Clinical trial results:
A Phase 1 randomised, double-blind, placebo-controlled study to assess the safety and tolerability of Bacteroides thetaiotaomicron in young people aged 16 to 18 years with stable Crohn's disease.

Summary

EudraCT number	2014-005666-29
Trial protocol	GB
Global end of trial date	10 April 2018

Results information

Result version number	v1 (current)
This version publication date	01 November 2018
First version publication date	01 November 2018
Summary attachment (see zip file)	Theta-001-synopsis (Theta-001-synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	Theta 001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02704728
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	4D Pharma Research Ltd
Sponsor organisation address	9 Bond Court, Leeds, United Kingdom, LS1 2JZ
Public contact	Chief Medical Officer, 4D Pharma Plc, +44 113 895 0130, john.weinberg@4dpharmaplc.com
Scientific contact	Chief Medical Officer, 4D Pharma Plc, +44 113 895 0130, john.weinberg@4dpharmaplc.com

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	31 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 April 2018
Global end of trial reached?	Yes
Global end of trial date	10 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess the tolerability and safety of B. theta when administered as a single dose and in multiple doses.

Protection of trial subjects:

This was a first in man safety study. Individual subject stopping rules were defined in the protocol relating to exacerbation of Crohn's disease and systemic infection. Subjects were asked to record their body temperature twice daily at home and to contact the hospital/study team in the event of a fever.

Background therapy:

None

Evidence for comparator:

Placebo comparator randomized 4: active:placebo

Actual start date of recruitment	05 October 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	15
Adults (18-64 years)	3
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

D-28: screening visit: check of subject’s ability and willingness to swallow 3× size 0 placebo capsules
D-3 - D0: 2 stool samples requested

Period 1

Period 1 title	Single Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo single dose

Arm description:

Placebo single dose (single dose consisting of 3 capsules)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Off white intrinsically enteric size 0 capsules containing microcrystalline cellulose.

Arm title	Thetanix Single dose

Arm description:

Experimental single dose (single dose consisting of 3 capsules)

Arm type	Experimental
Investigational medicinal product name	Thetanix
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Off white intrinsically enteric size 0 capsules containing lyophilised B. thetaiotaomicron. Each capsule contains 10^7.73±1.43 colony forming units (CFUs) and microcrystalline cellulose.

Arm title	Placebo multiple doses

Arm description:

Placebo multiple doses (twice daily dosing period of 7.5 days)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Off white intrinsically enteric size 0 capsules containing microcrystalline cellulose.

Arm title	Thetanix multiple doses

Arm description:

Experimental multiple doses (twice daily dosing period of 7.5 days)

Arm type	Experimental
Investigational medicinal product name	Thetanix
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Off white intrinsically enteric size 0 capsules containing lyophilised B. thetaiotaomicron. Each capsule contains 10^7.73±1.43 colony forming units (CFUs) and microcrystalline cellulose.

Number of subjects in period 1	Placebo single dose	Thetanix Single dose	Placebo multiple doses
Started	2	6	2
Completed	2	6	2

Number of subjects in period 1	Thetanix multiple doses
Started	8
Completed	8

Baseline characteristics

Reporting groups

Reporting group title	Single Period

Reporting group description: -

Reporting group values	Single Period	Total	
Number of subjects	18	18	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	15	15	
Adults (18-64 years)	3	3	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
geometric mean	16.75		
standard deviation	± 0.886	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	14	14	

End points

End points reporting groups

Reporting group title	Placebo single dose
Reporting group description: Placebo single dose (single dose consisting of 3 capsules)	
Reporting group title	Thetanix Single dose
Reporting group description: Experimental single dose (single dose consisting of 3 capsules)	
Reporting group title	Placebo multiple doses
Reporting group description: Placebo multiple doses (twice daily dosing period of 7.5 days)	
Reporting group title	Thetanix multiple doses
Reporting group description: Experimental multiple doses (twice daily dosing period of 7.5 days)	

Primary: Adverse events

End point title	Adverse events[1]
End point description: All AEs were coded by the MedDRA.	
End point type	Primary
End point timeframe: by study completion	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis were performed for this study due to the small sample size which would give erroneous results

End point values	Placebo single dose	Thetanix Single dose	Placebo multiple doses	Thetanix multiple doses
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	6	2	8
Units: Adverse Events	2	6	2	8

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Single dose: Pre-dose/ 2, 4, 8h post inpatient dose/ 24 h post-dose/ Day 7
Multiple dose: Pre-dose/ 2,4 h post first inpatient dose/ 24h post first dose/ pre-, 2, 4h post last dose/ day 14/ day 56
Completion of a diary card. AE followed to resolution

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Placebo (Part A)

Reporting group description:

single oral dose (a dose consisted of 3 capsules)

Reporting group title	Thetanix single dose (Part A)

Reporting group description:

single oral dose (a dose consisted of 3 capsules)

Reporting group title	Placebo (Part B)

Reporting group description: -

Reporting group title	Thetanix multiple dose (Part B)

Reporting group description: -

Serious adverse events	Placebo (Part A)	Thetanix single dose (Part A)	Placebo (Part B)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	Thetanix multiple dose (Part B)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	Placebo (Part A)	Thetanix single dose (Part A)	Placebo (Part B)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	2 / 6 (33.33%)	1 / 2 (50.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Eructation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Flatulence			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux			
subjects affected / exposed	0 / 2 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 6 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1

Non-serious adverse events	Thetanix multiple dose (Part B)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 8 (50.00%)		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Eructation			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Flatulence			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

Back pain subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Rhinitis subjects affected / exposed occurrences (all)	 1 / 8 (12.50%) 1 0 / 8 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2016	Temporary halt (delay in the start of dosing)
09 May 2016	Reinitiation of the clinical trial following the Temporary Halt
09 May 2016	Placebo shelf life extension
16 September 2016	Change in Drug Product Shelf-life (Revision of the method of determination)
20 December 2016	New protocol version
15 May 2017	Manufacturing Process Changes
14 July 2017	New protocol version

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 March 2016	Delay in the start of dosing for the study due to supply issues	26 May 2016

Notes:

Limitations and caveats

None reported