PiPS: Trial of probiotic administered early to prevent infection and necrotising enterocolitis

Statistical Analysis Plan

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1. INTRODUCTION

This document details the proposed presentation and analyses for the main publications reporting results from the HTA funded multicentre randomised placebo controlled trial of early administration of the probiotic *Bifidobacterium breve* strain BBG (*B. breve* BBG) to preterm infants (PiPS). The results reported in these publications will follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, although they are expected to follow the broad principles described. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The analysis plan will be available on request when the principal manuscripts are submitted for publication. Suggestions for subsequent analyses by journal editors or referees will be considered carefully and carried out, as far as possible, in line with the principles of this analysis plan.

Any deviations from the statistical analysis plan will be described and the rationale given in the final report of the trial. The analysis will be carried out by an identified, appropriately qualified and experienced statistician, who will ensure the integrity of the data during processing. Examples of such procedures include quality control and evaluation procedures. This document and the interim and final analyses will be produced in line with NPEU Standard Operating Procedures ST 105 Statistical Analysis Plan; ST 104 Interim Statistical Analysis; and ST 106 Final Statistical Analysis and Reporting.

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2. BACKGROUND INFORMATION

2.1 Aims of the Trial

The aims of the trial were pre-specified in the protocol and are set out here.

2.1.1 Primary aims

To evaluate if early administration of the probiotic *Bifidobacterium breve* strain BBG (*B. breve* BBG) to preterm infants compared to placebo reduces the risk of:

- late onset blood stream infection diagnosed on a sample drawn after 72 hours,
- necrotising enterocolitis,
- death before discharge from hospital.

2.1.2 Secondary aims

To evaluate the effect of early administration of the probiotic *Bifidobacterium breve* strain BBG (*B. breve* BBG) to preterm infants compared to placebo on:

- The composite outcome of any, or a combination of, the three primary outcomes
- microbiological outcomes such as blood steam infection with skin commensals, number of babies with a blood culture taken, number of blood cultures taken per baby;
- other clinical outcomes such as the use of antibiotics for treatment of infection, broncho-pulmonary dysplasia, hydrocephalus, retinopathy of prematurity, length of stay in the neonatal unit;

- nutritional and gastroenterological outcomes such as achieving full feeds and weight gain.

The presence of the probiotic intervention strain in stool samples will also be reported as a process outcome by trial arm.

2.2 Trial Design

PiPS is a multi-centre double blind randomised controlled trial of the early administration to preterm infants of the probiotic *Bifidobacterium breve* strain BBG (B. breve BBG) or placebo.

Date of start of recruitment:	July 2010
Target end date of recruitment:	July 2013
Target number of participants:	650 in each arm
Recruiting centres:	23 UK neonatal units

2.3 Eligibility

The eligibility criteria for the trial were pre-specified in the protocol and are set out here.

2.3.1 Hospital eligibility

Hospitals with neonatal units admitting around 50 babies or more each year born before 31 completed weeks of gestation (up to and including 30 weeks + 6 days) were eligible to join the study.

2.3.2 Infant eligibility

Inclusion criteria:
Babies with all of the following criteria wereeligible for recruitment to the study:

- gestational age between or equal to 23 weeks and 0 days and 30 weeks and 6 days by the best estimate of Expected Date of Delivery (usually by first trimester antenatal ultrasound, alternatively by 'certain' LMP);
- less than 48 hours old;
- with written informed parental consent.

Babies already on antibiotics for suspected or proven infection were eligible for recruitment to the study.

Exclusion criteria:
Babies with any of the following criteria were excluded from the study:

- a lethal congenital abnormality known at trial entry;
- any known gastrointestinal malformation;
- no realistic prospect of survival.

2.4 Treatment Interventions

2.4.1 Investigational medicinal product and placebo

The investigational product tested was *Bifidobacterium breve* strain BBG (*B. breve* BBG). The product was supplied freeze dried with corn starch; the placebo was corn starch alone.

2.4.2 Preparation and Dose

The freeze dried powder was suspended in 3 ml 1/8 strength (1 scoop to 240 ml sterile water) of the elemental infant formula Neocate and allowed to settle for 30 minutes.
1 ml of supernatant was withdrawn and given to the baby; for the active product this contained 6.7×10^7 - 6.7×10^9 colony forming organisms.

2.4.3 Dosing schedule

Once daily.

2.4.4 Route of administration

The products were administered via a naso-gastric or oro-gastric tube or, for babies no longer tube fed, directly into the mouth using a syringe.

2.4.5 Treatment period

Starting as soon as possible after randomisation and continued until 36 completed weeks of post-menstrual age (36 weeks + 0 days) or death or discharge from hospital if sooner. If the baby was transferred between different neonatal units, e.g. transferred back to a local unit when he/she no longer needed intensive care, where possible the intervention was continued until the course was completed.

2.5 Principal Comparisons of Interest

The comparison of primary interest is whether there is a difference in any of three primary outcomes, infection, NEC or death, between the groups of the trial. As the primary analysis is by intention-to-treat, the outcomes will be compared across randomised groups for all infants recruited regardless of whether, or for how long, they received the PiPS trial interventions.

2.6 Definition of Primary and Secondary Outcomes

2.6.1 Primary outcomes

1. Any baby with an episode of blood stream infection, with any organism other than a skin commensal, diagnosed on a sample of blood drawn more than 72 hours after birth and before 46 weeks post-menstrual age, death or discharge from hospital, whichever is soonest. Skin commensals include coagulase negative staphylococci (CoNS) and Corynebacteria (definitions in Appendix 1);

2. Necrotising enterocolitis, Bell stage II or III (definitions in Appendix 2);

3. Death before discharge from hospital.

Data will be censored at the date of the final database lock (see section 3.3). Therefore if a baby is still in hospital at this time, they will be considered alive for the purposes of defining this primary outcome.

2.6.2 Secondary outcomes

1. Number of babies with the composite outcome of any or a combination of the 3 primary outcomes.

Microbiological outcomes: (definitions in Appendix 1)

(Outcomes 2 to 7 are for samples taken more than 72 hours after birth and before 46 weeks post-menstrual age, death or discharge home, whichever is soonest)

2. Number of babies with any positive blood culture with an organism recognised as a skin commensal e.g. CoNS or Corynebacteria;

3. Number of babies with blood cultures taken;

4. Number of blood cultures taken per baby;

5. Number of babies with episodes of blood stream infection with organisms other than skin commensals by organism: e.g. *E. coli*, *Klebsiella* spp., fungi; and by antibiotic resistance types: specifically MRSA, vancomycin resistant enterococci (VRE) and extended spectrum betalactamase producing Gram negative bacteria (ESBL);

6. Number of babies with isolates of organisms other than skin commensals from a normally sterile site other than blood: e.g. CSF, supra-pubic aspiration of urine, pleural cavity etc.;

7. Number of babies with a positive culture of *B. breve* BBG from any normally sterile site;

8. Total duration of days of antibiotics and/or anti-fungals administered per baby after 72 hours and until 46 weeks post-menstrual age, death or discharge from hospital whichever is sooner for treatment of suspected or proven sepsis i.e. excluding prophylactic use;

9. The number of babies colonised with the administered probiotic strain defined by the isolation of *B. breve* BBG from stool samples at 2 weeks post-natal and at 36 weeks post-menstrual age;

10. Stool flora: the number of babies colonised with MRSA, VRE (vancomycin resistant enterococci) or extended spectrum betalactamase producing Gram

negative bacteria (ESBL) at 2 weeks post-natal and at 36 weeks postmenstrual age.

Nutritional and gastroenterological outcomes:

11. Age at achieving full enteral nutrition (defined as 150 ml/kg/day for 1 day);

12. Change of weight Z score from birth to 36 weeks post-menstrual age or discharge from hospital if sooner.

Other clinical outcomes:

13. Broncho-pulmonary dysplasia: (definitions in Appendix 3);

14. Hydrocephalus and / or intraparenchymal cysts confirmed by cerebral ultrasound scan performed during the baby's in-patient stay;

15. Worst stage of retinopathy of prematurity in either eye at any time before discharge or death;

16. Length of stay in intensive, high dependency and special care (BAPM 2001: definitions in Appendix 4).

2.7 Data Collection Schedule

Information was collected at the following times:

- at trial entry – confirmation of eligibility and baseline data;
- daily until the post-natal age of 2 weeks - details of type of milk given and antibiotics administered;
- until discharge from hospital or death – data on suspected or proven episodes of NEC to facilitate classification, and microbiology data on samples taken from normally sterile sites;
- at 36 weeks post-menstrual age or sooner if discharged earlier, and at discharge – static data on clinical outcomes;
- 2 weeks post-natal and 36 weeks post-menstrual age – stool samples for detection of colonisation of the probiotic strain administered and other bacteria.

2.8 Sample Size & Power

Neonatal sepsis:
The percentage of babies with bloodstream infection in our pilot study was 44%. This included infection with skin commensals. The number of babies fulfilling criteria for the primary endpoint in this study will be lower, as infections with skin commensals

are excluded. Assuming a 5% level of statistical significance, a trial of 1,300 babies will have 90% power to detect a 40% relative risk reduction from 15% to 9.1%; likewise if the incidence is closer to 12%, a trial of this size will still have 90% power to be able to detect a 44% relative risk reduction from 12% to 6.7%, and a 44% reduction from 10% to 5.6%.

NEC:
The incidence of NEC is estimated to be 15%. This is based on NEC incidence at the Homerton Hospital over a 3 year period in babies less than 1,000g birthweight. A sample size of 1300 will have 90% power (at a 5% significance level) to be able to detect a 40% relative risk reduction in this outcome from 15% to 9%.

Death:
The incidence of death is also estimated to be 15%. This is based on survival of babies below 31 weeks gestational age in London extracted from pan-London data collected by the Thames Regional Perinatal Group. The sample size of 1300 will have 90% power (at a 5% significance level) to be able to detect a 40% relative risk reduction in this outcome from 15% to 9%.

2.9 Treatment Allocation

Allocation used a web-based randomisation service (with telephone back-up) based at the National Perinatal Epidemiology Unit (NPEU) Clinical Trials Unit, University of Oxford. The randomisation program used a minimisation algorithm to ensure balance on hospital, sex, gestational age at birth and whether or not randomisation occurs sooner than 24 hours after birth.

2.10 Interim Analyses and Stopping Rules

2.10.1 Interim analyses

Interim analyses were supplied, in strict confidence, to an independent Data Monitoring Committee (DMC) as frequently as its Chair requested and according to the DMC Charter as agreed by the DMC and TSC at their first combined meeting.

2.10.2 Criteria for determining termination of the trial

In the light of interim data and other evidence from relevant studies the DMC informed the Trial Steering Committee (TSC) that, in their view, there was no proof beyond reasonable doubt that the data indicated that the trial should be terminated. Recommendations to continue the trial were made to the TSC based, in part, on statistical considerations.

Appropriate proof beyond reasonable doubt cannot be specified precisely. A difference of at least 3 standard errors in the interim analysis of a major endpoint was needed to justify halting or modifying the study prematurely.

2.11 Independent Data Monitoring Committee Membership

Chair Professor Diana Elbourne
Statistician
Professor of Health Care Evaluation, The London School of Hygiene & Tropical
XXXX

Dr Benjamin Stenson
Consultant neonatologist, Simpson Centre for Reproductive Health
XXXX

Dr Jim Gray
Consultant Microbiologist, Birmingham Children's Hospital
XXXX

2.12 Trial Reporting

The trial will be reported according to the principles of the CONSORT statement[1].

3. DATA MANAGEMENT

3.1 Data Collection

All data for trial analyses, apart from stool samples, are routine clinical items that should be available from clinical notes or local microbiological laboratory records.

3.1.1 Form 1 – Trial Entry (1 form per baby)

At entry into PiPS, along with eligibility and randomisation data, maternal and obstetric information was abstracted from the maternal case notes and neonatal information was abstracted from the infant's medical records and entered onto Form 1 (Trial Entry Form). Form 1 was completed by the person randomising the infant into the PiPS trial.

3.1.2 Form 2 – Daily Data (1 form per baby per hospital)

Daily data collection until the post-natal age of 2 weeks collecting details of type of milk given and total daily volume; antibiotics and antifungals administered; and whether systemic ranitidine / proton pump inhibitor were given. Where a baby was transferred between hospitals within this 2 week time period, the form accompanied the baby.

3.1.3 Form 3 – Baby Transfer, Discharge or Death (multiple forms per baby)

When the baby was transferred to another hospital, discharged home or died, and at discharge home. Information about the infant's clinical outcomes whilst at that hospital were abstracted from the infant's medical records and recorded on Form 3. This form captured data from birth to discharge from that hospital or death at that hospital, on infections, whether full feeds were reached, results of any cerebral

ultrasound scans, treatment for patent ductus arteriosus, congenital malformations, retinopathy of prematurity, use of antimicrobials after the first 14 days since birth, any surgical procedures, use of level 1 and level 2 care, detail on any periods of omitting the intervention, and details of death or transfer to another hospital for continuing care. This form also captured data at 36 weeks post-menstrual age if the baby reached this age.

3.1.4 Form 4 – Abdominal Pathology (multiple forms per baby)

Data until transfer, discharge home or death around suspected or proven episodes of NEC whilst at that hospital to facilitate classification (definitions at Appendix 2).

3.1.5 Form 5 – Serious Adverse Event (SAE) & Suspected Unexpected Serious Adverse Reaction (SUSAR) (multiple forms per baby)

All details relating to a SAE or SUSAR including a description of the event, prescribed treatment details, concomitant treatments and further investigations.

3.1.6 Form 6 – Permanent Intervention Discontinuation or Trial Withdrawal (one form per baby)

Details regarding who and why the intervention was permanently stopped, and/or the baby withdrawn from the trial.

3.1.7 Stool Sample Analysis Report Form (two forms per baby)

This form was used to aid processing and recording of detailed colony types identified in faecal specimens collected as close as possible to 2 weeks post-natal age and 36 weeks post-mentrual age. Summary data were also recorded on these forms and entered onto the PiPS OpenClinica database. *B. breve* was identified using culture and Polymerase Chain Reaction (PCR) techniques at 2 weeks and culture only at 36 weeks. Quantities were recorded in units of log Colony Forming Units (CFU)/g for culture and ng DNA for PCR results. The following were identified using culture only: MRSA, VRE, MRGNB, ESBL.

3.1.8 Microbiology data (one record on database per baby)

Microbiological information obtained from the local microbiological laboratory on all samples taken from normally sterile sites, including blood, after 72 hours and before 46 weeks post-menstrual age, discharge home or death, whichever was soonest. Data recorded included details of organisms grown together with their antibiotic sensitivities. Summary data were entered directly onto the PiPS OpenClinica database, recording the number of blood cultures taken, episodes of infection with skin and non-skin commensals, what organisms were cultured and from which sterile sites, and if *B. breve* was cultured.

3.2 Data Entry, Cleaning and Validation

All completed Data Collection Forms (Forms 1 to 6) were sent to the NPEU CTU and double-entered onto a web-based clinical database, OpenClinica. Data were entered according to NPEU CTU OpenClinica data entry conventions. All personal details were entered into a Microsoft Access database. Validation programs performed a series of range, logic and missing data checks to identify any inconsistencies within and across forms on an ongoing basis. Some queries were resolved at NPEU according to predefined protocols, those that could be resolved were communicated to the appropriate centres by the Trial Co-ordinator and/or Data Manager, resolved where possible, and documented.

3.3 Database lock

The database will be locked for the final analysis on or close to 31st January 2014. However, information on deaths will continue to be collected after database lock and up until submission of the publication. The final lock of the database will therefore be the date of first submission of the publication.

3.4 Derivation of Variables

See Appendix 5 for derivation of variables.

3.5 Reliability

Data were double-entered into a MHRA compliant program by experienced data processors. Validity checks were run automatically by the computer program and 'unrealistic' values flagged, checked, and amended as necessary following NPEU CTU SOPs. On-site training of local staff by the trial research nurses was continuous throughout the trial.

Regular site visits were made by the study research nurse to ensure adherence to the protocol and to deal with any specific site issues. A major focus of these visits was to confirm that procedures to minimise the risk of cross contamination with the probiotic organism were followed both in the milk kitchen and in clinical areas.

Studies that have reported stool colonisation with the active probiotic bacterium, including our pilot, have reported cross-contamination of the placebo group. A system was established to monitor colonisation rates with the intention that the nurses reinforce training at any site where colonisation rates were outliers suggesting that there was excessive cross-colonisation.

All Form 4s containing data on Abdominal Pathology were reviewed by the Chief Investigator and one other clinician. The main purpose of the review was to confirm the occurrence, stage and number of any NEC episodes. These data were entered onto an Excel spread sheet and are considered the definitive data for the NEC related outcomes.

4. SERIOUS ADVERSE EVENT REPORTING

A Serious Adverse Event (SAE) is defined as the occurrence of an AE after trial entry where the death of the participant resulted or was otherwise threatened or where the participant required prolonged hospital stay; or resulted in persistent or significant disability or incapacity.

The group of infants in the PiPS trial have many serious adverse events and these were recorded in the case report forms. We anticipated the following SAEs in our infant population: death, culture positive infection with organisms other than *Bifidobacterium breve* strain BBG, necrotising enterocolitis or focal intestinal perforation, broncho-pulmonary dysplasia, intracranial abnormality (haemorrhage or focal white matter damage) on cranial ultrasound scan or other imaging, pulmonary haemorrhage, patent ductus arteriosus, retinopathy of prematurity requiring retinal surgery. All of these conditions were recorded on the case report form but none required immediate reporting to the sponsor.

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as the occurrence of an adverse reaction after trial entry the nature or severity of which is not consistent with the known safety profile of the study intervention.
The only recognised possible adverse reactions associated with probiotic administration are:

- Positive culture of the probiotic organism *Bifidobacterium breve* strain BBG from a normally sterile site – This is a very rare event and with this organism it has only been reported once.
- Intestinal obstruction caused by starch – this was reported when this product was first used but has not been reported with the product prepared as it will be in this study administering only the supernatant after suspension and allowing the starch to settle.

Planned reporting procedures of the PIs and CI

- Any event which is described in the Protocol as expected will not be reported to the sponsor in an expedited manner.
- The CI will ensure that PIs are asked about any untoward SAEs / SUSARs occurring since the previous contact.
- The PIs will ensure that all anticipated SAEs are recorded in the infant's case report form; these were reviewed by the DMC during the trial.
- The PIs will report SUSARs to the Clinical Trials Unit, NPEU by telephone/fax/email at the earliest opportunity and within one working day of them becoming aware of the occurrence.
- The PI will provide a written detailed report to the Clinical Trials Unit, NPEU within 3 days of first knowledge of a fatal SUSAR and within 7 days of a non-fatal SUSAR.

- The CI or person with delegated responsibility will review all SAEs/SUSARs as reported on Form 5 within one working day of their receipt, and will consider causality and expectedness. Where there is any suspicion that an event is linked to the PiPS trial intervention that event will be classified as a SUSAR and reported accordingly.
- All expected SAEs will be recorded on the case report form, and reviewed by the Data Monitoring Committee during the trial. SUSARs are to be sent to the chair of the DMC for regular review.
- The CI will notify the MHRA and South Central - Oxford A REC and Sponsor of all SUSARs reported to them by the PIs within 7 days if the SUSAR is linked to a death or considered life-threatening; with additional information sent within a further 8 days. All other SUSARs will be notified to the MHRA/REC within 15 days of first knowledge of the event.
- As soon as practicable, the CI will inform PIs in all participating Neonatal Intensive Care Units in PiPS of the notified SUSAR.
- The CI will maintain a detailed record of all SAEs and SUSARs reported to them by the PIs. The record will be kept electronically in a secure computer file at the NPEU, with off-site back up. The CI will send details of this record in the annual safety report to the MHRA and South Central - Oxford A REC and Sponsor. A copy will be made available to the MHRA at any time on receipt of a written request.
- SUSARs will be reported for each infant for the period of the trial supplementation **plus** two weeks or discharge from hospital (whichever is first).

5. PROTOCOL VIOLATIONS AND DEVIATIONS

5.1 Protocol Violation

A protocol violation was defined as failure to comply with the final study protocol as approved by Ethics Committee and Research Department. A violation is a serious non-compliance with the protocol resulting from error, fraud or misconduct and results in the exclusion of a patient from the study. A violation will be reported to the Sponsor and Ethics Committee as soon as possible.

5.2 Protocol Deviation

A protocol deviation is a less serious non-compliance, for instance:

• Inclusion/ exclusion criteria not fulfilled
• Incorrectly performed/ missing tests

6. PATIENT GROUPS FOR ANALYSIS

6.1 Post-randomisation exclusions

Losses to the trial post randomisation are defined as any of the following:-

- babies for whom a valid consent was not received;
- babies for whom consent to use their data was withdrawn.

The numbers (with percentages of the randomised population) of post-randomisation exclusions will be reported by randomised treatment group, and reasons summarised.

Parents can specify whether data collected up to the point of withdrawal can be used. If the response is 'No', then they will be considered post-randomisation exclusions. If the response is 'Yes', then they will be reported as 'missing' for any data not collected after withdrawal.

6.2 Primary Analysis Strategy

For the primary analysis, infants will be analysed in the groups into which they were randomly allocated e.g. comparing the outcome of all infants allocated *B. breve* with all those allocated placebo regardless of intervention received.

6.2.1 Descriptive analysis population

Baseline demographic and clinical characteristics – all infants randomised for whom we have data available, excluding any post-randomisation exclusions (see section 6.1).

6.2.2 Comparative analysis population

All infants will be included in the analysis except any post-randomisation exclusions (see section 6.1).

6.2.3 Safety analysis population

All infants will be included in the analysis except any post-randomisation exclusions (see section 6.1).

6.2.4 Interim analysis population

The interim analyses presented baseline data, and primary and secondary outcomes. Some outcomes are based on microbiology data retrieved from electronic laboratory sources. These data are requested in batches for babies who are known to have completed the study (i.e. forms received indicating that the baby had died or been discharged home). In addition, if a baby was still in hospital at the time of analysis, they were still at risk of NEC or death. It was therefore considered appropriate to present all outcome data on the same group of babies described as 'completers' (i.e. babies died or discharged home).

7. DESCRIPTIVE ANALYSES

7.1 Representativeness of Trial Population and Participant Throughput

We will summarise the flow of participants through each stage. Specifically, for each treatment group we will report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome. Protocol deviations from the study will be described, together with reasons.

The number of ineligible patients randomised, if any, will be reported, with reasons for ineligibility.

The total number of eligible babies was not collected during the conduct of this study as it was considered heavy on resources and would not be sufficiently reliable. It is planned to use data collected routinely by the Neonatal Data Analysis Unit (NDAU) to assess representativeness of the trial population for the recruiting hospitals and the broader population of English neonatal admissions during the recruitment period of the PiPS trial.

7.2 Baseline Comparability of Randomised Groups

Baseline characteristics of each treatment group will be described (all data taken from Form 1). See Appendix 6, Tables 1.1 and 1.2 for characteristics included.

Numbers (with percentages) for binary and categorical variables and means (and standard deviations), or medians (with lower and upper quartiles) for continuous variables will be presented.

7.3 Analysis of Adherence

Adherence to intervention will be assessed by calculating the total days between post-menstrual age at first dose and last dose and subtracting the total number of days when the intervention was stopped temporarily. Since this duration will depend on the babies' gestational ages at birth, (i.e. the 'time at risk' will be different depending on the gestation of the baby at birth), this will be expressed as a proportion of the total days that a baby should have been on the intervention (i.e. from the date of randomisation to the date at which the baby was 36 weeks post-menstrual age). These data will be presented by gestational age at birth using categories as used in the minimisation algorithm, in order to assess patterns of adherence for different gestational ages.

Adherence to study protocol will be assessed using post-natal age in hours at randomisation and gestational age at birth.

These data will be presented as means and standard deviations, if approximately normally distributed, by treatment group, and compared using differences in means and 95% confidence intervals (CI). If the data are considered non-normal then medians and interquartile ranges will be presented with comparisons made using differences in medians and 95% CIs.

7.4 Unblinding of Randomised Treatments

Numbers and percentages of any unblinding of treatments will be reported.

8. COMPARATIVE ANALYSES

8.1 Analysis strategy

An adjusted analysis will be performed on all comparative analyses adjusting for the variables used in the minimisation algorithm - hospital, sex, gestational age at birth (23w, 24w, 25w, 26-27w and 28-30w) and whether or not randomisation occurs sooner than 24 hours after birth[2] (see section 2.9) The adjusted analysis will also account for the correlation of outcomes among babies from multiple births included in the trial.

Risk ratios will be estimated using generalised estimating equations (GEE), or a similar method. This method of analysis will account for the correlation in outcomes between multiple births. Binary outcomes will be analysed using log binomial regression models and results will be presented as adjusted risk ratios with corresponding confidence intervals (CI). If the model does not converge, then centre will be removed as a stratification factor in the first instance. If the model is still unstable then log Poisson regression models with robust variance estimation will be used[3]. Continuous outcomes will be analysed using linear regression models and results will be presented as adjusted differences in means with associated confidence intervals. Transformations will be applied for non-normal data.

Outcomes will be summarised with counts (percentages) for categorical variables; the mean (standard deviation [SD]) for normally distributed continuous variables, or the median (interquartile [IQR] or entire range, whichever appropriate) for other continuous variables.

To establish the magnitude and direction of the treatment effects, comparative statistical analysis will entail calculating the adjusted risk ratios (RR) plus confidence intervals (CI) for binary outcomes, the adjusted mean differences (CIs) for normally distributed continuous outcomes, or the unadjusted median differences (plus CIs) for skewed continuous variables (unless the data can be transformed to Normality).

95% Confidence Intervals (CIs) will be presented to compare the risks of the primary outcomes between the treated and placebo groups. 99% CIs will be presented for all other outcomes.

Identification of *B. breve* BBG from stool samples at 2 weeks is made using both culture and PCR techniques. The analysis using colonisation status of *B. breve* BBG based on stools collected at 2 weeks will report that *B. breve* BBG is positive if either technique reports a positive result. The 36 week data will be based on culture results only.

8.2 Analyses of Primary Outcomes

8.2.1 Primary analysis

The primary analysis of the three primary outcomes will be under intention-to-treat i.e. according to the randomised groups for whom we have an outcome, and excluding post-randomisation exclusions (see section 6.1), and will adopt the analysis strategy set out in 8.1.

8.2.2 Secondary analyses

A secondary analysis of all three primary outcomes will be performed according to the colonisation status of the baby at 2 weeks post randomisation. This analysis will be conducted on the analysis population as defined in section 6.2.2 for babies for whom colonisation data are available, and will adopt the analysis strategy set out in 8.1. Data will be presented by whether or not the baby was colonised with *B.breve* BBG.

8.2.3 Pre-specified Subgroup Analysis

A statistical test for interaction will be used to assess the consistency of the adjusted treatment effect on the primary outcomes. The following pre-specified subgroup analyses will be performed on the primary outcomes stratified by:

- whether randomised in the 1st or 2nd 24 hours after birth
- gestational age at birth as per minimisation: 23w, 24w, 25w, 26/27w, 28/29/30w.
- male versus female
- colonised versus not colonised at 2 weeks
- gestational age <28+0 versus ≥28+0

Results will be presented on forest plots with the interaction results alongside.

The subgroup analysis by age at randomisation is included as an unbiased surrogate marker for age at first dose. The additional subgroup analysis by gestational age is included in order that a comparison with the ProPrems study[4] can be made. The subgroup analysis by colonisation status is included as an unbiased assessment of the effect of colonisation status taking into account the randomised groupings. This will be used to complement the secondary analysis described in section 8.2.2.

8.2.4 Exploratory Analysis

For those babies who are colonised with *B.-breve* BBG at 2 weeks an exploratory analysis will be undertaken to investigate if adjusting for the quantity of *B. breve* BBG found using culture and separately using the PCR technique impacts on the adjusted effect estimates of the primary outcomes. The adjusted analysis described in section 8 will be extended to include the quantitative results of the culture and PCR techniques. Results will be considered as hypothesis generating only.

The adjusted model will be altered to include gestational age as a continuous variable, rather than as a categorical variable, to evaluate the impact of this on the effect estimate.

8.3 Analyses of Secondary Outcomes

8.3.1 Primary analysis

The primary analysis of all secondary outcomes will be under intention-to-treat i.e. according to the randomised groups for whom we have an outcome, and excluding post-randomisation exclusions (see section 6.1), and will adopt the analysis strategy set out in 8.1.

For specific secondary outcomes the following analyses will be undertaken:The number of babies with isolates of organisms other than skin commensals from a normally sterile site other than blood (secondary outcome 6) will be summarised by trial arm, by type of sterile site as well as overall. A relative risk and 99% confidence interval will be presented for the number overall only.

Stool flora (secondary outcome 10) data are based on culture results only and will be analysed for each of the type of flora cultured (MRSA, VRE, ESBL) at 2 weeks post-natal and at 36 weeks postmenstrual age, with relative risks and 99% confidence intervals for each.

Age at achieving full enteral nutrition (secondary outcome 11) will be analysed as a time to event outcome, with the time defined as post-natal age and the event as achieving full enteral nutrition (defined as 150 ml/kg/day for 1 day). The analysis will use Cox-proportional hazards methods adjusting for the minimisation factors as set out in section 8.1. A hazards ratio with 99% confidence intervals for the treatment group comparison will be presented.

Change of weight z-score (secondary outcome 12) will be assessed using an Analysis of Covariance (ANCOVA) to adjust for weight at birth.

Broncho-pulmonary dysplasia (BPD) (secondary outcome 13) will be considered positive if categorised as moderate or severe according to the definitions detailed in Appendix 3.

Worst stage of retinopathy (secondary outcome 15) will be categorised as grade 3 or

above and compared to grade 2 or less for the purposes of analysis.

8.3.2 Secondary Analysis

A secondary analysis of all secondary outcomes will be performed according to the colonisation status of the baby at 2 weeks post randomisation. This analysis will be conducted on the analysis population as defined in section 6.2.2 for babies for whom colonisation data are available , and will adopt the analysis strategy set out in 8.1. Data will be presented by whether or not the baby was colonised with *B. breve* BBG.

8.4 Significance Levels and Multiplicity

For all analyses on the primary outcomes 95% confidence intervals (CI) will be presented, and a significance level of 5% (consistent with a 95% CI) will be used to indicate statistical significance.

For all analyses on secondary outcomes 99% confidence intervals (CI) will be presented, and a significance level of 1% (consistent with a 99% CI) will be used to indicate statistical significance.

p-values will not be presented for comparative analyses but will be presented for tests of interaction.

8.5 Missing Data

All comparative analyses will be carried out ignoring missing data. The reason for missing data (consent withdrawn, lost to follow-up, removed from study due to serious side effects, death) will be indicated where possible. The primary analysis on each of the primary outcomes will be repeated using multiple imputation techniques if more than 5% of each of the primary outcomes is missing and the missing completely at random assumption is considered appropriate. These will be treated as a sensitivity analysis. For missing colonisation data, generalisability will be assessed using cross tabulations of baseline characteristics for babies with missing colonisation data versus babies with valid colonisation data.

8.6 Statistical Software Employed

Stata statistical analysis software will be used for all analyses.

9. SAFETY DATA ANALYSIS

9.1 Serious Adverse Events

Any serious adverse event occurring whilst an infant was in the PiPS trial, up to death or discharge home or the date of the final database lock, will be recorded and tabulated in full. A comparison of serious adverse events between each arm of the trial will be assessed.

10. ADDITIONAL EXPLORATORY ANALYSIS

The following further exploratory analyses will be performed to provide context to the results or to generate hypotheses for future testing:

1) A logistic regression analysis to study determinants of successful colonisation with *B. breve* BBG at 2 weeks in those babies allocated to receive probiotic. A forward stepwise regression model will be used to assess the following factors:

- postnatal age at receiving first dose of probiotic
- duration of antibiotic use in the first 14 days
- type of antibiotics received
- type of milk received
- postnatal age at starting milk
- number of days any milk received in first 14 days
- gestational age at birth
- singleton/multiple.

2) An adjusted analysis (according to the strategy set out in section 8.1) to investigate the treatment effect on the use of post-natal corticosteroids given to prevent BPD.

3) Cross-tabulations of

- colonisation with *B. breve* BBG at 2 weeks postnatal age by colonisation with *B. breve* BBG at 36 weeks postmenstrual age by randomisation group;
- post-natal age at randomisation by randomisation group;
- post-natal age at first dose by randomisation group;
- post-natal steroid use by randomisation group.

4) A summary by treatment group of the following variables:-

- number of episodes of NEC ≥ stage 2
- worst stage of NEC

- age of onset of NEC ≥ stage 2
- surgical NEC
- fatal NEC
- Spontaneous Intestinal Perforation

5) In order to be able to give the outcome used in the meta-analyses we will report the outcome of number of babies with any positive blood culture (i.e. the primary outcome and secondary outcome 2 combined) by treatment group.

Any analyses not specified in this analysis plan will be exploratory in nature and a 1% significance level will be used to declare statistical significance; 99% confidence intervals will be presented.

11. DEVIATION FROM ANALYSIS DESCRIBED IN PROTOCOL

None yet.

12. REFERENCES

12.1 NPEU Clinical Trials Unit Standard Operating Procedures

ST 104 Interim Statistical Analysis
ST 105 Statistical Analysis Plan
ST 106 Final Statistical Analysis and Reporting

12.2 Trial documents

NPEU OpenClinica Data Entry Guide version 1

All other trial documents are available at: https://www.npeu.ox.ac.uk/pips

12.3 References

1) Schulz KF, Altman DG, Moher D, Group for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *British Medical Journal* 2010; 340: 698-702.
2) Brennan C. Kahan and Tim P. Morris. Analysis of multicentre trials with continuous outcomes: when and how should we account for centre effects? *Statistics in Medicine* 2013; 32: 1136-1149
3) Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol.* 2004 Apr 1;159(7):702-6.
4) Susan E. Jacobs, Jacinta M. Tobin, Gillian F. Opie, Susan Donath, Sepehr N. Tabrizi, Marie Pirotta, Colin J. Morley and Suzanne M. Garland. Probiotic Effects on Late-onset Sepsis in Very Preterm Infants: A Randomized Controlled Trial. *Pediatrics* 2013; 132:1055-1062

12.4 Acknowledgements

This Statistical Analysis Plan is based on a template written by Ed Juszczak and Ros Weatherall whilst at the Centre of Statistics in Medicine, University of Oxford.

13. APPENDICES

Appendix 1: Rationale and definitions for microbiological endpoints

The primary outcome: *'An episode of blood stream infection, with any organism other than a skin commensal, diagnosed on a sample of blood drawn after 72 hours and before 46 weeks post-menstrual age, death or discharge from hospital whichever is soonest. Skin commensals include coagulase negative staphylococci (CoNS) and Corynebacteria.'*

Late onset blood stream infection in the preterm baby carries high mortality and morbidity; this is particularly true for infections with *Staphylococcus aureus* and Gram negative bacilli (GNB) which make up around 15% of positive blood cultures. The main reservoir of these organisms in the baby is in the gut from which it is believed that they invade the bloodstream by translocation of the intestinal wall. If probiotic administration is to be effective in reducing infection in the newborn it is most likely that it will be through a combination of reducing colonisation of the gut by these organisms and promoting intestinal epithelial health.

The majority of positive blood cultures are with Coagulase-negative Staphylococci (CoNS). These organisms likewise colonise the gut of infants but they are also important skin commensals of healthcare workers; this reservoir of colonisation will not be affected by probiotic administration to infants. CoNS bloodstream infection is thought usually to arise as a result of colonisation of an intravascular device, most importantly an intravenous central feeding line, during handling and manipulation by healthcare workers, rather than from bacterial translocation through the intestinal wall. Thus while probiotic use, if it is associated with better nutrition and better general health, might reduce need for intravascular devices and might be related to less CoNS sepsis it seems probable that the greater benefit of probiotics in neonatal infection will be through reduction of the more serious infections with organisms that have colonised the intestine such as GNB, *S. aureus* and fungi such as Candida. Furthermore there is a difficulty in accurate diagnosis of CoNS infection. While a positive blood culture with the clearly pathogenic *Staphylococcus aureus* or GNB is taken as definite evidence of infection it is widely acknowledged that many CoNS positive blood cultures are contaminants, arising largely through deficient blood culture technique with inadequate skin cleansing. Many schemes have been presented, to explore whether the presence of an organism in a culture sample represents real infection rather than a contaminant. These involve different combinations of clinical signs (lethargy, temperature instability, etc.) and laboratory markers of sepsis (WBC counts, CRP etc.). None of these is accepted as a gold standard and if used in a clinical trial such as PiPS would result in a significant increase in the burden of data collection for participating centres without clear evidence of benefit in the specific circumstances of this randomised trial.

In summary: because of the greater clinical importance of blood stream infection with non skin commensals, the possibility that they are more likely to be reduced by probiotic administration and in the cause of simple clearly defined items for data collection it has been agreed that the microbiological primary endpoint for this study should be blood stream infection with non skin commensals, i.e. positive cultures with bacteria such as *E. coli, Klebsiella, S. aureus* and with fungi such as *Candida*.

Secondary outcomes:

While the single most important microbiological clinical outcome is reduction of blood stream infection with non skin commensals there are other possible effects of probiotic use that are important to study:

Infection with skin commensals, secondary outcomes #2-4:
Because details of clinical events and markers of sepsis are not being collected around episodes of suspected infection, the total number of positive blood cultures with skin commensals (the majority of which will be CoNs) will include contaminants; it will however give a guide as to whether or not probiotic use is impacting on skin commensal sepsis as the contaminants should be balanced between the two arms of the study. This information will be augmented by studying whether or not there is a difference in the extent of sampling (secondary outcomes 3&4) in the two arms.
Infections with pathogens: GNB, S. aureus etc. by organism and antibiotic resistance, secondary outcome #5:
The bowel provides a major reservoir for antibiotic resistant bacteria and is also an important site for the transfer of antibiotic resistance genes. If probiotics are not associated with the hoped for reduction in serious blood stream infection they may nonetheless impact upon the type of organisms causing infection and be associated with less antibiotic resistance. To explore this, the types of organisms causing blood stream infection and their patterns of antibiotic resistance will be studied in the two arms of the study.
Blood culture negative episodes of infection:
A further complication in the accurate assessment of the burden of infection is the difficulty of reliably identifying clinical episodes that are considered by the attending staff to be infections but are associated with a negative blood culture; this may arise because the sample of blood is too small but is more often because the baby, at the time of sampling, is already on antibiotics which inhibit bacterial growth. The total number of samples taken, secondary outcome #4, will to some extent provide a surrogate for this.
Data collection to support these endpoints:
Investigators will provide the study centre with details of admission and discharge dates; this might involve multiple hospitals per baby. Microbiological data will be obtained directly from hospital microbiological laboratories who will be asked to provide a download with details of all microbiological investigations from admission, including time and site of sampling and details of any positive cultures with information about antibiotic resistance.
The total days of antibiotic use, for treatment of suspected or proven sepsis, and excluding prophylactic use, will be collected using the study data collection forms.
Stool samples will be collected for the study as close as possible to 2 weeks post-natal age and 36 weeks postmenstrual age and sent to the study centre where they will be examined for colonisation with *Bifidobacterium breve* BBG and subjected to quantitative microbiology to study patterns of microbiological colonisation and antibiotic resistance.

Appendix 2: Definitions of Necrotising Enterocolitis

NEC will be classified using Modified Bell's criteria[1] with further minor modification excluding recording of positive occult blood in stools and noting of bowel sounds:

Bell stage	Systemic signs	Gastro-intestinal signs	Radiographic signs
Stage IIA (Definite NEC: mildly ill)	Increased desaturations and/or bradycardia Temperature instability Lethargy	Increased pre-feed gastric aspirate Definite abdominal distension Possible abdominal tenderness Possibly bloody stools	Definite abdominal dilatation Pneumotosis intestinalis
Stage IIB (Definite NEC: moderately ill)	As Stage IIA with platelets <100 x 10_{12} and/or metabolic acidosis: base excess <-8meq/l	Abdominal distension with definite tenderness Possible abdominal wall oedema and/or erythema	As IIA with portal vein gas Possible ascites
Stage IIIA (Advanced NEC: bowel intact)	As IIB plus mixed acidosis: pH <7.2 DIC Neutropaenia <1x10_9/l Severe apnoea Hypotension requiring inotropes	Generalised peritonitis with severe tenderness with abdominal wall induration	As IIA with definite ascites
Stage IIIB (Advanced NEC: bowel perforated)	As IIIA	As IIIB	As IIIA with pneumoperitoneum

References

1. Walsh MC, Kliegman RM. Necrotising enterocolitis: treatment based on staging criteria. Pediat Clin North Am, 1986;33:179-201

Appendix 3: Bronchopulmonary dysplasia (BPD)

Principal definition for secondary outcome: A baby who is still receiving supplementary oxygen at 36 weeks postmenstrual age.

BPD is one of the most important complications of preterm birth, lengthening hospital stay, increasing the burden on parents particularly through the frequent need for home oxygen and being associated with longer term morbidity. The definition above, which is the standard version that has been used in many clinical trials and clinical studies of neonatal outcomes is imprecise in that whether or not a baby receives oxygen is to a considerable extent dependent upon local practice and the whim of the clinical staff looking after the baby on that particular day. There has been considerable interest in making the definition more objective either by relating it more precisely to physiological measures of gas exchange[1,2] or by strengthening the underpinning clinical information[3]. This outcome is of particular importance and interest for this study since in the pilot study undertaken by the investigators there was a significant reduction of BPD in association with *B. breve* BBG colonisation. The 'physiological' assessment of BPD severity is not yet adequately evaluated in terms of its reliability and reproducibility to use it as an outcome measure in a clinical trial such as this. Clinical data to support the categorisation of babies using the system proposed by the NICHD[3] has been collected for babies in EPICure 2 (all births <27w in 2006). Preliminary analysis of data from 869 of 870 possible surviving infants show a significant relationship between the severity of BPD using this classification at 36w pma and the likelihood of going home in oxygen. It is proposed that babies in PiPS are likewise classified at 37w using this scheme and the numbers of babies with different degrees of severity of BPD compared between the probiotic and placebo groups:

No BPD: in air by 28d post natal age.

Mild BPD: in oxygen at 28d pna but in air and not receiving mechanical ventilatory support at 36w post menstrual age.

Moderate BPD: in oxygen but <30% or≤0.1l/min or on mechanical support in air at 36w post menstrual age.

Severe BPD in oxygen ≥30% or >0.1l/min at 36w post menstrual age

References

1. Walsh MC, Wilson-Costello D, Zadell A, Newman N, Fanaroff A. Safety, reliability and validity of a physiological definition of broncho-pulmonary dysplasia. J Perinatol. 2009;23:451-456

2. Quine D, Wong CM, Boyle EM, Jones JG, Stenson BJ. Non-invasive measurement of reduced ventilation:perfusion ratioand shunt in infants with bronchopulmonary dysplasia: a physiological definition of the disease. Arch Dis Childh. 2006;91:F409 –F414

3. Jobe AH & Bancalari E. NICHD/NHLBI/ORD Workshop Summary: Bronchopulmonary Dysplasia. Am J Respir Crit Care Med. 2001;163:1723-1729

Appendix 4: BAPM definitions of intensive, high-dependency and special care

Standards for hospitals providing intensive and high-dependency care: British Association of Perinatal Medicine, 2001

Intensive Care

Any baby who is:

1. receiving any respiratory support via a tracheal tube and in the first 24 hours after its withdrawal
2. receiving NCPAP for any part of the day and less than five days old
3. below 1000g current weight and receiving NCPAP for any part of the day and for 24 hours after withdrawal
4. less than 29 weeks gestational age and less than 48 hours old
5. requiring major emergency surgery, for the pre-operative period and post-operatively for 48 hours
6. requiring complex clinical procedures:

- full exchange transfusion
- peritoneal dialysis
- infusion of an inotrope, pulmonary vasodilator or prostaglandin and for 24 hours afterwards

7. a baby on the day of death.

High Dependency Care
Any baby who is:
1. receiving NCPAP for any part of the day and not fulfilling any of the criteria for intensive care
2. below 1000g current weight and not fulfilling any of the criteria for intensive care
3. receiving parenteral nutrition
4. having convulsions
5. receiving oxygen therapy and below 1500g current weight
6. requiring treatment for neonatal abstinence syndrome
7. requiring specified procedures that do not fulfil any criteria for intensive care:

- Care of an intra-arterial catheter or chest drain
- Partial exchange transfusion
- Tracheostomy care until supervised by a parent

8. requiring frequent stimulation for severe apnoea.

Special Care
Special care is provided for all other babies who could not reasonably be expected to be looked after at home by their mother.

Appendix 5 – Derivation of variables

	Derived Variable	Derivation	Contributing questions	Form: Q no
1	Gestational age	The number of weeks between the expected delivery date and the date of birth subtracted from 40 weeks. The gestational age will be displayed to 1 decimal place.	Baby's date of birth Expected delivery date	F1:A2 F1:A1
2	Birth weight z-score	Calculated according to Pan H, Cole TJ. LMSgrowth, a Microsoft Excel add-in to access growth references based on the LMS method. Version 2.77. http://www.healthforallchildren.co.uk/; 2012. The British 1990 reference chart is referenced. Cole TJ, Freeman JV, Preece MA. British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood. *Statistics in Medicine* 1998;17:407-429.	Expected delivery date Date of birth Sex Weight at birth	F1:A1 F1:A2 F1:A3 F1:D7
3	CRIB II	Calculated according to Parry et al. Lancet 2003; 361: 1789-91.	Birth weight Gestational age Sex Temperature at admission Base excess	F1:D7 Derived 1. F1:A3 F1:D10 F1.D12
4	Day of first feed	On form 2, the first day from DOB when the 'No Milk given' box is not ticked will be selected as the day of first feed.	From form 2; No Milk	F2:C
5	Any Formula Milk in first 2 weeks	The type of feed will be categorised into 'maternal breast milk' yes / no (preterm formula or term formula). This variable will be yes in any formula was received in the first 2 weeks, otherwise it will be no.	From form 2; Preterm formula Term Formula	F2:C F2:C
6	Maternal breast milk in first 2 weeks	The type of feed will be categorised into 'maternal breast milk' yes / no (expressed maternal milk or fed directly from the breast), This variable will be yes in any breast milk was received in the first 2 weeks, otherwise it will be no.	From form 2; Expressed maternal milk Fed directly from breast	F2:C F2:C
7	Days on antibiotics (post 72 hours)	For day 4 to 14, each day one or more of the antibiotics listed in form two were taken is counted as one day.	From form 3; For how many days in total were antibiotics taken?	F3:B8 F2:D

	Derived Variable	Derivation	Contributing questions	Form: Q no
		The response to question 'For how many days in total were antibiotics taken?' will be summed across all form 3s to give the number of days antibiotics were taken after 14 days. Therefore 'Days on antibiotics' will be the sum of days 4 to 14 and the total days after day 14.	From form 2; Any penicillin Any aminoglycoside Any cephalosporin Any glycopeptide Any carbapenem Any β lactum / inhibitor Other antiobiotic	
8	Days on antifungals to treat suspected or proven infection. (post 72 hours)	For the day 4 to 14, each day antifungal to treat suspected or proven infection was taken, as collected in form two will be summed to give days taken from day 4 to 14. The response to question 'For how many days in total were antifungals taken?' will be summed across all form 3s to give the number of days antifungals were taken after 14 days. Therefore 'Days on antifungals to treat suspected infection' will be the sum of days 1 to 14 and the total days after day 14.	From form 3; For how many days in total were antifungals taken? From Form 2; Antifungal to treat suspected or proven infection.	F3:B8 F2:D
9	Time to first full feed	The time from randomisation to first full feed will be derived from the number of days between the randomisation date and the date of first full feed. If multiple dates are given, date will initially be queried, if not resolved the first date given will be used.	While in this hospital did the baby reach full feeds for the first time? Date of first full feed.	F3:B3
10	BPD, none, mild, moderate and severe	None and Mild; cannot be defined with data collected, no information available at 28 days post natal age . Moderate; in oxygen <30% or ≤0.1l/m or on mechanical support at 36 weeks post menstrual age. Severe; in oxygen ≥30% or >0.1l/m at 36 weeks post menstrual age.	Was the baby still receiving mechanical respiratory support? Was the baby receiving supplementary oxygen? Oxygen <30% or ≥ 30% Oxygen ≤0.1l/m or >0.1l/m	F3:C2i F3:C2iii
11	Hydrocephalus	If the baby does not have valid cerebral	While in this hospital	F3:B4

	Derived Variable	Derivation	Contributing questions	Form: Q no
	and / or intraparenchymal cysts	ultra sound scan data (i.e. While in this hospital did the baby have any cerebral ultrasound scans? is blank) then this variable will be missing. If hydrocephalus, porencephalic cyst or periventricular leucomalacia was present on either the left or right side, at any hospital, this variable will be yes. Any other non-missing ultrasound result will make this variable no.	did the baby have any cerebral ultrasound scans?	
12	Total hospital stay	The last date in hospital will be the latest of the discharge home date and the death date. Total hospital stay will be last date in hospital minus the baby's date of birth plus one.	Discharged home Death Date of birth	F3:D1 F3:D3 F1:A2
13	Intensive care stay	The sum of all intensive care days at each hospital.	While in this hospital, what was the total number of days in intensive care?	F3:B10
14	High dependency care stay	The sum of all high dependency care days at each hospital.	While in this hospital, what was the total number of days in high dependency care?	F3:B10
15	Special care stay	Total stay minus the intensive care days and the high dependency care days.	Discharged home Death Date of birth While in this hospital, what was the total number of days in intensive care / high dependency care?	F3:D1 F3:D3
16	Post menstrual age at first dose. (hours)	The number of weeks between the expected delivery date and the date of first dose from 40 weeks.	First dose date Expected delivery date	F1:A2 F1:A1
17	Post menstrual age at last dose. (days)	Date of last dose is the maximum of permanent discontinuation date, last date trial intervention was given and withdrawal date. The number of weeks between the expected delivery date and the date of last	Permanent discontinuation date Study Withdrawal date Last date trial intervention given. Expected delivery	F3:C5 F3:B12 F6:B1 F1:A1

	Derived Variable	Derivation	Contributing questions	Form: Q no
		dose subtracted from 40 weeks.	date	
18	Total duration.	Date of last dose is the maximum of permanent discontinuation date, last date trial intervention was given and withdrawal date. Total duration is the difference between the first dose date and last dose date plus one. If the days total days of interruption is greater than the total duration this will be queried. If not resolved both the days of interruption and the total duration will take missing values.	Permanent discontinuation date Study Withdrawal date Last date trial intervention was given. Date of first dose.	F3:C5 F3:B12 F6:B1 F1:B3
19	Total duration of temporary interruptions.	The sum of all temporary discontinuations across all hospitals. If the days total days of interruption is greater than the total duration this will be queried. If not resolved both the days of interruption and the total duration will take missing values.	For how many days in total was the trial intervention discontinued.	F3:B12
20	Percent of recommended doses taken.	The date at which the baby will be 36 weeks post menstrual will be the expected delivery date minus 28 days (4 weeks). The number of days between the randomisation date and the date the baby reaches 36 weeks post menstrual age gives the number of recommended days which is the denominator for the percentage. The number of days the intervention is taken is the total duration minus the total days of interruption. The percent of recommended doses taken is the number of days the intervention was taken, divided by the recommended days. The result is multiplied by 100 to give a percentage. If the days total days of interruption is greater than the total duration this will be	Expected delivery date Randomisation date. Total duration Date of first dose. For how many days in total was the trial intervention discontinued.	F1:A1 derived19 F1:B3 F3:B12

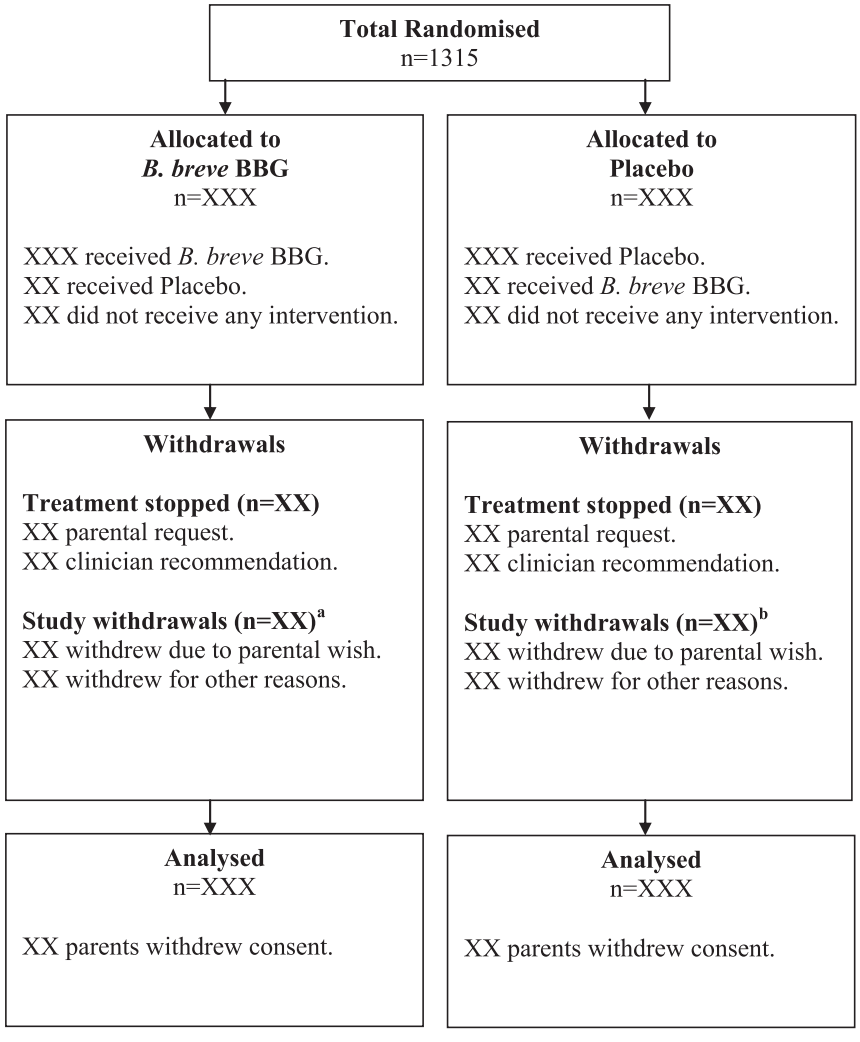
	Derived Variable	Derivation	Contributing questions	Form: Q no
		queried. If not resolved both the days of interruption and the total duration will take missing values.		
21	Post natal age at randomisation (hours).	The number of hours between randomisation date and time and the date of birth, date and time.	Date of birth Time of birth Date of first dose Time of first dose	F1:A2
22	Post natal age at first dose (hours).	The number of hours between the first dose date and time and the date of birth, date and time.	Date of birth Time of birth Date of last dose Time of last dose	F1:A2 F1:B3
23	Multiples	Identification of siblings; Any multiple babies born on the same day to a mother with the same DOB will be included in one cluster. Singletons will be in a cluster of size 1. Checks will ensure that a multiple baby will not be included in a cluster larger than the number of babies born.	Baby's DOB Mother's DOB Multiple/Singleton Number of babies born	F1:A2 F1:C3 F1:A4 F1:D8

Appendix 6 – Dummy Tables

Outline of tables

		ALL PARTICIPANTS	ITT POPULATION	
			BY TRIAL ARM	BY COLONISATION
FIGURE 1	PARTICIPANT FLOW	X		
TABLE 1.1	BASELINE DATA: MOTHER'S CHARACETERISTICS		X	X
TABLE 1.2	BASELINE DATA: BABY'S CHARACETERISTICS		X	X
TABLE 2.1	PRIMARY ANALAYSIS OF PRIMARY OUTCOMES: NEC, SEPSIS AND DEATH		X	X
TABLE 3.1	PRIMARY ANALYSIS OF SECONDARY OUTCOMES: COMPOSITE RESULTS		X	X
TABLE 3.2	PRIMARY ANALYSIS OF SECONDARY OUTCOMES: MICROBIOLOGY		X	X
TABLE 3.3	PRIMARY ANALYSIS OF SECONDARY OUTCOMES: MICROBIALS		X	X
TABLE 3.4	PRIMARY ANALYSIS OF SECONDARY OUTCOMES: COLONISATION OF STOOLS		X	X
TABLE 3.5	PRIMARY ANALYSIS OF SECONDARY OUTCOMES: TIME TO FIRST FULL FEED		X	X
TABLE 3.6	PRIMARY ANALYSIS OF SECONDARY OUTCOMES: OTHER DIAGNOSES		X	X
TABLE 3.7	PRIMARY ANALYSIS OF SECONDARY OUTCOMES: HOSPITAL STAY		X	X
TABLE 4.1	ADHERENCE TO PROTOCOL		X	
TABLE 4.2	ADHERENCE TO TRIAL INTERVENTION		X	
TABLE 4.3	ADHERENCE TO TRIAL INTERVENTION BY GESTATIONAL AGE		X	
FIGURE 2	ADHERENCE TO TRIAL INTERVENTION BU GESTATIONAL AGE		X	
TABLE 4.3	HARMS		X	
TABLE 4.4	INVESTIGATOR UNBLINDING		X	
TABLE 5.1	SUBGROUP ANALYSIS		X	
FIGURE 3	FOREST PLOT OF SUBGROUP ANALYSIS		X	
TABLE 5.2	BABY'S OUTCOME		X	
TABLE 6	OTHER OUTCOME DATA COLLECTED		X	
TABLE 7	NECOROTISING ENTEROCOLITIS		X	
TABLE 8	POST NATAL AGE AT RANDOMISATION		X	
TABLE 9	COLONISATION WITH *B. BREVE* BBG AT 2 WEEKS POST NATAL AGE VS 36 WEEKS POST MENSTRUAL AGE		All	
TABLE 10	SIGNIFICANCE OF DETERMINANTS OF SUCCESSFUL COLONISATION WITH *B. BREVE* BBG	*B. breve* BBG treatment arm only		

FIGURE 1: PARTICIPANT FLOW



[a] Includes XX who withdrew consent
[b] Includes XX who withdrew consent

TABLE 1.1: BASELINE DATA: MOTHER'S CHARACTERISTICS (INTENTION TO TREAT)

Form: Q no			*B. breve* BBG (n=XXX)	Placebo (n=XXX)
F1:C6	Ethnic Group.			
	White	n(%)	XX (XX.X)	XX (XX.X)
	Indian	n(%)	XX (XX.X)	XX (XX.X)
	Pakistani	n(%)	XX (XX.X)	XX (XX.X)
	Bangladeshi	n(%)	XX (XX.X)	XX (XX.X)
	Black African	n(%)	XX (XX.X)	XX (XX.X)
	Black Caribbean	n(%)	XX (XX.X)	XX (XX.X)
	Other	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX
F1:C3	Mother's Age (years).	n	XXX	XXX
		Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)
		(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
F1:C7	Antenatal Steroid Use.			
	Yes, <24 hours before birth.	n(%)	XX (XX.X)	XX (XX.X)
	Yes, ≥24 hours before birth.	n(%)	XX (XX.X)	XX (XX.X)
	None	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX
F1:C8	Membrane Rupture > 24 hours before birth.			
	Yes	n(%)	XX (XX.X)	XX (XX.X)
	No	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX
F1:C9	Chorioamnionitis in 24 hours before birth.			
	Yes	n(%)	XX (XX.X)	XX (XX.X)
	No	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX
F1:C10	Antibiotics in 24 hours before birth.			
	Yes	n(%)	XX (XX.X)	XX (XX.X)
	No	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX

TABLE 1.2: BASELINE DATA: BABY'S CHARACTERISTICS (INTENTION TO TREAT)

Form: Q no			*B. breve* BBG (n=XXX)	Placebo (n=XXX)
	Enrolling Centre			
	Centre 1	n(%)	XX (XX.X)	XX (XX.X)
	Centre 2	n(%)	XX (XX.X)	XX (XX.X)
	Centre 3	n(%)	XX (XX.X)	XX (XX.X)
	Centre 4	n(%)	XX (XX.X)	XX (XX.X)
	Centre 5	n(%)	XX (XX.X)	XX (XX.X)
	Centre 6	n(%)	XX (XX.X)	XX (XX.X)
	Centre 7	n(%)	XX (XX.X)	XX (XX.X)
	Centre 9	n(%)	XX (XX.X)	XX (XX.X)
	Centre 10	n(%)	XX (XX.X)	XX (XX.X)
	Centre 11	n(%)	XX (XX.X)	XX (XX.X)
	Centre 12	n(%)	XX (XX.X)	XX (XX.X)
	Centre 13	n(%)	XX (XX.X)	XX (XX.X)
	Centre 19	n(%)	XX (XX.X)	XX (XX.X)
	Centre 21	n(%)	XX (XX.X)	XX (XX.X)
	Centre 22	n(%)	XX (XX.X)	XX (XX.X)
	Centre 23	n(%)	XX (XX.X)	XX (XX.X)
	Centre 24	n(%)	XX (XX.X)	XX (XX.X)
	Centre 25	n(%)	XX (XX.X)	XX (XX.X)
	Centre 26	n(%)	XX (XX.X)	XX (XX.X)
	Centre 39	n(%)	XX (XX.X)	XX (XX.X)
	Centre 40	n(%)	XX (XX.X)	XX (XX.X)
	Centre 41	n(%)	XX (XX.X)	XX (XX.X)
	Centre 42	n(%)	XX (XX.X)	XX (XX.X)
	Centre 43	n(%)	XX (XX.X)	XX (XX.X)
RN data	Age at Randomisation (hours)	Median	XX.X	XX.X
		(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)
		(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
	<24 hours	n(%)	XX (XX.X)	XX (XX.X)
	24 to <48 hours	n(%)	XX (XX.X)	XX (XX.X)
	>48 hours	n(%)	XX (XX.X)	XX (XX.X)
F1:A1, A2	Gestational Age (weeks) at birth	Median	XX.X	XX.X
		(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)
		(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
	23 to <24 weeks	n(%)	XX (XX.X)	XX (XX.X)
	24 to <25 weeks	n(%)	XX (XX.X)	XX (XX.X)
	25 to <26 weeks	n(%)	XX (XX.X)	XX (XX.X)
	26 to <28 weeks	n(%)	XX (XX.X)	XX (XX.X)
	28 to <30 weeks	n(%)	XX (XX.X)	XX (XX.X)
	≥30 weeks	n(%)	XX (XX.X)	XX (XX.X)
F1:A3	Sex			
	Male	n(%)	XX (XX.X)	XX (XX.X)
	Female	n(%)	XX (XX.X)	XX (XX.X)
	Indeterminate	n(%)	XX (XX.X)	XX (XX.X)

Table 1.2: Continued

Form: Q no			*B. breve* BBG (n=XXX)	Placebo (n=XXX)
F1:A4	Singleton	n(%)	XX (XX.X)	XX (XX.X)
	Multiple	n(%)	XX (XX.X)	XX (XX.X)
F1:D8	Babies born.			
	1	n(%)	XX (XX.X)	XX (XX.X)
	2	n(%)	XX (XX.X)	XX (XX.X)
	3	n(%)	XX (XX.X)	XX (XX.X)
	≥ 4	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX
F1:C1	Born in enrolling hospital.			
	Yes	n(%)	XX (XX.X)	XX (XX.X)
	No	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX
F1:D4	Mode of delivery.			
	Vaginal birth	n(%)	XX (XX.X)	XX (XX.X)
	Caesarean before labour onset	n(%)	XX (XX.X)	XX (XX.X)
	Caesarean after labour onset	n(%)	XX (XX.X)	XX (XX.X)
	Other	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX
	Forceps or ventouse used.			
	Yes	n(%)	XX (XX.X)	XX (XX.X)
	No	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX
F1:D6	Main cause of preterm birth.			
	Pre labour rupture of membranes	n(%)	XX (XX.X)	XX (XX.X)
	Preterm labour	n(%)	XX (XX.X)	XX (XX.X)
	APH	n(%)	XX (XX.X)	XX (XX.X)
	PIH	n(%)	XX (XX.X)	XX (XX.X)
	Other maternal illness	n(%)	XX (XX.X)	XX (XX.X)
	Poor fetal growth (mother well)	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX
F1:D7	Birth weight. (g)	n	XXX	XXX
		Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)
		(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
	Birth weight z-score.	n	XXX	XXX
		Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)
		(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
F1:D9	Heart rate >100bpm 5 minutes after birth.			
	Yes	n(%)	XX (XX.X)	XX (XX.X)
	No	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX

Table 1.2: Continued

Form: Q no			*B. breve* BBG (n=XXX)	Placebo (n=XXX)
F1:D11	Apgar score 5 minutes after birth.			
	1-3	n(%)	XX (XX.X)	XX (XX.X)
	4-6	n(%)	XX (XX.X)	XX (XX.X)
	7-10	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX
F1:D12	Baby's worst base excess in 1 hour after birth.			
		n	XXX	XXX
		Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)
		(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
F1:D10	Temperature on admission to neonatal unit.			
		n	XXX	XXX
		Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)
		(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
	CRIB II[a]	n	XXX	XXX
		Mean(StdDev)	XX.X (XX.XX)	XX.X (XX.XX)
		(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
F3:B6	Any Congenital Malformations			
	Yes	n(%)	XX (XX.X)	XX (XX.X)
	No	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX
	If Yes:			
	type 1	n(%)	XX (XX.X)	XX (XX.X)
	type 2	n(%)	XX (XX.X)	XX (XX.X)
	type 3	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX
F2	Post natal age at first feed (days)[b]	n	XXX	XXX
		Mean(StdDev)	XX.X (XX.XX)	XX.X (XX.XX)
		Median	XX.X	XX.X
		(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)
		(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
		Missing	XX	XX
F2	Type of milk received (0 to 14 days)[b]			
	Maternal breast milk	n(%)	XX (XX.X)	XX (XX.X)
	Donor breast milk	n(%)	XX (XX.X)	XX (XX.X)
	Formula	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX
	Maternal breast milk only (0 to 14 days)[b]			
	Yes	n(%)	XX (XX.X)	XX (XX.X)
	No	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX

[a] Parry et al. Lancet 2003; 361: 1789-91
[b] These data were collected post randomisation.

TABLE 2.1: PRIMARY ANALYSIS OF PRIMARY OUTCOMES: NEC, SEPSIS AND DEATH (INTENTION TO TREAT)

	***B. breve* BBG (n=XXX)**	**Placebo (n=XXX)**	**Adjusted Risk Ratio (95% CI)**
Primary Analysis[a]			
Sepsis[b]	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
NEC[c]	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
Death	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)

[a] Adjusted for centre, sex, gestational age at birth, randomisation < 24 hours of age. Clusters for correlations between multiple births are accounted for.
[b] Sepsis is defined as blood stream infection with non-skin commensals after 72 hours post natal age and < 46 weeks post menstrual age.
[c] Necrotising Enterocolitis (Bell stage II or higher)

TABLE 3.1: PRIMARY ANALYSIS OF SECONDARY OUTCOMES: COMPOSITE RESULTS (INTENTION TO TREAT)

	***B. breve* BBG (n=XXX)**	**Placebo (n=XXX)**	**Adjusted Risk Ratio (99% CI)**
Sepsis[a], NEC[b] or Death	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)

[a] Sepsis is defined as blood stream infection with non-skin commensals after 72 hours post natal age and < 46 weeks post menstrual age. Clusters for correlations between multiple births are accounted for.
[b] Necrotising Enterocolitis (Bell stage II or higher)

TABLE 3.2: PRIMARY ANALYSIS OF SECONDARY OUTCOMES: MICROBIOLOGY (INTENTION TO TREAT)

Form: Q no		*B. breve* BBG (n=XXX)	Placebo (n=XXX)	Adjusted Risk Ratio / Mean difference (99% CI)
Micro Q3	Blood culture positive for skin commensal			
	Yes	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
	No	XX (XX.X)	XX (XX.X)	
	Missing	XX	XX	
Micro Q2	Any blood culture taken			
	Yes	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
	No	XX (XX.X)	XX (XX.X)	
	Missing	XX	XX	
Micro Q2	Number of blood cultures taken per baby			
	n	XXX	XXX	
	Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.X to XX.X)
	(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)	
	0	XX (XX.X)	XX (XX.X)	
	1	XX (XX.X)	XX (XX.X)	
	2	XX (XX.X)	XX (XX.X)	
	3	XX (XX.X)	XX (XX.X)	
	4	XX (XX.X)	XX (XX.X)	
	5	XX (XX.X)	XX (XX.X)	
	6	XX (XX.X)	XX (XX.X)	
	7	XX (XX.X)	XX (XX.X)	
	8	XX (XX.X)	XX (XX.X)	
	9	XX (XX.X)	XX (XX.X)	
	≥ 10	XX (XX.X)	XX (XX.X)	
	Missing	XX	XX	

Table 3.2 Continued

Form: Q no		*B. breve* BBG (n=XXX)	Placebo (n=XXX)	Adjusted Risk Ratio / Mean difference (99% CI)
Micro Q5, Q8	Antibiotic resistant blood stream infection			
	MRSA[a]	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
	VRE[b]	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
	ESBL[c]	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
Micro Q5	Blood stream infection			
	Enterobacteriaceae	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
	Enterococcus	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
	Staphylococcus	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
	Fungi	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
	Non-skin	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
Micro Q10	Isolates of organisms from normally sterile site (other than blood)			
	Site 1	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
	Site 2	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
	…			
	Site n	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
Micro Q13	*B. breve* BBG culture from normally sterile site			
	Site 1	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
	Site 2	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
	…			
	Site n	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)

[a] methicillin-resistant *Staphylococcus aureus*
[b] vancomycin resistant enterococci
[c] extended spectrum betalactamase producing Gram negative bacteria

TABLE 3.3: PRIMARY ANALYSIS OF SECONDARY OUTCOMES: ANTIMICROBIALS[A] (INTENTION TO TREAT)

Form: Q no			*B. breve* BBG (n=XXX)	Placebo (n=XXX)	Risk Ratio/ Mean difference (99% CI)
F3:B8 F2	Total days of antibiotics (post 72 hours)	n	XXX	XXX	
		Mean(StdDev)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.X to XX.X)
		Median	XX.X	XX.X	
		(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)	
		(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)	
		Missing	XX	XX	
F3:B8 F2	Total days of antifungals for treatment (post 72 hours)	n	XXX	XXX	
		Mean(StdDev)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.X to XX.X)
		Median	XX.X	XX.X	
		(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)	
		(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)	
		Missing	XX	XX	

[a] Contrary to the protocol, antimicrobials were collected and reported from birth until the earlier of hospital discharge, death or database lock.

TABLE 3.4: PRIMARY ANALYSIS OF SECONDARY OUTCOMES: COLONISATION OF STOOLS (INTENTION TO TREAT)

		***B. breve* BBG (n=XXX)**	**Placebo (n=XXX)**	**Adjusted Risk Ratio (99% CI)**
2 weeks				
Culture				
B. breve BBG	n(%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
MRSA[a]	n(%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
VRE[b]	n(%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
ESBL[c]	n(%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
PCR				
B. breve BBG	n(%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
MRSA[a]	n(%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
VRE[b]	n(%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
ESBL[c]	n(%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
36 weeks pma				
Culture				
B. breve BBG	n(%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
MRSA[a]	n(%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
VRE[b]	n(%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
ESBL[c]	n(%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
PCR				
B. breve BBG	n(%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
MRSA[a]	n(%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
VRE[b]	n(%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
ESBL[c]	n(%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)

[a] methicillin-resistant *Staphylococcus aureus*
[b] vancomycin resistant enterococci
[c] extended spectrum betalactamase producing Gram negative bacteria

TABLE 3.5: PRIMARY ANALYSIS OF SECONDARY OUTCOMES: TIME FROM BIRTH TO FIRST FULL FEED (POST NATAL AGE), (INTENTION TO TREAT)

Form: Q no			*B. breve* BBG (n=XXX)	Placebo (n=XXX)	Adjusted 99% CI
F3:B3	Reached full feeds				
	Yes	n(%)	XXX (XX.X)	XXX (XX.X)	
	Censored - due to death	n(%)	XXX (XX.X)	XXX (XX.X)	
	Censored - due to discharge	n(%)	XXX (XX.X)	XXX (XX.X)	
F3:B3	Post natal age at first full feed	Median	XX.X	XX.X	
		(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)	
		99% CI	(XX.X to XX.X)	(XX.X to XX.X)	XX.X (XX.X to XX.X)
	Change in weight z-score (from baseline to 36 weeks pma)				
		n	XXX	XXX	
		Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.X to XX.X)
		(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)	

TABLE 3.6: PRIMARY ANALYSIS OF SECONDARY OUTCOMES: OTHER DIAGNOSES (INTENTION TO TREAT)

Form: Q no			*B. breve* BBG (n=XXX)	Placebo (n=XXX)	Adjusted Risk ratio (99% CI)
F3:C2	Bronchopulmonary Dysplasia at 36 weeks				
	Yes	n(%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
	No	n(%)	XX (XX.X)	XX (XX.X)	
	Missing	n	XX	XX	
	If Yes;				
	Moderate	n(%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
	Severe	n(%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
	Missing	n	XX	XX	
F3:B4	Hydrocephalus and / or intraparenchymal cysts[a]				
	Yes	n(%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
	No	n(%)	XX (XX.X)	XX (XX.X)	
	Missing	n	XX	XX	
F3:B7	Any Retinopathy of Prematurity (ROP) Examination				
	Yes	n(%)	XX (XX.X)	XX (XX.X)	
	No	n(%)	XX (XX.X)	XX (XX.X)	
	Missing	n	XX	XX	
	If yes, ROP present				
	Yes	n(%)	XX (XX.X)	XX (XX.X)	
	No	n(%)	XX (XX.X)	XX (XX.X)	
	Missing	n	XX	XX	
	If yes, worst Stage of ROP				
	1	n(%)	XX (XX.X)	XX (XX.X)	
	2	n(%)	XX (XX.X)	XX (XX.X)	
	3	n(%)	XX (XX.X)	XX (XX.X)	
	4	n(%)	XX (XX.X)	XX (XX.X)	
	5	n(%)	XX (XX.X)	XX (XX.X)	
	Missing	n	XX	XX	
F3:B7	Treated for ROP				
	Yes	n(%)	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
	No	n(%)	XX (XX.X)	XX (XX.X)	
	Missing	n	XX	XX	

[a] Intraparenchymal cyst defined as any cyst within the parenchyma and includes both porencephaly and cystic periventricular leucomalacia.

TABLE 3.7: PRIMARY ANALYSIS OF SECONDARY OUTCOMES: HOSPITAL STAY (INTENTION TO TREAT)

Form: Q no			*B. breve* BBG (n=XXX)	Placebo (n=XXX)	*Mean Difference (99% CI)*
dates	Total hospital stay	n	XXX	XXX	
		Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.X to XX.X)
		Median	XX.X	XX.X	
		(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)	
		(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)	
		Missing	XX	XX	
F3:B10	Intensive care	n	XXX	XXX	
		Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.X to XX.X)
		Median	XX.X	XX.X	
		(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)	
		(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)	
		Missing	XX	XX	
F3:B10	High-dependency care	n	XXX	XXX	
		Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.X to XX.X)
		Median	XX.X	XX.X	
		(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)	
		(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)	
		Missing	XX	XX	
	Special care	n	XXX	XXX	
		Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.X to XX.X)
		Median	XX.X	XX.X	
		(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)	
		(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)	
		Missing	XX	XX	

XX babies were still in hospital at the time of analysis.

TABLE 4.1: ADHERENCE TO PROTOCOL (INTENTION TO TREAT)

		***B. breve* BBG (n=XXX)**	**Placebo (n=XXX)**
Randomisation > 48 hours post-natal age	n(%)	XX (XX.X)	XX (XX.X)
Gestational age < 23^{+0} weeks	n(%)	XX (XX.X)	XX (XX.X)
Gestational age ≥ 30^{+6} weeks	n(%)	XX (XX.X)	XX (XX.X)

TABLE 4.2: ADHERENCE TO TRIAL INTERVENTION (INTENTION TO TREAT)

		B. breve BBG (n=XXX)	Placebo (n=XXX)
First dose given			
Yes	n(%)	XX (XX.X)	XX (XX.X)
No	n(%)	XX (XX.X)	XX (XX.X)
Missing	n	XX	XX
Post menstrual age at first dose (weeks)	n	XXX	XXX
	Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)
	Median	XX.X	XX.X
	(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)
	(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
	Missing	XX	XX
Post menstrual age at last dose (weeks)	n	XXX	XXX
	Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)
	Median	XX.X	XX.X
	(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)
	(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
	Missing	XX	XX
Total Duration (days)	n	XXX	XXX
	Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)
	Median	XX.X	XX.X
	(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)
	(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
	Missing	XX	XX
Total Duration of interruption(s) (days)	n	XXX	XXX
	Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)
	Median	XX.X	XX.X
	(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)
	(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
	Missing	XX	XX
Percent of recommended doses taken [a]	n	XXX	XXX
	Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)
	Median	XX.X	XX.X
	(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)
	(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
	Missing	XX	XX
Permanent early discontinuation	n(%)	XX (XX.X)	XX (XX.X)
Reason for permanent early discontinuation			
Parental request	n(%)	XX (XX.X)	XX (XX.X)
Clinician recommendation	n(%)	XX (XX.X)	XX (XX.X)
Missing	n	XX	XX

[a] randomisation to 36 weeks post menstrual age. Proportions will be > 100% if the more doses than recommended were taken.

TABLE 4.3 ADHERENCE TO TRIAL INTERVENTION BY GESTATIONAL AGE AT BIRTH (INTENTION TO TREAT)

		***B. breve* BBG (n=XXX)**	**Placebo (n=XXX)**
Percent of recommended doses taken [a]			
23 weeks gestational age	n	XXX	XXX
	Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)
	Median	XX.X	XX.X
	(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)
	(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
	Missing	XX	XX
24 weeks gestational age	n	XXX	XXX
	Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)
	Median	XX.X	XX.X
	(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)
	(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
	Missing	XX	XX
25 weeks gestational age	n	XXX	XXX
	Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)
	Median	XX.X	XX.X
	(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)
	(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
	Missing	XX	XX
26 - 27 weeks gestational age	n	XXX	XXX
	Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)
	Median	XX.X	XX.X
	(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)
	(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
	Missing	XX	XX
28 - 30 weeks gestational age	n	XXX	XXX
	Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)
	Median	XX.X	XX.X
	(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)
	(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
	Missing	XX	XX

[a] randomisation to 36 weeks post menstrual age. Proportions will be > 100% if the more doses than recommended were taken.

FIGURE 2 ADHERENCE TO TRIAL INTERVENTION BY GESTATIONAL AGE (INTENTION TO TREAT)

This figure will present a plot of error bars for adherence as calculated according to section 7.3, by gestational age group, by intervention arm.

TABLE 4.3 HARMS (INTENTION TO TREAT)

Event		*B. breve* BBG (n=XXX)	Placebo (n=XXX)
XXXXXXXXXXXXXXXXXXXXXXXXXX	n(%)	XX (XX.X)	XX (XX.X)
XXXXXXXXXXXXXXXXXXXXXXXXXX	n(%)	XX (XX.X)	XX (XX.X)
XXXXXXXXXXXXXXXXXXXXXXXXXX	n(%)	XX (XX.X)	XX (XX.X)

TABLE 4.4: INVESTIGATOR UNBLINDING (INTENTION TO TREAT)

		B. breve BBG (n=XXX)	Placebo (n=XXX)
Investigator unblinded	n(%)	XX (XX.X)	XX (XX.X)

TABLE 5.1: SUBGROUP ANALYSIS (INTENTION TO TREAT)

	B. breve BBG (n=XXX)	Placebo (n=XXX)	Adjusted Risk Ratio (95% CI)
Sepsis			
By Gestational Age, p=0.XXXX			
23 weeks	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
24 weeks	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
25 weeks	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
26-27 weeks	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
28-30 weeks	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
By Sex, p=0.XXXX			
Male	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
Female	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
By Randomisation time, p=0.XXXX			
< 24 hours	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
≥ 24 hours	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
By *B. breve* BBG Colonisation, p=0.XXXX			
Yes	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
No	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
NEC			
By Gestational Age[b], p=0.XXXX			
23 weeks	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
24 weeks	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
25 weeks	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
26-27 weeks	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
28-30 weeks	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
By Sex, p=0.XXXX			
Male	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
Female	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
By Randomisation time, p=0.XXXX			
< 24 hours	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
≥ 24 hours	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
By *B. breve* BBG Colonisation, p=0.XXXX			
Yes	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
No	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)

[a] Adjusted for sex, gestational age at birth, randomisation < 24 hours of age. Clusters for correlations between multiple births are accounted for.
[b] Effect of increasing gestational age by 1 week is XX.X (XX.X to XX.X).

Table 5.1 Continued

	***B. breve* BBG (n=XXX)**	**Placebo (n=XXX)**	**Adjusted Risk Ratio (95% CI)**
Death			
By Gestational Age, p=0.XXXX			
23 weeks	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
24 weeks	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
25 weeks	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
26-27 weeks	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
28-30 weeks	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
By Sex, p=0.XXXX			
Male	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
Female	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
By Randomisation time, p=0.XXXX			
< 24 hours	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
≥ 24 hours	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
By *B. breve* BBG Colonisation, p=0.XXXX			
Yes	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)
No	XX (XX.X)	XX (XX.X)	XX.X (XX.X to XX.X)

[a] Adjusted for sex, gestational age at birth, randomisation < 24 hours of age. Clusters for correlations between multiple births are accounted for.

FIGURE 3: FOREST PLOT OF SUBGROUP ANALYSIS (INTENTION TO TREAT)

TABLE 5.2: BABY'S OUTCOME (INTENTION TO TREAT)

		***B. breve* BBG (n=XXX)**	**Placebo (n=XXX)**
In hospital	n(%)	XX (XX.X)	XX (XX.X)
Discharged Home	n(%)	XX (XX.X)	XX (XX.X)
Death	n(%)	XX (XX.X)	XX (XX.X)
Respiratory failure	n(%)	XX (XX.X)	XX (XX.X)
Congenital malformation	n(%)	XX (XX.X)	XX (XX.X)
Brain injury	n(%)	XX (XX.X)	XX (XX.X)
Infection	n(%)	XX (XX.X)	XX (XX.X)
NEC	n(%)	XX (XX.X)	XX (XX.X)
Other gut pathology	n(%)	XX (XX.X)	XX (XX.X)
Other	n(%)	XX (XX.X)	XX (XX.X)

TABLE 6: OTHER OUTCOME DATA COLLECTED (INTENTION TO TREAT)

Form: Q no			*B. breve* BBG (n=XXX)	Placebo (n=XXX)
F3:B4	Cerebral Ultrasound Scan performed			
	Yes	n(%)	XX (XX.X)	XX (XX.X)
	No	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX
F3:B4	Cerebral Ultrasound Results			
	No abnormal results	n(%)	XX (XX.X)	XX (XX.X)
	IVH	n(%)	XX (XX.X)	XX (XX.X)
	HPI	n(%)	XX (XX.X)	XX (XX.X)
	Hydrocephalus	n(%)	XX (XX.X)	XX (XX.X)
	Porencephalic cyst	n(%)	XX (XX.X)	XX (XX.X)
	Periventricular leucomalacia	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX
F3:B5	Treatment for patent ductus			
	Yes	n(%)	XX (XX.X)	XX (XX.X)
	No	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX
F3:B5	If Yes;			
	Indometacin or ibuprofen	n(%)	XX (XX.X)	XX (XX.X)
	Surgical Ligation	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX
	Any positive blood culture			
	Yes	n(%)	XX (XX.X)	XX (XX.X)
	No	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX
F3:C2	Post natal corticosteroids			
	Yes	n(%)	XX (XX.X)	XX (XX.X)
	No	n(%)	XX (XX.X)	XX (XX.X)
	Missing	n	XX	XX

TABLE 7: NECOROTISING ENTEROCOLITIS (INTENTION TO TREAT)

		B. breve BBG (n=XXX)	Placebo (n=XXX)
Number of episodes of NEC stage ≥ II			
None	n(%)	XX (XX.X)	XX (XX.X)
1	n(%)	XX (XX.X)	XX (XX.X)
2	n(%)	XX (XX.X)	XX (XX.X)
3	n(%)	XX (XX.X)	XX (XX.X)
4 or more	n(%)	XX (XX.X)	XX (XX.X)
Missing	n	XX	XX
Worse stage NEC			
Stage I	n(%)	XX (XX.X)	XX (XX.X)
Stage II A or B	n(%)	XX (XX.X)	XX (XX.X)
Stage III A	n(%)	XX (XX.X)	XX (XX.X)
Stage III B	n(%)	XX (XX.X)	XX (XX.X)
Post menstrual age at first NEC	n	XXX	XXX
	Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)
	Median	XX.X	XX.X
	(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)
	(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
	Missing	XX	XX
Surgery for any NEC			
No	n(%)	XX (XX.X)	XX (XX.X)
Peritoneal drainage alone	n(%)	XX (XX.X)	XX (XX.X)
Laparotomy, no enterostomy	n(%)	XX (XX.X)	XX (XX.X)
Laparotomy, with enterostomy	n(%)	XX (XX.X)	XX (XX.X)
Missing	n	XX	XX
Death due to any NEC			
Yes	n(%)	XX (XX.X)	XX (XX.X)
No	n(%)	XX (XX.X)	XX (XX.X)
Missing	n	XX	XX
Spontaneous intestinal perforation			
Yes	n(%)	XX (XX.X)	XX (XX.X)
No	n(%)	XX (XX.X)	XX (XX.X)
Missing	n	XX	XX

TABLE 8: POST NATAL AGE (INTENTION TO TREAT)

		***B. breve* BBG (n=XXX)**	**Placebo (n=XXX)**
Post natal age at randomisation (days)	n	XXX	XXX
	Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)
	Median	XX.X	XX.X
	(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)
	(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
	Missing	XX	XX
Post natal age at first dose (days)	n	XXX	XXX
	Mean (StdDev)	XX.X (XX.XX)	XX.X (XX.XX)
	Median	XX.X	XX.X
	(Q1 to Q3)	(XX.X to XX.X)	(XX.X to XX.X)
	(Min to Max)	(XX.X to XX.X)	(XX.X to XX.X)
	Missing	XX	XX

TABLE 9: COLONISATION WITH *B. BREVE* BBG AT 2 WEEKS POST NATAL AGE VS 36 WEEKS POST MENSTRUAL AGE (INTENTION TO TREAT)

		Colonised with *B. breve* BBG at 2 weeks post natal age		
		Yes	**No**	**Total**
***B. breve* BBG**				
Colonised with *B. breve* BBG 36 weeks post menstrual age				
Yes	n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
No	n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Total	n	XX	XX	XX
Placebo				
Colonised with *B. breve* BBG 36 weeks post menstrual age				
Yes	n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
No	n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Total	n	XX	XX	XX
Total				
Colonised with *B. breve* BBG 36 weeks post menstrual age				
Yes	n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
No	n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Total	n	XX	XX	XX

TABLE 10: SIGNIFICANCE OF DETERMINANTS OF SUCCESSFUL COLONISATION WITH *B. BREVE* BBG (INTENTION TO TREAT)

	Single Factor Models	Model 2	Model 3	…	Model N
Parameter 1	XX.X, 0.XXXX		XX.X, 0.XXXX		XX.X, 0.XXXX
Parameter 2	XX.X, 0.XXXX	XX.X, 0.XXXX	XX.X, 0.XXXX		XX.X, 0.XXXX
Parameter 3	XX.X, 0.XXXX				
Parameter 4	XX.X, 0.XXXX	XX.X, 0.XXXX	XX.X, 0.XXXX		XX.X, 0.XXXX
Parameter 5	XX.X, 0.XXXX				
Parameter 6	XX.X, 0.XXXX				XX.X, 0.XXXX

Approval

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