



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 |
|-----------------------|------------|

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 | Subject, Investigator, Carer |

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 |
|------------------|-------------------|

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 |
|------------------|---------|

Arm description:

Placebo dose consists of applicable matching placebo capsules.

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|---------------|
| 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 qPCR 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 qPCR 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 qPCR 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 (\pm 241.32252) | -310.1802 (\pm 279.45651) | -259.2520 (\pm 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 (log10 copies) |
|-----------------|--|

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: log10 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 |
|----------------------------|---------------------------------------|

| | |
|---|------------------------|
| 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 |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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: log10 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 |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 (\pm 2.10030) | 3.5592 (\pm 1.88389) | 3.4792 (\pm 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 |
| End point description: | |
| End point type | Secondary |
| 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 | |
| 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 | |
| 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 |
|----------------------|--------------------|

| | |
|---|---------------------------------------|
| 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 |
|-----------------|------------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------|
| Reporting group title | 400 mg |
|-----------------------|--------|

Reporting group description: -

| | |
|-----------------------|--------|
| Reporting group title | 600 mg |
|-----------------------|--------|

Reporting group description: -

| | |
|-----------------------|----------|
| Reporting group title | Combined |
|-----------------------|----------|

Reporting group description: -

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

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 | 0 / 20 (0.00%) | 0 / 20 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Application site discolouration | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 20 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (0.00%) | 1 / 40 (2.50%) |
| occurrences (all) | 1 | 0 | 1 |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 20 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 3 / 20 (15.00%) | 7 / 20 (35.00%) | 10 / 40 (25.00%) |
| occurrences (all) | 3 | 7 | 10 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 20 (0.00%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 20 (5.00%) | 1 / 40 (2.50%) |
| occurrences (all) | 0 | 1 | 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) Oropharyngeal pain subjects affected / exposed occurrences (all) | 3 / 20 (15.00%) 3 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) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) Blood bilirubin increased | 3 / 20 (15.00%) 0 0 / 20 (0.00%) 0 0 / 20 (0.00%) 0 | | |

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

| | | | |
|--|---------------------|--|--|
| 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) | 1 / 20 (5.00%) 1 | | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | | |
| Cellulitis subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 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