Clinical trial results:
The probiotic Bifidobacterium breve strain BBG-01 admistered early to preterm infants to prevent infection, necrotising enterocolitis and death.

Summary

EudraCT number	2006-003445-17
Trial protocol	GB
Global end of trial date	04 September 2014

Results information

Result version number	v1 (current)
This version publication date	10 March 2017
First version publication date	10 March 2017

Trial information

Trial identification

Sponsor protocol code	BBG001

Additional study identifiers

ISRCTN number	ISRCTN05511098
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Queen Mary University of London
Sponsor organisation address	Mile End Road, London, United Kingdom, E1 4NS
Public contact	Joint R&D Office, Queen Mary University of London, m.rickard@qmul.ac.uk
Scientific contact	Joint R&D Office, Queen Mary University of London, m.rickard@qmul.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 September 2014
Global end of trial reached?	Yes
Global end of trial date	04 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether early administration of B breve BBG to preterm infants reduces the incidence of episodes of infection, necrotising enterocolitis and death.

Protection of trial subjects:

N/A

Background therapy:

Standard neonatal care

Evidence for comparator: -

Actual start date of recruitment	01 July 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 1315
Worldwide total number of subjects	1315
EEA total number of subjects	1315

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	1315
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place in 24 hospitals within 60 miles of London between July 1, 2010, and July 31, 2013
Multiple births were randomised individually.

Pre-assignment

Screening details:

Inclusions: Gestational age >= 23 weeks and 0 days and <= 30 weeks and 6 days, less than 48 hours old, with written informed parental consent, babies already on antibiotics for suspected or proven infection.
Exclusions: lethal congenital abnormality, gastrointestinal malformation, no realistic prospect of survival.

Period 1

Period 1 title	Trial entry
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject, Monitor, Carer, Assessor

Blinding implementation details:

The investigational product was supplied freeze dried with corn starch; the placebo was corn starch alone. Both products were manufactured in Japan at the Yakult Fujisusono Pharmaceutical Plant by the Yakult Honsha Co. Ltd., and provided in identical foil sachets each containing 1 gram of product. In order that the products could not be distinguished both were suspended in 3 ml 1/8 strength (1 scoop to 240 ml sterile water) of the elemental infant formula Neocate and allowed to settle.

Arms

Are arms mutually exclusive?	Yes
Arm title	B. breve BBG

Arm description:

The product is a probiotic supplied freeze dried with corn starch.

Arm type	Experimental
Investigational medicinal product name	BBG-001 (Bifidobacterium breve)
Investigational medicinal product code	
Other name	B breve BBG
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Nasogastric use , Oral use

Dosage and administration details:

The powder is suspended in 3 ml 1/8 strength (1 scoop to 240 ml sterile water) of the elemental infant formula Neocate and the corn starch is allowed to settle for 30 minutes. 1 ml of supernatant is withdrawn to be given to the baby; this contains 6.7 x 107 - 6.7 x 109 colony forming organisms. The products are administered via a naso-gastric or oro-gastric tube or, for babies no longer tube fed, directly into the mouth using a syringe.
The intervention will be given once daily starting as soon as possible after randomisation and continuing until 36 completed weeks of post-menstrual age (36 weeks + 0 days) or death or discharge from hospital if sooner.

Arm title	Placebo

Arm description:

Freeze dried corn starch

Arm type	Placebo

Investigational medicinal product name	BBG-001 (Placebo)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Nasogastric use , Oral use

Dosage and administration details:

The powder is suspended in 3 ml 1/8 strength (1 scoop to 240 ml sterile water) of the elemental infant formula Neocate and the corn starch is allowed to settle for 30 minutes. 1 ml of supernatant is withdrawn to be given to the baby. The products are administered via a naso-gastric or oro-gastric tube or, for babies no longer tube fed, directly into the mouth using a syringe.
The intervention will be given once daily starting as soon as possible after randomisation and continuing until 36 completed weeks of post-menstrual age (36 weeks + 0 days) or death or discharge from hospital if sooner.

Number of subjects in period 1	B. breve BBG	Placebo
Started	654	661
Completed	650	660
Not completed	4	1
Consent withdrawn by subject	4	1

Period 2

Period 2 title	Discharge
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

The investigational product was supplied freeze dried with corn starch; the placebo was corn starch alone. Both products were manufactured in Japan at the Yakult Fujisusono Pharmaceutical Plant by the Yakult Honsha Co. Ltd., and provided in identical foil sachets each containing 1 gram of product. In order that the products could not be distinguished both were suspended in 3 ml 1/8 strength (1 scoop to 240 ml sterile water) of the elemental infant formula Neocate and allowed to settle.

Arms

Are arms mutually exclusive?	Yes
Arm title	B. breve BBG

Arm description:

The product is a probiotic supplied freeze dried with corn starch.

Arm type	Experimental
Investigational medicinal product name	Bifidobacterium breve strain BBG freeze dried with corn starch
Investigational medicinal product code	
Other name	B breve BBG
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Nasogastric use , Oral use, Other use

Dosage and administration details:

The powder is 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 is withdrawn to be given to

the baby; this contains 6.7 x 107 - 6.7 x 109 colony forming organisms. The products are administered via a naso-gastric or oro-gastric tube or, for babies no longer tube fed, directly into the mouth using a syringe.
The intervention will be given once daily starting as soon as possible after randomisation and continuing until 36 completed weeks of post-menstrual age (36 weeks + 0 days) or death or discharge from hospital if sooner.

Arm title	Placebo
Arm description:	
Freeze dried corn starch	
Arm type	Placebo
Investigational medicinal product name	BBG-01 DT (Placebo)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Nasogastric use , Oral use, Other use

Dosage and administration details:

The powder is 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 is withdrawn to be given to the baby; this contains 6.7 x 107 - 6.7 x 109 colony forming organisms. The products are administered via a naso-gastric or oro-gastric tube or, for babies no longer tube fed, directly into the mouth using a syringe.
The intervention will be given once daily starting as soon as possible after randomisation and continuing until 36 completed weeks of post-menstrual age (36 weeks + 0 days) or death or discharge from hospital if sooner.

Number of subjects in period 2	B. breve BBG	Placebo
Started	650	660
Completed	650	660

Baseline characteristics

Reporting groups	
Reporting group title	B. breve BBG
Reporting group description:	
The product is a probiotic supplied freeze dried with corn starch.	
Reporting group title	Placebo
Reporting group description:	
Freeze dried corn starch	

Reporting group values	B. breve BBG	Placebo	Total
Number of subjects	654	661	1315
Age categorical			
Postnatal age at randomisation			
Units: Subjects			
<24 hrs	167	172	339
24 to <=48 hrs	482	487	969
>48 hrs	1	1	2
Excluded from analysis	4	1	5
Gender categorical Units: Subjects			
Female	276	290	566
Male	374	370	744
Excluded from analysis	4	1	5

End points

End points reporting groups

Reporting group title	B. breve BBG
Reporting group description:	
The product is a probiotic supplied freeze dried with corn starch.	
Reporting group title	Placebo
Reporting group description:	
Freeze dried corn starch	
Reporting group title	B. breve BBG
Reporting group description:	
The product is a probiotic supplied freeze dried with corn starch.	
Reporting group title	Placebo
Reporting group description:	
Freeze dried corn starch	

Primary: Sepsis

End point title	Sepsis
End point description:	
Blood stream infection with non-skin commensals	
End point type	Primary
End point timeframe:	
After 72 hours postnatal age and <46 weeks post menstrual age	

End point values	B. breve BBG	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	650	660		
Units: Babies				
Yes	73	77		
No	577	583		

Statistical analyses

Statistical analysis title	Adjusted risk ratio
Statistical analysis description:	
Adjusted for sex, gestational age at birth, randomisation<24 hours of age. Allowances for correlations between multiple births are accounted for.	
Comparison groups	B. breve BBG v Placebo

Number of subjects included in analysis	1310
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.29

Primary: NEC

End point title	NEC
End point description:	
Necrotising Enterocolitis (Bell stage II or higher)	
End point type	Primary
End point timeframe:	
Between randomisation and discharge	

End point values	B. breve BBG	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	650	660		
Units: Babies				
Yes	61	66		
No	589	594		

Statistical analyses

Statistical analysis title	Adjusted risk ratio
Statistical analysis description:	
Adjusted for sex, gestational age at birth, randomisation<24 hours of age. Allowances for correlations between multiple births are accounted for.	
Comparison groups	Placebo v B. breve BBG
Number of subjects included in analysis	1310
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.27

Primary: Death before discharge home

End point title	Death before discharge home

End point description:

End point type	Primary

End point timeframe:

Between randomisation and discharge home

End point values	B. breve BBG	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	650	660		
Units: Babies				
Yes	54	56		
No	596	604		

Statistical analyses

Statistical analysis title	Adjusted risk ratio

Statistical analysis description:

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

Comparison groups	B. breve BBG v Placebo
Number of subjects included in analysis	1310
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.3

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Safety was assessed continuously during each baby's stay in the neonatal unit, between randomisation and discharge home.

Adverse event reporting additional description:

Adverse events are foreseeable due to the nature of the patient population, their routine care and treatment. No adverse drug reactions are expected from BBG. Consequently, only those adverse events (or reactions) identified as serious will be recorded for this trial.

Assessment type	Systematic

Dictionary used

Dictionary name	None used
Dictionary version	1

Reporting groups

Reporting group title	B. breve BBG

Reporting group description:

The product is a probiotic supplied freeze dried with corn starch.

Reporting group title	Placebo

Reporting group description:

Freeze dried corn starch

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Due to the nature of the patient population, neonates in intensive care, a high incidence of adverse events is foreseeable during their routine care and treatment. Consequently, only those adverse events identified as serious were recorded for the trial.

Serious adverse events	B. breve BBG	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 654 (0.15%)	1 / 661 (0.15%)	
number of deaths (all causes)	54	56	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary haemorrhage			
subjects affected / exposed	1 / 654 (0.15%)	0 / 661 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Toxic epidermal necrolysis			
subjects affected / exposed	0 / 654 (0.00%)	1 / 661 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	B. breve BBG	Placebo	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 654 (0.00%)	0 / 661 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26628328