skin cell, mucus membrane and stool are collected. This is done during regular hospital visits (no additional visits for the study are required). At the visit at 2 years of age the blood pressure of the infant is assessed.

What are the possible benefits and risks of participating?
It is unknown whether treatment with the product (a combination of probiotics, prebiotics and free amino acid) has any benefits for very early born infants. Previous studies showed that

treatment of very early born infants with either probiotics or prebiotics or free amino acid is safe. These studies showed that treatment with probiotics may result in fewer deaths and fewer serious bowel infections. Prebiotics play an important role in the development of a healthy immune system and treatment with free amino acid may lead to an improved function of the bowel and immune system. Possible side effects of different components of the product are mild flatulence, mild abdominal pain and loose stools. In very rare cases the probiotic may cause an infection. This is unexpected for this study, but if it occurs it will be treated with antibiotics.

Where is the study run from?
The study will take place at two enrolling hospitals and a number of regional hospitals. The infants enter the study at the enrolling hospitals: the Wilhelmina Children's Hospital of the University Medical Center Utrecht and a second hospital, which will be activated at a later stage. Once the infants are stabilized they are transferred to a regional hospital where the study treatment continues.

When is the study starting and how long is it expected to run for?
March 2015 to September 2025

Who is funding the study?
This study is funded by the Athena Grant, a collaboration of the University Medical Centre Utrecht, Nutricia Research and 'Utrecht Center for Food and Health – research program specialized nutrition', subsidy from the Dutch Ministry of Economic Affairs, Utrecht Province and the municipality of Utrecht.

Who is the main contact?
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2. Prof. Dr Ruurd van Elburg
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# Contact information

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Scientific

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### Type(s)
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gerda.vanwijhe@danone.com

# Additional identifiers

**EudraCT/CTIS number**

**IRAS number**

**ClinicalTrials.gov number**

**Secondary identifying numbers**
15BL89970 (BRA.2.C/A/0)

# Study information

**Scientific Title**
A randomised, double-blind, controlled trial to evaluate the effects of a nutritional product on brain integrity in preterm infants

**Acronym**
NutriBrain

**Study objectives**
The study aims to evaluate the benefits of a specific mixture of probiotics, prebiotics and free amino acid, added to the regular hospital feeding of extremely preterm infants, on white matter integrity, infectious morbidity and subsequent neurodevelopmental outcome. It is hypothesized that the effect of administering the specific mixture is at least equal to the effect of administering a placebo control product with respect to white matter microstructure integrity.

**Ethics approval required**
Old ethics approval format

**Ethics approval(s)**
Medische Ethische Toestingscommissie (Medical Ethical Committee) of the UMC Utrecht, 17/08/2016, ref: 5-213/M NL 49902.041.14

**Study design**
Multicentre randomised double-blind controlled study

**Primary study design**

Interventional

## Secondary study design
Randomised controlled trial

## Study setting(s)
Hospital

## Study type(s)
Treatment

## Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

## Health condition(s) or problem(s) studied
Extremely and very preterm infants (born between 24 week and 30 weeks of pregnancy)

## Interventions
Current intervention as of 21/04/2021:
Infants are randomised to be treated with either:
1. Intervention group: a mixture of probiotics, prebiotics and free amino acid
2. Control group: maltodextrin, casein and whey protein hydrolysates

Treatment will be provided from 48-72 hours after birth until 36 weeks postmenstrual age (meaning 36 weeks of the expected pregnancy duration) or discharge home, whichever comes first. If the infant is transferred to a regional hospital the treatment will continue at that hospital. Thereafter, the infants will be followed until 2 years corrected age.

During the treatment period feeding details (intake and tolerance) will be collected. In addition, a number of samples will be collected. These samples include stool samples, swabs from skin, oral cavity and nasopharynx and in total 6 blood samples of 0.5 to 1 ml. The blood samples will only be collected during regular blood samples, which are being taken as part of standard care.

At the expected date of delivery, and in some cases also at 30 weeks of the expected pregnancy duration, a scan of the brain (MRI scan) will be performed to measure growth, development and possible injury of the brain.

During the first 2 years of the infants, additional swabs from skin, oral cavity and nasopharynx and stool will be collected. This will be done during regular hospital visits (no additional visits for the study will be required). At the visit at 2 years of age the neurodevelopment of the infant will be assessed once.

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Previous intervention:
Infants are randomised to be treated with either:
1. Intervention group: a mixture of probiotics, prebiotics and free amino acid
2. Control group: maltodextrin, casein and whey protein hydrolysates

Treatment will be provided from 48-72 hours after birth until 36 weeks postmenstrual age (meaning 36 weeks of the expected pregnancy duration). If the infant is transferred to a regional hospital the treatment will continue at that hospital. Thereafter, the infants will be followed until 2 years corrected age.

During the treatment period feeding details (intake and tolerance) will be collected. In addition, a number of samples will be collected. These samples include stool samples, samples of skin cells; samples of mucus membrane from the nose and mouth and in total 6 blood samples of 0.5 to 1 ml. The blood samples will only be collected during regular blood samples, which are being taken as part of standard care.

At the expected date of delivery, and in some cases also at 30 weeks of the expected pregnancy duration, a scan of the brain (MRI scan) will be performed to measure growth, development and possible injury of the brain.

During the first 2 years of the infants, additional samples of skin cell, mucus membrane and stool will be collected. This will be done during regular hospital visits (no additional visits for the study will be required). At the visit at 2 years of age the blood pressure of the infant will be assessed once.

## Intervention Type
Supplement

## Primary outcome measure
Current primary outcome measure as of 21/04/2021:
Fractional Anisotropy of the white matter tracts, analysed using Tract-Based Spatial Statistics (TBSS), as assessed using magnetic resonance diffusion tensor imaging at Term Equivalent Age (TEA).

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Previous primary outcome measure:
Fractional anisotropy in the posterior limb of the internal capsule, assessed on diffusion tensor imaging-MRI at Term Equivalent Age (TEA)

## Secondary outcome measures
Current secondary outcome measures as of 21/04/2021:
During the intervention period (from randomisation until and including TEA):
1. White matter injury score assessed according to Kidokoro et al. on T2 and T1 weighted MR images measured at TEA
2. Brain tissue volumes (cerebellar, cortical grey matter, unmyelinated white matter, deep nuclear grey matter and ventricular volumes, and extracerebral cerebrospinal fluid) and cortical morphology (sulcation index, cortical surface area, and cortical thickness) assessed on T2 and T1 weighted MR images measured at TEA
3. Occurrence of serious neonatal infections (defined as culture proven infection with clinical symptoms of an infection; clinically significant necrotising enterocolitis (i.e., Bell's stage two or higher); and/or meningitis with or without positive culture; or clinical respiratory infection ≥4 white blood cells per field associated with a specific pathogen in the tracheal aspirates; according to the categories proposed by Stoll et al.) until TEA
4. Serum concentrations of specific circulating inflammatory markers such as IL-6, IL-10, TNF-α and IL-8/CXCL8, measured at fixed time points until TEA, optional, and on the condition that blood is sampled at that time-point for routine clinical purposes

During the follow-up period (after TEA until 24 months corrected age):
5. Neurodevelopmental outcome at 24 months corrected age as measured by Bayley Scales of Infant and Toddler Development-Third Edition scores on three subscales (cognitive, fine and gross motor) at 24 months corrected age

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Previous secondary outcome measures:
1. White matter injury score, assessed according to Woodward et al. and Kidokoro et al. on T2 and T1 weighted MR images measured at TEA
2. Brain tissue volumes (cerebellar, cortical grey matter, unmyelinated white matter, deep nuclear grey matter and ventricular volumes, and cerebrospinal fluid) and cortical morphology (sulcation index and cortical thickness), assessed on T2 and T1 weighted MR images measured at TEA
3. Cognitive, fine and gross motor development, assessed using Bayley Scales of Infant and Toddler Development-Third Edition at 24 months corrected age
4. Occurrence of serious neonatal infections (defined as culture proven infection with clinical symptoms of an infection; clinically significant necrotising enterocolitis (defined as Bell's stage two or higher); and/or meningitis with or without positive culture; or clinical respiratory infection ≥ 4 white blood cells per field associated with a specific pathogen in the tracheal aspirates; according to the categories proposed by Stoll et al.) until TEA
5. Serum concentrations of specific circulating inflammatory markers such as IL-6, IL-10, TNF-α and IL-8/CXCL8, measured at fixed time points

### Overall study start date
01/03/2015

### Completion date
01/04/2025

## Eligibility

### Key inclusion criteria
Current inclusion criteria as of 21/04/2021:
1. Gestational age of 24+0 to <30+0 weeks (by the best estimate of expected date of delivery)
2. Less than 72 h old, and the intention to receive the first administration of study product between 48-72 h after birth
3. Written informed consent from custodial parent(s)

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Previous inclusion criteria:
1. Gestational age of 24+0 to <30+0 weeks (by the best estimate of expected date of delivery)
2. Less than 72 hours old, and the possibility to receive the first administration of study product between 48-72 hours after birth
3. Written informed consent from custodial parent(s)

### Participant type(s)
Patient

### Age group
Neonate

### Sex
Both

### Target number of participants
98

### Total final enrolment
99

### Key exclusion criteria
Current exclusion criteria as of 21/04/2021:
1. Any relevant proven or suspected chromosomal anomaly, metabolic disorder, genetic syndrome or congenital central nervous system malformation
2. Presence of a congenital central nervous system infection
3. Presence of any gastrointestinal malformation
4. No realistic prospect of survival
5. Concomitant participation in other intervention studies (for example, but not exclusively, those studies involving investigational or marketed nutritional or pharmaceutical products) that could impact on the main outcome parameters and/or subject safety
6. Expected or foreseen inability of the subject and/or their families to adhere to protocol instructions
7. Admission from an extra regional hospital, unless that hospital is a study site
8. Current use of gastric acid inhibitors: H2-receptor antagonists (including ranitidine) or proton pump inhibitors (including omeprazole)

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Previous exclusion criteria:
1. Any relevant proven or suspected chromosomal anomaly, metabolic disorder, genetic syndrome or congenital central nervous system malformation
2. Presence of a congenital central nervous system infection
3. Presence of any gastrointestinal malformation
4. No realistic prospect of survival
5. Concomitant participation in other intervention studies (for example, but not exclusively, those studies involving investigational or marketed nutritional or pharmaceutical products) that could impact on the main outcome parameters and/or subject safety
6. Expected or foreseen inability of the subject and/or their families to adhere to protocol instructions
7. Admission from an extra regional hospital, unless that hospital is a study site
8. Current use of anti-reflux medication

### Date of first enrolment
31/10/2018

### Date of final enrolment
31/05/2022

## Locations

### Countries of recruitment
Netherlands

**Study participating centre**
**Wilhelmina Kinder ZiekenHuis; Universitair Medisch Centrum Utrecht**
Lundlaan 6
Utrecht
Netherlands
3584 EA

**Study participating centre**
**ETZ Tilburg**
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5022 GC

**Study participating centre**
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**Study participating centre**
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**Study participating centre**
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**Study participating centre**
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**Study participating centre**
**Ziekenhuis Rivierenland**
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# Sponsor information

**Organisation**
Nutricia Research

**Sponsor details**
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3584 CT
+31 (0)30 209 5000
nutriciaresearchinfo@danone.com

**Sponsor type**
Industry

**Website**
http://www.nutriciaresearch.com/

**ROR**
https://ror.org/00vt3ry76

# Funder(s)

### Funder type
Industry

### Funder Name
This study is funded by the Athena Grant, a collaboration of the University Medical Centre Utrecht, Nutricia Research and 'Utrecht Center for Food and Health – research program specialized nutrition', subsidy from the Dutch Ministry of Economic Affairs, Utrecht Province and the municipality of Utrecht

# Results and Publications

### Publication and dissemination plan
Current publication and dissemination plan as of 26/11/2024:
It is planned to have the study results published in a high-impact peer-reviewed journal. The first publication is planned within 12 months after all the data on the primary outcome is available (currently planned for 31/03/2025).

Previous publication and dissemination plan:
It is planned to have the study results published in a high-impact peer-reviewed journal. The first publication is planned within 12 months after all the data on the primary outcome is available (currently planned for 31/03/2024).

### Intention to publish date
30/06/2025

### Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

### IPD sharing plan summary
Data sharing statement to be made available at a later date

### Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Protocol article | | 17/03/2021 | 21/04/2021 | Yes | No |