PRIMAL Clinical Study: Efficacy of probiotics to prevent gut dysbiosis in very preterm infants (VPIs) and moderate preterm infants of 28+0 - 32+6 weeks of gestation: A randomized, placebo-controlled double-blind study

Aim: Gut dysbiosis is associated with acute and long-term health problems. Probiotics are widely used to prevent dysbiosis in extremely preterm infants. Yet, the evidence from studies is inconclusive and focused on short term effects. We aim to define the potential of probiotics for modulating both the intestinal microbiota and the developing immune system in preterm infants.

Gut dysbiosis, defined as a significant deviation of the gut microbiome from a healthy state (eubiosis), is associated with long-term health problems, specifically in vulnerable populations such as preterm infants. It appears that the developing flora of the newborn infant is particularly sensitive to disturbances, which may lead to long term dysbiosis. Specific diseases, such as sepsis and necrotizing enterocolitis, are associated with gut dysbiosis and immunological dysregulation. Dysbiosis might be ameliorated with probiotics and aggravated as a side effect of antibiotic treatment, which is administered to > 50% of preterm infants. However, multi-center, randomized-controlled studies in a well-defined cohort of VPI are few, focus on acute outcomes like necrotizing enterocolitis, and none has directly assessed the effects of probiotics and other interventions on the microbiome at high resolution and with respect to comprehensive immunophenotyping.
Organizational Data

- DRKS-ID: **DRKS00013197**
- Date of Registration in DRKS: **2018/03/23**
- Date of Registration in Partner Registry or other Primary Registry: [---]*
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **17-130 , Ethik-Kommission Universität zu Lübeck Medizinische Fakultät des Universitätsklinikums Schleswig-Holstein**

Secondary IDs

ICD10: **K63.8 - Other specified diseases of intestine**

Health condition or Problem studied

- **ICD10: K63.8 - Other specified diseases of intestine**

Interventions/Observational Groups

- **Arm 1:** *Lactobacillus acidophilus and Bifidobacterium longum and Bifidobacterium infantis, 1 /day p.o. (capsule), for 28 days*
- **Arm 2:** *Placebo, 1 /day p.o. (capsule), for 28 Tage*

Characteristics

- **Study Type:** Interventional
- **Study Type Non-Interventional:** [---]*
- **Allocation:** Randomized controlled trial
- **Blinding:** [---]*
- **Who is blinded:** patient/subject, investigator/therapist, caregiver, assessor
- **Control:** Placebo
- **Purpose:** Prevention
- **Assignment:** Parallel
- **Phase:** N/A
- **Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels):** N/A

Primary Outcome
Determination of intestinal dysbiosis on day 28-30 using stool sample

Secondary Outcome

In both groups significant deviations of the microbiome are determined. Further secondary endpoints are assumed symptoms or consequences of intestinal dysbiosis a) infection-related and b) metabolism.

Countries of recruitment

- DE Germany

Locations of Recruitment

- University Medical Center Klinik für Kinder- und Jugendmedizin, UKSH Campus Lübeck, Lübeck
- Medical Center Klinikum Aschaffenburg-Alzenau, Klinik für Kinder- und Jugendmedizin, Aschaffenburg
- University Medical Center Universitätskinderklinik Bochum, St. Elisabeth-Hospital, Bochum
- University Medical Center Universitätsklinikum Bonn (AöR), Zentrum für Kinderheilkunde, Bonn
- Medical Center Klinikum Links der Weser GmbH, Klinik für Kinder- und Jugendmedizin, Abt. f. Neonatologie und päd. Intensivmedizin, Bremen
- University Medical Center Universitätskinderklinik Essen, Essen
- University Medical Center Universitätsklinikum Freiburg, Zentrum für Kinder- u. Jugendmedizin Neonatologie / Intensivmedizin, Freiburg im Breisgau
- University Medical Center Universitätsklinikum Halle, Klinik und Poliklinik für Pädiatrie I, Halle Saale
- Medical Center Katholisches Kinderkrankenhaus Wilhelmstift gemeinnützige GmbH, Hamburg
- University Medical Center Medizinische Hochschule Hannover, Kinderklinik I, Hannover
- University Medical Center Universitätsklinik Heidelberg, Zentrum für Kinder- und Jugendmedizin, Klinik für Neonatologie, Heidelberg
- University Medical Center Universitätsklinikum des Saarlandes und Medizinische Fakultät der Universität des Saarlandes, Klinik für Allgemeine Pädiatrie und Neonatologie, Homburg (Saarland)
- University Medical Center Universitätsklinikum Jena, Klinik für Kinder- und Jugendmedizin, Sektion Neonatologie, Jena
- University Medical Center Klinikum der Universität zu Köln, Klinik und Poliklinik für Allgemeine Kinderheilkunde, Neonatologie und Pädiatrische Intensivmedizin, Köln
- Medical Center St. Vincenz Krankenhaus GmbH, Klinik für Kinder- und Jugendmedizin St. Louise, Neonatologie und päd. Intensivmedizin, Paderborn
- Medical Center Klinikum Südstadt Rostock, Abteilung für Neonatologie, Rostock
Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2018/04/01**
- Target Sample Size: **654**
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **28 Weeks of pregnancy**
- Maximum Age: **32 Weeks of pregnancy**

Additional Inclusion Criteria

Key inclusion criteria for participating in the PRIMAL trial in the first 48 hours of life are:
1. Patients (or as appropriate whose legal guardian) have been informed about the study procedures and interventions and have given written informed consent; 2. Female or male preterm infants born between 28 0/7 to 32 6/7 gestational weeks of any ethnic background, who are admitted to one of the listed study sites within the first 48h of life.

Exclusion criteria

1. Infants with lethal malformations or severe gastrointestinal malformations, which preclude appropriate enteral feeding or require surgery within the primary observational time of 28 days. 2. Infants who primarily present with NEC (Bell’s stage ≥ 1B) or with any medical condition that is likely to be lethal in the first 48h of life.

Addresses

- Primary Sponsor
  Universitätsklinikum Schleswig-Holstein
  Mr. Prof. Dr. med. Christoph Härtel
  Ratzesburger Allee 160
Primary Sponsor

Universitätsklinikum Schleswig-Holstein
Mr. Prof. Dr. med. Christoph Härtel
Ratzeburger Allee 160
23538 Lübeck
Germany

Telephone: 0451 500 42801
Fax: 0451 500 43064
E-mail: christoph.haertel at uksh.de
URL: uksh.de

Contact for Scientific Queries

Universitätsklinikum Schleswig-Holstein
Mr. Prof. Dr. med. Christoph Härtel
Ratzeburger Allee 160
23538 Lübeck
Germany

Telephone: 0451 500 42801
Fax: 0451 500 43064
E-mail: christoph.haertel at uksh.de
URL: uksh.de

Contact for Public Queries

Universitätsklinikum Schleswig-Holstein
Mr. Prof. Dr. med. Christoph Härtel
Ratzeburger Allee 160
23538 Lübeck
Germany

Telephone: 0451 500 42801
Fax: 0451 500 43064
E-mail: christoph.haertel at uksh.de
URL: uksh.de

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Bundesministerium für Bildung und Forschung Dienstsitz Bonn (Projektträger DLR, Heinrich-Konen-Str. 1, 53227 Bonn)
Heinemannstr. 2
53175 Bonn
Germany
Public funding institutions financed by tax money/Government funding body (German Research Foundation (DFG), Federal Ministry of Education and Research (BMBF), etc.)

Bundesministerium für Bildung und Forschung Dienst­sitz Bonn (Projektträger DLR, Heinrich-Konen-Str. 1, 53227 Bonn)
Heinemannstr. 2
53175 Bonn
Germany

Telephone: [---]*
Fax: [---]*
E-mail: [---]*
URL: www.bmbf.de

Status

- Recruitment Status: Recruiting ongoing
- Study Closing (LPLV): [---]*

Trial Publications, Results and other documents

* This entry means the parameter is not applicable or has not been set.
*** This entry means that data is not displayed due to insufficient data privacy clearing.