PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Supplementation with Bifidobacteria longum subspecies infantis EVC001 for mitigation of type 1 diabetes autoimmunity - The GPPAD-SINT1A randomised controlled trial protocol
AUTHORS	Ziegler, Anette; Arnolds, Stefanie; Kölln, Annika; Achenbach, Peter; Berner, Reinhard; Bonifacio, Ezio; Casteels, Kristina; Elding Larsson, Helena; Gündert, Melanie; Hasford, Joerg; Kordonouri, Olga; Lundgren, Markus; Oltarzewski, Mariusz; Pekalski, Marcin; Pfirrmann, Markus; Snape, Matthew; Szypowska, Agnieszka; Todd, John; Study group, GPPAD

VERSION 1 – REVIEW

REVIEWER	Kostic, Alex Harvard Medical School, Microbiology
REVIEW RETURNED	15-Aug-2021

GENERAL COMMENTS	The authors present a detailed and well-formulated clinical trial design to test whether probiotic supplementation with Bifidobacterium infantis in infants at risk for type 1 diabetes can result in a change in autoantibody positivity. The study design is overall robust. I have a few questions regarding the details of administration of B. infantis: Where and how is the formulation being produced? What is the shelf stability/expiry and what is the variance in CFUs between doses? What time of day is the dose administered? Perhaps coinciding with breastfeeding can help engraftment.

REVIEWER	Bock, Patricia Universidade Federal do Rio Grande do Sul
REVIEW RETURNED	23-Aug-2021

GENERAL COMMENTS	The study is interesting, the manuscript is very well written, and the issue not yet explored. However, I have some suggestions and questions to improve the manuscript quality, as follows: 1. Methods: The study protocol could follow the SPIRIT recommendation and the order of the checklist. 2. Primary outcome: Define multiple autoantibodies. Two will be considered multiple? 3. Dose: How the daily dose was chosen? 4. The authors could describe the Strategies for trial retention.

	5. Describe the method of generating the allocation sequence, mechanism of implementing the allocation sequence, blinding, plans for data management

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Alex Kostic, Harvard Medical School

Comments to the Author:
The authors present a detailed and well-formulated clinical trial design to test whether probiotic supplementation with Bifidobacterium infantis in infants at risk for type 1 diabetes can result in a change in autoantibody positivity.
The study design is overall robust. I have a few questions regarding the details of administration of B. infantis:

Where and how is the formulation being produced?

Response: Active and placebo products are provided by Evolve Biosystems, USA. Blinding, packing, and distribution to clinical study sites is performed by the pharmacy, University of Heidelberg, Germany (please see the addition in paragraph “Intervention” on page 12.

What is the shelf stability/expiry and what is the variance in CFUs between doses?

Response: The actual concentration as per batch certificate of analysis ranged from 13.8 x 10^9 to 15.8 x 10^9 CFU per sachet; the shelf-life is 15 months please see paragraph “Intervention”, page 12.

What time of day is the dose administered? Perhaps coinciding with breastfeeding can help engraftment.

Response: The solution will be administered using a feeding syringe, preferably in the morning. Parent(s) will be instructed in the administration and storage of the sachets (should be kept frozen until use) at or prior to their baseline visit, please see also paragraph “Intervention”, page 12.

Reviewer: 2
Dr. Patricia Bock, Universidade Federal do Rio Grande do Sul

Comments to the Author:
The study is interesting, the manuscript is very well written, and the issue not yet explored. However, I have some suggestions and questions to improve the manuscript quality, as follows:

Methods: The study protocol could follow the SPIRIT recommendation and the order of the checklist.

Response: The checklist was added to the manuscript and the paragraph “Intervention” was moved further up according to SPIRIT.

Primary outcome: Define multiple autoantibodies. Two will be considered multiple?

Response: Persistent confirmed multiple beta-cell autoantibodies (primary outcome) is defined as confirmed IAA, confirmed GADA, confirmed IA-2A, or confirmed ZnT8A in two consecutive samples, AND at least one other confirmed antibody from these four antibodies in one sample. The sentence in the paragraph “Criteria for persistent confirmed beta-cell autoantibodies” was adapted accordingly, page 8.

Dose: How the daily dose was chosen?

Response: The dose was selected according to the previous IMPRINT study. Please see the additional information in the paragraph “Intervention” on page 12.

The authors could describe the Strategies for trial retention.

Response: A special family friendly retention concept has been developed to make families feel as part of the research team. Special care and support is offered for families who participate in the study and small gifts for the children are given out during the visits. Families are reminded of the advantages of study participation. Strategies for retention also include newsletters and reports on islet- and celiac autoantibody testing, and activities on community building. Please see the paragraph “Retention strategies” added to the manuscript on page 16.

Describe the method of generating the allocation sequence, mechanism of implementing the allocation sequence, blinding, plans for data management

Response: Subjects will be centrally randomised in a 1:1 ratio to one of the two intervention arms via IVRS/IWRS at the baseline visit. The participant and the treating physician and the central research team will be blinded. The study product packages will not indicate whether the content is B. infantis or placebo, but kit numbers. The IVRS /IWRS will assign the appropriate kit numbers for each participant following a randomisation list. Emergency unblinding will be available through the IVRS / helpdesk. (please see the updated paragraph “Randomisation”, page 11).