Author’s response to reviews

Title: Nutritional adequacy of a novel human milk fortifier from donkey milk in feeding preterm infants: study protocol of a randomized controlled clinical trial

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We want to thank the reviewers for their kind comments and useful suggestions that have been taken in due account in the present revised form. In particular:

1. Methods section: Please, state the trial was registered and provide the registration number.

The trial was registered ISRCTN Registry BioMed Central (Registration number: ISRCTN70022881).
2. Methods section >> Page 8, Line 58 >> Informed written consent should not be considered an inclusion criteria because this is an ethical requirement. Inclusion criteria refers to characteristics that the prospective participants must have if they are to be included in the study.

We followed your suggestion.

3. Methods section >> Page 10, Line 57 >> Outcome measures: the number of feeding intolerance episodes is reported as both a primary and secondary outcome. Is that a slip-up?

We thank the reviewer for signaling that the difference between the primary and the secondary endpoint concerning feeding intolerance was not clear. The primary endpoint is a dychotomous variable: Success=no episode of feeding intolerance / Failure= at least one episode of feeding intolerance within the 21th day of observation. As a consequence, a subject who underwent one episode only is a failure just as a subject who underwent two or more episodes. As for the secondary endpoint, we considered the number of feeding intolerance episodes within the 21th day of observation, as a measure of the severity of feeding intolerance.

Accordingly, we changed the text at pag11 line 49 as follows: Primary Endpoint: occurrence of at least one episode of feeding intolerance, defined as interruption of enteral feeding for at least eight consecutive hours during the observation period.

4. Methods section >> Page 12 Line 51 >> Statistical analysis: The whole statistical analysis will be probably done using SAS, not just the model fitting.

Yes, you are right. We moved this statement at the bottom of paragraph.

5. Methods section >> Page 12 >> Statistical analysis: The type of statistical test to compare groups will depend on the type of variable (continuous or categorical) and their distribution. If the primary variable is the number of episodes of intolerance, the variable is ordinal and a Mantel-Henzel test should be used.

In the case of the secondary outcome variables, when comparing by groups the statistical test in the bivariate analysis will depend again on the type of variable and its distribution. It would also be convenient to compare these variables. It seems reasonable to start with a bivariate analysis and if it is necessary to adjust for other influences to move to the linear model. In all outcome types, it will be necessary to use repeated measures analysis not only in the case of the secondary outcomes, to account for the correlation that exists between the observations in the same individual.

As for primary endpoint we have one observation only per subject (who is classified as a success or a failure). The difference between arms will be tested with Fisher exact test. All secondary endpoints will be modelled in the framework of generalised linear model (Nelder & Wedderburn 1972) allowing, when appropriate, for relevant covariates. The number of episodes of feeding intolerance (0, 1 … k) will be modelled as a Poisson variable. Total hours of enteral feeding
interruption, time required to reach full enteral feeding, hospital stay duration, gastric emptying time will be modelled (after proper scale transformation, if required) as normal variables. The occurrence of clinical outcomes, assessed as dichotomous variable (yes/no) will be modelled as binomial variables. Metabolic and auxological outcomes, which are repeatedly during study period, will be modelled (after proper scale transformation, if required) as normal variables, with a model allowing for repeated measures.

We changed the methods section accordingly.