



Clinical trial results:

A Randomised, Phase 2a, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Antiviral Activity Against Respiratory Syncytial Virus Infection, and the Pharmacokinetics of Multiple Oral Doses of BTA-C585 in the Virus Challenge Model

Summary

EudraCT number	2015-004296-77
Trial protocol	GB
Global end of trial date	08 December 2016

Results information

Result version number	v1 (current)
This version publication date	23 September 2018
First version publication date	23 September 2018

Trial information

Trial identification

Sponsor protocol code	BTA585-003
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02718937
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biota Pharma Europe Limited
Sponsor organisation address	2500 Northwinds Parkway, Suite 100, Alpharetta, United States, 30009
Public contact	Regulatory Affairs, hVIVO Services Limited, +44 02079891313 , regsubmissions@hvivo.com
Scientific contact	Regulatory Affairs, hVIVO Services Limited, +44 02079891313 , regsubmissions@hvivo.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	08 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 December 2016
Global end of trial reached?	Yes
Global end of trial date	08 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the antiviral effect of oral BTA-C585 compared to placebo after inoculation with RSV-A Memphis 37b virus.

Protection of trial subjects:

The study was performed in accordance with applicable regulatory and ethical guidelines including the Declaration of Helsinki and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP), and any applicable national and local laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 March 2016
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: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

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)	0
Adults (18-64 years)	60
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a single-center study conducted in the United Kingdom (UK). An additional affiliated site was used for screening and subject recruitment only, which also located in the UK. The study period was March 23, 2016 to December 8, 2016.

Pre-assignment

Screening details:

Subjects completed a Screening visit within 90 days prior to admission to the quarantine unit. Depending on the length of the Screening period, the duration of a subject's participation from the screening visit to the last scheduled follow-up visit could have been between approximately 1 to 4 months.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	400 mg BID BTA585

Arm description:

400 mg dose consists of 4x 100 mg capsules of BTA585

Arm type	Experimental
Investigational medicinal product name	BTA-C585
Investigational medicinal product code	DV0026664AA
Other name	BC73987, BC00073987, PM303103602
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

400 mg BTA585 administered via oral route

Arm title	600 mg BID BTA585
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Arm description:

600 mg dose consists of 6x 100 mg capsules of BTA585

Arm type	Experimental
Investigational medicinal product name	BTA-C585
Investigational medicinal product code	DV0026664AA
Other name	BC73987, BC00073987, PM303103602
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

600 mg BTA585 administered via oral route

Arm title	Placebo
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Arm description:

Placebo dose consists of applicable matching placebo capsules.

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

Dosage and administration details:

Matching placebo capsules administered by oral route.

Number of subjects in period 1	400 mg BID BTA585	600 mg BID BTA585	Placebo
Started	20	20	20
Completed	20	20	20

Baseline characteristics

Reporting groups

Reporting group title	400 mg BID BTA585
Reporting group description: 400 mg dose consists of 4x 100 mg capsules of BTA585	
Reporting group title	600 mg BID BTA585
Reporting group description: 600 mg dose consists of 6x 100 mg capsules of BTA585	
Reporting group title	Placebo
Reporting group description: Placebo dose consists of applicable matching placebo capsules.	

Reporting group values	400 mg BID BTA585	600 mg BID BTA585	Placebo
Number of subjects	20	20	20
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	20	20	20
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	25.8	26.5	25.1
standard deviation	± 8.23	± 6.79	± 5.13
Gender categorical			
Units: Subjects			
Female	8	9	3
Male	12	11	17

Reporting group values	Total		
Number of subjects	60		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
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)	60		

From 65-84 years	0		
85 years and over	0		

Age continuous Units: years arithmetic mean standard deviation			
Gender categorical Units: Subjects			
Female	20		
Male	40		

Subject analysis sets

Subject analysis set title	400 mg
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

all randomized subjects who received at least one dose of study drug and Challenge Virus, and provided a positive PCR per the qicPCR prior to randomization, and had at least one quantifiable viral load during quarantine

Subject analysis set title	600 mg
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

all randomized subjects who received at least one dose of study drug and Challenge Virus, and provided a positive PCR per the qicPCR prior to randomization, and had at least one quantifiable viral load during quarantine

Subject analysis set title	Placebo
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

all randomized subjects who received at least one dose of study drug and Challenge Virus, and provided a positive PCR per the qicPCR prior to randomization, and had at least one quantifiable viral load during quarantine

Reporting group values	400 mg	600 mg	Placebo
Number of subjects	13	12	13
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over	13	12	13
Age continuous Units: years arithmetic mean standard deviation	±	±	±

Gender categorical			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	400 mg BID BTA585
Reporting group description: 400 mg dose consists of 4x 100 mg capsules of BTA585	
Reporting group title	600 mg BID BTA585
Reporting group description: 600 mg dose consists of 6x 100 mg capsules of BTA585	
Reporting group title	Placebo
Reporting group description: Placebo dose consists of applicable matching placebo capsules.	
Subject analysis set title	400 mg
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: all randomized subjects who received at least one dose of study drug and Challenge Virus, and provided a positive PCR per the qicPCR prior to randomization, and had at least one quantifiable viral load during quarantine	
Subject analysis set title	600 mg
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: all randomized subjects who received at least one dose of study drug and Challenge Virus, and provided a positive PCR per the qicPCR prior to randomization, and had at least one quantifiable viral load during quarantine	
Subject analysis set title	Placebo
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: all randomized subjects who received at least one dose of study drug and Challenge Virus, and provided a positive PCR per the qicPCR prior to randomization, and had at least one quantifiable viral load during quarantine	

Primary: Area Under Curve of RSV-A Memphis 37b viral load as Determined by RT-qPCR Assay

End point title	Area Under Curve of RSV-A Memphis 37b viral load as Determined by RT-qPCR Assay
End point description: The primary efficacy endpoint was the AUC of RSV-A Memphis 37b viral load as determined by RT-qPCR assay of nasal wash from the first viral load measurement post initial study drug dosing through Study Day 12	
End point type	Primary
End point timeframe: First viral load measurement post initial study drug dosing through Study Day 12	

End point values	400 mg	600 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	12	13	
Units: log ₁₀ copies/mL*hours				
arithmetic mean (standard deviation)	502.72 (± 223.91)	519.81 (± 291.89)	548.65 (± 303.88)	

Statistical analyses

Statistical analysis title	Statistical Analysis - 400 vs Placebo
Comparison groups	400 mg v Placebo
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.523 ^[1]
Method	ANCOVA
Confidence interval	
sides	2-sided
lower limit	332.266
upper limit	636.876

Notes:

[1] - The p-value corresponds to pairwise comparisons of each active group versus placebo created from linear contrasts of the ANCOVA model

Statistical analysis title	Statistical Analysis - 600 vs Placebo
Comparison groups	600 mg v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.868 ^[2]
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	376.931
upper limit	692.845

Notes:

[2] - The p-value corresponds to pairwise comparisons of each active group versus placebo created from linear contrasts of the ANCOVA model

Statistical analysis title	Statistical Analysis - Combined
Comparison groups	400 mg v 600 mg v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.641
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	400.885
upper limit	618.573

Primary: Area Under Curve of RSV-A Memphis 37b viral load as Determined by RT-qPCR Assay Using PFUe

End point title	Area Under Curve of RSV-A Memphis 37b viral load as Determined by RT-qPCR Assay Using PFUe
End point description:	
End point type	Primary
End point timeframe:	
First dose of study drug through Study Day 12	

End point values	400 mg	600 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	12	13	
Units: llog10 PFUe/mL*hours)				
arithmetic mean (standard deviation)	-335.4597 (± 241.32252)	-310.1802 (± 279.45651)	-259.2520 (± 284.02210)	

Statistical analyses

Statistical analysis title	Statistical Analysis - 400 vs Placebo
Comparison groups	400 mg v Placebo
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.349 [3]
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-501.9907
upper limit	-204.5268
Variability estimate	Standard deviation

Notes:

[3] - The p-value corresponds to pairwise comparisons of each active group versus placebo created from linear contrasts of the ANCOVA model

Statistical analysis title	Statistical Analysis - 600 vs Placebo
Comparison groups	600 mg v Placebo

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.703 ^[4]
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-449.6412
upper limit	-141.138
Variability estimate	Standard deviation

Notes:

[4] - The p-value corresponds to pairwise comparisons of each active group versus placebo created from linear contrasts of the ANCOVA model

Statistical analysis title	Statistical Analysis - Combined
Comparison groups	400 mg v 600 mg v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.444
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-430.615
upper limit	-218.0333
Variability estimate	Standard deviation

Primary: Area Under Curve of RSV-A Memphis 37b viral load as Determined by RT-qPCR Assay (log₁₀ copies)

End point title	Area Under Curve of RSV-A Memphis 37b viral load as Determined by RT-qPCR Assay (log ₁₀ copies)
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End point description:

End point type	Primary
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End point timeframe:

First dose of study drug through Study Day 12

End point values	400 mg	600 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	12	13	
Units: log ₁₀ copies/mL*hours				
arithmetic mean (standard deviation)	740.6381 (± 151.52373)	745.9596 (± 189.34238)	756.4048 (± 213.34022)	

Statistical analyses

Statistical analysis title	Statistical Analysis - 400 vs Placebo
Comparison groups	400 mg v Placebo
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.679 ^[5]
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	627.22
upper limit	830.262

Notes:

[5] - The p-value corresponds to pairwise comparisons of each active group versus placebo created from linear contrasts of the ANCOVA model

Statistical analysis title	Statistical Analysis - 600 vs Placebo
Comparison groups	Placebo v 600 mg
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.986 ^[6]
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	651.429
upper limit	862.442

Notes:

[6] - The p-value corresponds to pairwise comparisons of each active group versus placebo created from linear contrasts of the ANCOVA model

Statistical analysis title	Statistical Analysis - Combined
Comparison groups	400 mg v 600 mg v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.804
Method	ANCOVA

Confidence interval	
level	95 %
sides	2-sided
lower limit	500.7
upper limit	1137.709
Variability estimate	Standard deviation

Secondary: Area Under Curve of RSV-A Memphis 37b viral load as Determined by Plaque Assay

End point title	Area Under Curve of RSV-A Memphis 37b viral load as Determined by Plaque Assay
End point description:	
End point type	Secondary
End point timeframe:	
First dose of study drug through Study Day 12	

End point values	400 mg	600 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	11	12	
Units: log ₁₀ PFU/mL*hours				
arithmetic mean (standard deviation)	177.2841 (± 175.96635)	231.9255 (± 193.64278)	181.4222 (± 132.33089)	

Statistical analyses

Statistical analysis title	Statistical Analysis - 400 vs Placebo
Comparison groups	400 mg v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.281 ^[7]
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0908
upper limit	300.6546
Variability estimate	Standard deviation

Notes:

[7] - The p-value corresponds to pairwise comparisons of each active group versus placebo created from linear contrasts of the ANCOVA model.

Statistical analysis title	Statistical Analysis - 600 vs Placebo
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Comparison groups	600 mg v Placebo
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.927 ^[8]
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	114.413
upper limit	488.5367
Variability estimate	Standard deviation

Notes:

[8] - The p-value corresponds to pairwise comparisons of each active group versus placebo created from linear contrasts of the ANCOVA model.

Statistical analysis title	Statistical Analysis - Combined
Comparison groups	400 mg v 600 mg v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	106.3109
upper limit	345.5367
Variability estimate	Standard deviation

Secondary: Peak RSV-A Memphis 37b viral load as Determined by RT-qPCR Assay

End point title	Peak RSV-A Memphis 37b viral load as Determined by RT-qPCR Assay
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End point description:

End point type	Secondary
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End point timeframe:

Peak viral load from first dose of study drug was the maximum viral load occurring after the initiation of study drug.

End point values	400 mg	600 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	12	13	
Units: log ₁₀ copies/mL*hours				
arithmetic mean (standard deviation)	5.7480 (± 1.03010)	5.5098 (± 1.17046)	6.2440 (± 1.52718)	

Statistical analyses

Statistical analysis title	Statistical Analysis - 400 vs Placebo
Comparison groups	400 mg v Placebo
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.218 ^[9]
Method	ANCOVA
Confidence interval	
sides	2-sided
lower limit	4.9641
upper limit	6.354
Variability estimate	Standard deviation

Notes:

[9] - The p-value corresponds to pairwise comparisons of each active group versus placebo created from linear contrasts of the model stated above

Statistical analysis title	Statistical Analysis - 600 vs Placebo
Comparison groups	600 mg v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.173 ^[10]
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.863
upper limit	6.3045
Variability estimate	Standard deviation

Notes:

[10] - The p-value corresponds to pairwise comparisons of each active group versus placebo created from linear contrasts of the model stated above

Statistical analysis title	Statistical Analysis - Combined
Comparison groups	400 mg v 600 mg v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.133
Method	ANCOVA

Confidence interval	
level	95 %
sides	2-sided
lower limit	5.1247
upper limit	6.1181
Variability estimate	Standard deviation

Secondary: Peak Viral Load of RSV-A Memphis 37b as Determined by Plaque Assay

End point title	Peak Viral Load of RSV-A Memphis 37b as Determined by Plaque Assay
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End point description:

End point type	Secondary
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End point timeframe:

Peak viral load from the first dose of study drug is the maximum viral load occurring after the initiation of study drug

End point values	400 mg	600 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	12	13	
Units: PFUe/mL				
arithmetic mean (standard deviation)	3.1992 (± 2.10030)	3.5592 (± 1.88389)	3.4792 (± 1.92937)	

Statistical analyses

Statistical analysis title	Statistical Analysis - 400 vs Placebo
Comparison groups	Placebo v 400 mg
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05 ^[11]
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2757
upper limit	3.9832
Variability estimate	Standard deviation

Notes:

[11] - The p-value corresponds to pairwise comparisons of each active group versus placebo created from linear contrasts of the model stated above.

Statistical analysis title	Statistical Analysis - 600 vs Placebo
Comparison groups	600 mg v Placebo

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.464 ^[12]
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.8536
upper limit	6.2237
Variability estimate	Standard deviation

Notes:

[12] - The p-value corresponds to pairwise comparisons of each active group versus placebo created from linear contrasts of the model stated above.

Statistical analysis title	Statistical Analysis - Combined
Comparison groups	400 mg v 600 mg v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.134 ^[13]
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.5066
upper limit	4.6615
Variability estimate	Standard deviation

Notes:

[13] - The p-value corresponds to pairwise comparisons of each active group versus placebo created from linear contrasts of the model stated above.

Secondary: Time to Cessation of Viral Shedding by RT-qPCR Assay

End point title	Time to Cessation of Viral Shedding by RT-qPCR Assay
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End point description:

End point type	Secondary
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End point timeframe:

Time to Cessation of Viral Shedding from First Dose of Study Drug

End point values	400 mg	600 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	11	12	
Units: hours				
arithmetic mean (standard error)	148.95 (± 9.388)	155.37 (± 10.113)	168.26 (± 13.401)	

Statistical analyses

Statistical analysis title	Statistical Analysis - 400 vs Placebo
Comparison groups	400 mg v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.215
Method	Logrank
Confidence interval	
level	95 %
sides	2-sided
lower limit	130.97
upper limit	179.33
Variability estimate	Standard error of the mean

Statistical analysis title	Statistical Analysis - 600 vs Placebo
Statistical analysis description: Cessation of Viral Shedding was considered to occur at the time point where RT-qPCR was negative for RSV and remained negative for all subsequent values. Subjects who did not experience viral shedding were excluded from analysis. Subjects who did not experience cessation of viral shedding were censored at their last non-missing assessment for a given test.	
Comparison groups	Placebo v 600 mg
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25
Method	Logrank
Confidence interval	
level	95 %
sides	2-sided
lower limit	119.35
upper limit	179.42
Variability estimate	Standard error of the mean

Statistical analysis title	Statistical Analysis - Combined
Comparison groups	400 mg v 600 mg v Placebo

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.151
Method	Logrank
Confidence interval	
level	95 %
sides	2-sided
lower limit	125.91
upper limit	179.38
Variability estimate	Standard error of the mean

Secondary: Duration of Viral Shedding by RT-qPCR Assay

End point title	Duration of Viral Shedding by RT-qPCR Assay
End point description:	
End point type	Secondary
End point timeframe:	
Duration of viral shedding was calculated as the difference in the date/time of the Cessation of viral shedding and the Initiation of viral shedding.	

End point values	400 mg	600 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	11	12	
Units: hours				
arithmetic mean (standard deviation)	143.04 (± 13.729)	146.24 (± 14.245)	155.55 (± 19.212)	

Statistical analyses

Statistical analysis title	Statistical Analysis - 400 vs Placebo
Comparison groups	400 mg v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.427
Method	Logrank
Confidence interval	
level	95 %
sides	2-sided
lower limit	108
upper limit	168.07
Variability estimate	Standard deviation

Statistical analysis title	Statistical Analysis - 600 vs Placebo
Comparison groups	600 mg v Placebo
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.363
Method	Logrank
Confidence interval	
level	95 %
sides	2-sided
lower limit	131.93
upper limit	168.3
Variability estimate	Standard deviation

Statistical analysis title	Statistical Analysis - Combined
Comparison groups	400 mg v 600 mg v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.309
Method	Logrank
Confidence interval	
level	95 %
sides	2-sided
lower limit	119.97
upper limit	168.18
Variability estimate	Standard deviation

Secondary: Total Mucus Weight

End point title	Total Mucus Weight
End point description:	
End point type	Secondary
End point timeframe:	
First dose of study drug included all data from the measurement captured following the initiation of study drug through the last measurement captured on Study Day 12 or prior to the last dose of study drug	

End point values	400 mg	600 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	12	13	
Units: gram(s)				
arithmetic mean (standard deviation)	12.254 (\pm 12.0591)	17.208 (\pm 18.6472)	18.962 (\pm 29.4035)	

Statistical analyses

Statistical analysis title	Statistical Analysis - 400 vs Placebo
Comparison groups	400 mg v Placebo
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.737
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.575
upper limit	21.392
Variability estimate	Standard deviation

Statistical analysis title	Statistical Analysis - 600 vs Placebo
Comparison groups	600 mg v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.727
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.518
upper limit	31.362
Variability estimate	Standard deviation

Statistical analysis title	Statistical Analysis - Combined
Comparison groups	400 mg v 600 mg v Placebo

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.991
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.514
upper limit	22.834
Variability estimate	Standard deviation

Secondary: AUC of Mucus Weight

End point title	AUC of Mucus Weight
End point description:	
End point type	Secondary
End point timeframe:	
First dose of study drug included all data from the measurement captured following the initiation of study drug through the last measurement captured on Study Day 12 or prior to the last dose of study drug (as appropriate).	

End point values	400 mg	600 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	12	13	
Units: hours*grams				
arithmetic mean (standard deviation)	262.789 (± 263.4170)	390.751 (± 425.8803)	427.597 (± 660.8602)	

Statistical analyses

Statistical analysis title	Statistical Analysis - 400 vs Placebo
Comparison groups	400 mg v Placebo
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.657
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.565
upper limit	474.304

Variability estimate	Standard deviation
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Statistical analysis title	Statistical Analysis - 600 vs Placebo
Comparison groups	600 mg v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.769
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	166.865
upper limit	708.674
Variability estimate	Standard deviation

Statistical analysis title	Statistical Analysis - Combined
Comparison groups	400 mg v 600 mg v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.933
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	140.159
upper limit	510.98
Variability estimate	Standard deviation

Secondary: AUC of Subset Symptom Scores

End point title	AUC of Subset Symptom Scores
End point description:	
End point type	Secondary
End point timeframe:	
First Dose of Study Drug through Study Day 12	

End point values	400 mg	600 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	12	13	
Units: hours*score				
arithmetic mean (standard deviation)	152.03 (\pm 179.332)	277.56 (\pm 253.733)	212.28 (\pm 222.900)	

Statistical analyses

Statistical analysis title	Statistical Analysis - 400 vs Placebo
Comparison groups	400 mg v Placebo
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.407
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	29.33
upper limit	303.28

Statistical analysis title	Statistical Analysis - 600 vs Placebo
Comparison groups	600 mg v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.888
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	95.81
upper limit	384.83

Statistical analysis title	Statistical Analysis - Combined
Comparison groups	400 mg v 600 mg v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.696
Method	ANCOVA

Confidence interval	
level	95 %
sides	2-sided
lower limit	104.4
upper limit	302.23

Secondary: Time to Peak Subset Symptom Scores

End point title	Time to Peak Subset Symptom Scores
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End point description:

End point type	Secondary
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End point timeframe:

first dose of study drug was the maximum subset symptom score occurring after the initiation of study drug

End point values	400 mg	600 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	12	13	
Units: hours				
arithmetic mean (standard deviation)	83.20 (± 80.449)	73.46 (± 47.733)	126.22 (± 79.416)	

Statistical analyses

Statistical analysis title	Statistical Analysis - 400 vs Placebo
Comparison groups	400 mg v Placebo
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	42.15
upper limit	117.75

Statistical analysis title	Statistical Analysis - 600 vs Placebo
Comparison groups	600 mg v Placebo

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.237
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	42.05
upper limit	121.82

Statistical analysis title	Statistical Analysis - Combined
Comparison groups	400 mg v 600 mg v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.091
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	53.64
upper limit	108.24

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time of signed informed consent through Study Day 28 or the last study follow-up visit

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	400 mg
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Reporting group description: -

Reporting group title	600 mg
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Reporting group description: -

Reporting group title	Combined
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	400 mg	600 mg	Combined
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	1 / 40 (2.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Troponin I increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Troponin I increased			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	400 mg	600 mg	Combined
Total subjects affected by non-serious adverse events subjects affected / exposed	12 / 20 (60.00%)	12 / 20 (60.00%)	24 / 40 (60.00%)
General disorders and administration site conditions			
Catheter site erythema subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 20 (0.00%) 0	0 / 40 (0.00%) 0
Application site discolouration subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 20 (0.00%) 0	0 / 40 (0.00%) 0
Chest discomfort subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	1 / 40 (2.50%) 1
Reproductive system and breast disorders			
Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 20 (0.00%) 0	0 / 40 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Epistaxis subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3	7 / 20 (35.00%) 7	10 / 40 (25.00%) 10
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 20 (0.00%) 0	0 / 40 (0.00%) 0
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	1 / 40 (2.50%) 1
Investigations			

Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	1 / 40 (2.50%) 1
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	1 / 40 (2.50%) 1
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	1 / 40 (2.50%) 1
Blood bilirubin increased subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	1 / 40 (2.50%) 1
Electrocardiogram T wave inversion subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	1 / 40 (2.50%) 1
Troponin T increased subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	1 / 40 (2.50%) 1
Injury, poisoning and procedural complications Skin abrasion subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	1 / 40 (2.50%) 1
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	1 / 40 (2.50%) 1
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	1 / 20 (5.00%) 1	2 / 40 (5.00%) 2
Dizziness subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	2 / 20 (10.00%) 2	2 / 40 (5.00%) 2
Dysgeusia subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	1 / 40 (2.50%) 1

Sinus headache subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	1 / 40 (2.50%) 1
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3	1 / 20 (5.00%) 1	4 / 40 (10.00%) 4
Abdominal discomfort subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3	1 / 20 (5.00%) 1	4 / 40 (10.00%) 4
Food poisoning subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	1 / 40 (2.50%) 1
Lip ulceration subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 20 (0.00%) 0	0 / 40 (0.00%) 0
Mouth ulceration subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	1 / 40 (2.50%) 1
Oral mucosal erythema subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	1 / 40 (2.50%) 1
Skin and subcutaneous tissue disorders			
Dermatitis allergic subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	1 / 40 (2.50%) 1
Eczema subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 20 (0.00%) 0	0 / 40 (0.00%) 0
Ingrowing nail subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	1 / 40 (2.50%) 1
Pruritus subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	1 / 40 (2.50%) 1
Renal and urinary disorders			

Chromaturia subjects affected / exposed occurrences (all)	5 / 20 (25.00%) 5	6 / 20 (30.00%) 6	11 / 40 (27.50%) 11
Musculoskeletal and connective tissue disorders			
Pain in extremity subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	1 / 40 (2.50%) 1
Arthralgia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	1 / 40 (2.50%) 1
Back pain subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	1 / 40 (2.50%) 1
Infections and infestations			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	3 / 20 (15.00%) 3	4 / 40 (10.00%) 4
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	1 / 40 (2.50%) 1
Cellulitis subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	1 / 40 (2.50%) 1
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 20 (0.00%) 0	0 / 40 (0.00%) 0
Metabolism and nutrition disorders			
Hypernatraemia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	1 / 40 (2.50%) 1

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events subjects affected / exposed	12 / 20 (60.00%)		
General disorders and administration site conditions			

Catheter site erythema subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3		
Application site discolouration subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Chest discomfort subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3		
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 0		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Blood bilirubin increased			

<p>subjects affected / exposed occurrences (all)</p> <p>Electrocardiogram T wave inversion subjects affected / exposed occurrences (all)</p> <p>Troponin T increased subjects affected / exposed occurrences (all)</p>	<p>0 / 20 (0.00%) 0</p> <p>0 / 20 (0.00%) 0</p> <p>0 / 20 (0.00%) 0</p>		
<p>Injury, poisoning and procedural complications</p> <p>Skin abrasion subjects affected / exposed occurrences (all)</p>	<p>0 / 20 (0.00%) 0</p>		
<p>Cardiac disorders</p> <p>Palpitations subjects affected / exposed occurrences (all)</p>	<p>0 / 20 (0.00%) 0</p>		
<p>Nervous system disorders</p> <p>Headache subjects affected / exposed occurrences (all)</p> <p>Dizziness subjects affected / exposed occurrences (all)</p> <p>Dysgeusia subjects affected / exposed occurrences (all)</p> <p>Sinus headache subjects affected / exposed occurrences (all)</p>	<p>3 / 20 (15.00%) 3</p> <p>0 / 20 (0.00%) 0</p> <p>0 / 20 (0.00%) 0</p> <p>0 / 20 (0.00%) 0</p>		
<p>Gastrointestinal disorders</p> <p>Diarrhoea subjects affected / exposed occurrences (all)</p> <p>Abdominal discomfort subjects affected / exposed occurrences (all)</p>	<p>3 / 20 (15.00%) 3</p> <p>0 / 20 (0.00%) 0</p>		

Food poisoning subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Lip ulceration subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Mouth ulceration subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Oral mucosal erythema subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Skin and subcutaneous tissue disorders			
Dermatitis allergic subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 0		
Eczema subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Ingrowing nail subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Pruritus subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Renal and urinary disorders			
Chromaturia subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Musculoskeletal and connective tissue disorders			
Pain in extremity subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Arthralgia subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		

Back pain subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all) Cellulitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 0 / 20 (0.00%) 0 1 / 20 (5.00%) 1		
Metabolism and nutrition disorders Hypernatraemia subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2016	The amendment incorporated the data available to date from BTA585-001 and BTA585-002. Following the availability of this new data, the starting dose for Cohort 1 was determined and the dose for Cohort 2 identified. Urinalysis testing was removed at certain time points to reduce the risk of unblinding due to BTA585-related chromaturia
12 May 2016	Removed NPS Tolerance Test at the Screening visit; clarified the eligibility review process; clarified subject numbering; clarified pre-dose ECG time window; updated new Sponsor name (Aviragen Therapeutics Inc.); added additional cardiac enzymes at the Study Day 28 and follow-up visit to ensure adequate safety assessments took place
17 June 2016	The amendment included a notice of additional safety measures to be conducted in the study and to request agreement to lift the temporary halt of enrollment into Cohort 1. These safety measures included adding laboratory assessments (hematology, biochemistry, cardiac enzymes, coagulation parameters, and thyroid function) to additional visits and adding additional study stopping criteria based on Troponin I. The risk section was updated in regard to an SAE of increased Troponin I that occurred in Cohort 1. There were also administrative changes associated with the name change from Biota to Aviragen.
25 November 2016	The amendment notified the change in Principal Investigator from Dr. Samuel Israel to Dr. Andrea Guerra. Additional clarification was added to Study Stopping Criteria based on the MHRA substantial amendment approval letter, dated June 26, 2016.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
06 June 2016	Based on safety concerns, specifically from an SAE that occurred in a subject receiving BTA585 400 mg, the study was placed on temporary halt voluntarily by Aviragen with the agreement of the MHRA on June 6, 2016.	08 July 2016

Notes:

Limitations and caveats

None reported