A randomized, double blind, parallel group, dose escalation placebo-controlled multicenter study to investigate the safety and tolerability of IBP-9414 administered in preterm infants at risk of developing NEC

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Introduction

- Necrotizing enterocolitis (NEC) is a devastating and often fatal disease affecting preterm infants with no available preventive therapy
- Infant Bacterial Therapeutics is developing the pharmaceutical drug IBP-9414 for the prevention of NEC in preterm infants
- The clinical development program involves a Safety and Tolerability Trial (presented here) followed by a large, Pivotal Efficacy Trial
- Purpose and Objective of this clinical trial is to evaluate the safety of IBP-9414 at 2 dose levels in preterm infants at risk of NEC

- IBP-9414 is a live bacterial therapeutic
- Dietary supplements containing live bacteria (probiotics) are suggested to be effective in preventing NEC but they are not subject to FDA premarket review and approval requirements for safety and effectiveness or to the manufacturing and testing standards for products regulated as drugs by FDA
  - A premature infant within a US NICU died in 2014 of gastrointestinal mucormycosis caused by mold from a contaminated probiotic dietary supplement
  - FDA issued an Important Drug Warning to alert NICUs who use probiotics to treat, mitigate, cure or prevent a disease or condition to submit an Investigational New Drug Application (IND) for FDA review

Methods

- Randomized, double blind, dose escalation placebo-controlled Safety and Tolerability study.
- IND opened by FDA in December 2015.
- Registered on ClinicalTrials.gov: NCT02472769.

Inclusion criteria

- Gestational age ≤32w+6d
- <48 hours of age
- Birth weight 1,001 – 2,000 g (A&B)
  500 – 1,000 g (C&D)
- Written informed consent

Exclusion criteria

- Participation in another clinical trial
- Infants in extremis
- Congenital or acquired gastrointestinal pathology
- Other condition of the infant which in the opinion of the attending neonatologist preclude participation.

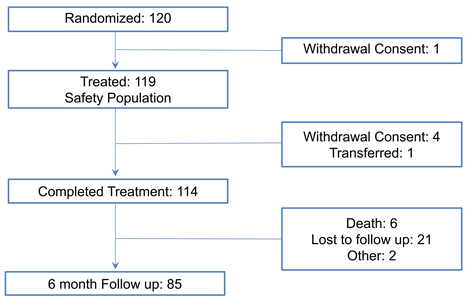
IBP-9414

- Freeze-dried powder in a prefilled, single-dose glass vial for reconstitution by hospital pharmacy in sterile water
- Administration through nasogastric or orogastric tube

Neu, Gainesville FL, PI
Del Moral, Miami FL
White, South Bend IN
Hand, Brooklyn NY
Hudak, I Jacksonville FL
Hudak II Jacksonville FL
Gerstmann, Orem UT
Porcelli, Wake Forest NC
Kona, Little Rock AR
Hirsch, Philadelphia PA
Kehinde, Philadelphia PA
Guthrie, Jackson TN
Garg, Los Angeles CA
Ashley, Durham NC
Bloom, Wichita KS

Results

Subject Disposition



Demographics

	Cohort A: Low dose (n=16)	Cohort A: Placebo (n=13)	Cohort B: High dose (n=16)	Cohort B: Placebo (n=14)	Cohort C: Low dose (n=14)	Cohort C: Placebo (n=16)	Cohort D: High dose (n=15)	Cohort D: Placebo (n=15)
Gestational Age (wks) (Mean±SD)	30.4±1.2	30.5±1.5	30.5±1.6	30.7±1.5	26.0±2.0	25.9±2.1	26.4±1.6	27.2±2.2
Male/Female (n)	8/8	6/7	5/11	9/5	5/9	8/8	5/10	7/8
Hispanic or Latino/Non-hispanic or Latino/Unknown (n)	0/16/0	1/12/0	1/14/1	0/14/0	4/10/0	0/16/0	2/13/0	4/11/0
Black or African American/White/Other (n)	8/7/1	4/9/0	7/8/1	8/5/1	8/5/1	8/6/2	4/9/2	8/4/3
Vaginal/Caesarian delivery (n)	4/12	5/8	9/7	6/8	5/9	5/11	3/12	3/12
Apgar Score [Mean±SD (n)] 1 Min	5.1±1.7 (15)	6.5±2.1 (13)	6.1±2.5 (16)	4.9±2.2 (14)	4.9±2.5 (14)	4.9±2.0 (14)	4.3±2.8 (15)	4.8±2.2 (15)
5 Min	7.8±0.9 (15)	7.8±2.0 (13)	8.0±1.3 (16)	7.1±2.3 (14)	6.7±2.1 (14)	7.0±2.0 (14)	7.1±1.7 (15)	7.2±1.2 (15)
10 Min	8.5±1.0 (4)	7.0±2.8 (2)	7.7±0.6 (3)	6.3±2.5 (4)	7.4±1.1 (8)	7.8±1.0 (8)	7.5±1.3 (8)	7.0±1.2 (5)
Length at birth in cm (Mean±SD)	39±3	41±2	40±3	40±2	33±4	32±2	33±2	33±3
Birth weight in g (Mean±SD)	1312±262	1470±210	1451±268	1418±252	723±174	738±128	787±116	834±116

Study Drug Administration

	Cohort A: Low dose (n=16)	Cohort A: Placebo (n=13)	Cohort B: High dose (n=16)	Cohort B: Placebo (n=14)	Cohort C: Low dose (n=14)	Cohort C: Placebo (n=16)	Cohort D: High dose (n=15)	Cohort D: Placebo (n=15)
Days (Mean±SD)	13.9±0.5	13.8±0.8	12.6±3.2	12.1±3.5	10.2±4.3	10.7±5.3	12.3±3.2	12.6±2.2

- High compliance with study drug with >12 days of administration overall
- No differences between active and placebo
- Slightly lower compliance in Cohort C with about 10.5 days of study drug administration overall

Primary Outcome

Adverse events during treatment with Study Drug

	Cohort A: Low dose (n=16)	Cohort A: Placebo (n=13)	Cohort B: High dose (n=16)	Cohort B: Placebo (n=14)	Cohort C: Low dose (n=14)	Cohort C: Placebo (n=16)	Cohort D: High dose (n=15)	Cohort D: Placebo (n=15)
Number of infants with Adverse Events (AEs)	9	11	10	6	13	12	14	14
Total number of AEs	29	30	51	24	51	48	64	58
Number infants with Serious Adverse Events (SAEs)	3	2	2	1	3	2	2	2
Total number of SAEs	6	3	2	3	5	4	2	4
Related AEs	0	0	1	0	3	2	0	2
Related SAEs	0	0	0	0	0	0	0	1
Number infants where AE led to Study Drug withdrawal	0	0	0	0	0	1	0	1
Death	0	0	0	0	0	0	0	0

Types of adverse events during treatment with Study Drug

	Cohort A: Low dose (n=16)	Cohort A: Placebo (n=13)	Cohort B: High dose (n=16)	Cohort B: Placebo (n=14)	Cohort C: Low dose (n=14)	Cohort C: Placebo (n=16)	Cohort D: High dose (n=15)	Cohort D: Placebo (n=15)
Most frequent AEs (no. of infants)								
Intraventricular hemorrhage neonatal	1	4	3	1	4	5	5	4
Anemia neonatal	0	0	2	1	5	3	8	7
Apnea neonatal	2	2	3	1	2	4	6	5
Patent ductus arteriosus	0	1	3	2	3	2	4	5
Hypernatremia	3	2	4	1	0	2	1	2
Hyperbilirubinemia neonatal	0	3	3	2	0	3	2	1
Hyponatremia	3	2	1	0	1	3	2	1
Sepsis neonatal	0	2	0	0	3	2	2	3
SAEs (no. of infants)								
Atrial thrombosis	1	0	0	0	0	0	0	0
Patent ductus arteriosus	0	0	0	0	0	0	1	0
Gastroesophageal reflux disease	1	0	0	0	0	0	0	0
Inguinal hernia	0	1	0	0	0	0	0	0
Intestinal perforation	0	0	0	0	0	1	0	0
Multi-organ failure	0	0	0	0	1	0	0	0
Bacterial sepsis	1	0	0	0	0	0	0	0
Sepsis neonatal	0	1	0	0	3	0	0	1
Urinary system X-ray	0	0	1	0	0	0	0	0
Failure to thrive	1	0	0	0	0	0	0	0
Hyperglycemia	0	0	0	0	0	1	0	0
Encephalomalacia	0	0	0	1	0	0	0	0
Intraventricular hemorrhage neonatal	0	1	1	1	1	1	0	0
Seizure	0	0	0	0	0	0	1	0
Acute kidney injury	0	0	0	0	0	0	0	1
Anuria	0	0	0	0	0	0	0	1
Azotemia	0	0	0	0	0	1	0	0
Pneumonia aspiration	0	0	0	0	0	0	0	1
Pneumothorax	2	0	0	0	0	0	0	0
Pulmonary hemorrhage	0	0	0	1	0	0	0	0

Adverse events during Follow-up to 6 month after last dose of Study Drug

	Cohort A: Low dose (n=16)	Cohort A: Placebo (n=13)	Cohort B: High dose (n=16)	Cohort B: Placebo (n=14)	Cohort C: Low dose (n=14)	Cohort C: Placebo (n=16)	Cohort D: High dose (n=15)	Cohort D: Placebo (n=15)
Total number of AEs	38	30	43	20	147	101	89	77
Total number of SAEs	4	4	6	4	7	15	5	10
Death	0	0	0	0	3	2	0	1

- 105 subjects (88% of all infants) across all study cohorts experienced any kind of AE
- 41 subjects experienced SAEs (35%) across all treatment groups
- AEs were reported in larger numbers in 500-1000g infants than in the 1001-2000g infants
- AEs and SAEs reported were generally consistent with the underlying condition of prematurity and the clinical conditions of the subjects
- The most frequently reported AE up to the end of Follow-up was neonatal anemia, which was reported in larger numbers in the lower birth weight cohorts
- No safety trends were apparent in the AEs or SAEs reported
- Very few SAEs or AEs were judged by the investigators to be related to study drug
- 6 subjects died during the study. Primary causes of death included disseminated intravascular coagulation (DIC), NEC, cerebral hypoxia, and severe aspiration pneumonia/respiratory failure.
- IBP-9414 appeared to be safe and well tolerated in premature infants between 500g and 2000g birth weights at both dose levels

Fecal Analysis – Real Time qPCR Analysis

	Cohort A: Low dose	Cohort A: Placebo	Cohort B: High dose	Cohort B: Placebo	Cohort C: Low dose	Cohort C: Placebo	Cohort D: High dose	Cohort D: Placebo
Last day of study treatment	61623* (111110) (n=11)	6 (12) (n=10)	25764* (173111) (n=12)	3 (112) (n=10)	1423^{NS} (10269) (n=5)	7 (874) (n=10)	58251* (311599) (n=8)	40 (75) (n=12)
30 days after last dose	160 (760) (n=7)	297 (371) (n=5)	184 (6437) (n=3)	473 (513) (n=5)	40 (61) (n=9)	59 (184) (n=8)	40 (87) (n=12)	18 (35) (n=12)

*Median (Interquartile range) for bacterial counts per qPCR reaction. * P<0.001 vs placebo and ^{NS} not significant vs placebo.*

- Treatment with IBP-9414 leads to presence of bacterium in the feces on day of last dose: all IBP-treated, 31491 (121875) vs all placebo, 10 (91); P<0.001, Rank sum Wilcoxon
- Cross-contamination did not occur in placebo treated infants
- Smaller infants needed the higher dose to display IBP-9414 in the feces
- 30 days after last dose, the bacteria have been washed out: all IBP-treated, 63 (184) vs all placebo, 42 (290); NS, Rank sum Wilcoxon

- There was no difference in growth between active and placebo treated infants
- There was no case of IBP-9414 bacteria being found in any normally sterile fluid in any infant

Conclusions

- IBP-9414 was safe and well-tolerated in preterm infants with birth weights 500g - 2000g
- There was high compliance with exposure to the Study Drug
- There was no evidence of cross-contamination with IBP-9414 in placebo treated infants

- The IBP-9414 drug clinical development program will now move forward with the planned Pivotal Efficacy trial for the prevention of NEC

IBP-9414 Clinical Development Program

BLA: Biologics License Application

- A large Pivotal Efficacy trial to evaluate the efficacy of the drug IBP-9414 in the prevention of NEC is now being initiated

- ≤32w GA and ≤1,500g birth weight infants
- Randomized, double-blind, placebo-controlled
- US, Canadian and European NICUs
- Under IND (US) and CTX (Europe)

- *Do you want your NICU to participate in this Pivotal Efficacy Trial? Contact Eamonn Connolly at IBT on eamonn.connolly@ibtherapeutics.com*

IND holder and Study Sponsor

Infant Bacterial Therapeutics