



## Clinical trial results:

**OPuS-2 A multicentre, randomised, double blind, placebo controlled, parallel group study to evaluate the efficacy and safety of two dose levels of BCX4161 for 12 weeks as an oral prophylaxis treatment for attacks of hereditary angioedema.**

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2014-002655-26    |
| Trial protocol           | GB DE HU BE FR IT |
| Global end of trial date | 08 January 2016   |

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 24 March 2021 |
| First version publication date | 24 March 2021 |

### Trial information

#### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | BCX4161-301 |
|-----------------------|-------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02303626 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | BioCryst Pharmaceuticals, Inc   |
| Sponsor organisation address | 4505 Emperor Blvd, Suite 200, Durham, United States, 27703                                  |
| Public contact               | Study Director, BioCryst Pharmaceuticals Inc, 001 919-859-1302, clinicaltrials@biocryst.com |
| Scientific contact           | Study Director, BioCryst Pharmaceuticals Inc, 001 919-859-1302, clinicaltrials@biocryst.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                       | 27 October 2016 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 08 January 2016 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 08 January 2016 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To determine the efficacy of prophylactic Avoralstat (BCX4161) 300 mg and 500 mg administered three times daily for 12 weeks compared to placebo

Protection of trial subjects:

This trial was conducted in compliance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines for conducting, recording, and reporting trials, and in accordance with the Declaration of Helsinki. The informed consent form (ICF), protocol and amendments for this trial were submitted to and approved by an appropriate Independent Ethics Committee (IEC). Routine monitoring was performed to verify that rights and well-being of subjects were protected. Emergency equipment and medications were available within the clinical unit as per current standard procedures. Any medication considered necessary for the subject's safety and well-being was given at the discretion of the Investigator. A signed informed consent form (ICF) was obtained from each subject prior to performing any study-related procedures. The informed consent process took place under conditions where the subject had adequate time to consider the risks and benefits associated with his/her participation in the study. The Investigator explained to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the trial and any discomfort it may entail.

Background therapy:

Subjects used their prescribed standard of care medication to treat any breakthrough HAE attacks on study

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 01 December 2014 |
| 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: 14 |
| Country: Number of subjects enrolled | Belgium: 2         |
| Country: Number of subjects enrolled | France: 6          |
| Country: Number of subjects enrolled | Germany: 17        |
| Country: Number of subjects enrolled | Hungary: 6         |
| Country: Number of subjects enrolled | Italy: 5           |
| Country: Number of subjects enrolled | Canada: 6          |
| Country: Number of subjects enrolled | United States: 54  |
| Worldwide total number of subjects   | 110                |
| EEA total number of subjects         | 50                 |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 103 |
| From 65 to 84 years                       | 7   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

A total of 110 subjects were randomized/enrolled into 1 of 3 parts.

### Pre-assignment

Screening details:

A total of 137 subjects were screened for the study and 110 subjects were randomized and dosed. 27 subjects were screening failures due to one of the following reasons: did not meet inclusion criteria (15), Investigator discretion (1), met exclusion criteria (5), subject consent withdrawn (4), and/or lost to follow-up (2).

### Period 1

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

Blinding implementation details:

This was a double-blind study; as such, the treatment assignment in each part was blinded to the PI, study subjects, staff involved in the clinical evaluation of the subjects and the analysis of data, and the Biometrics team.

The PI or designee(s) confirmed subject eligibility.

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Avoralstat 500mg |
|------------------|------------------|

Arm description:

5x 100 mg Avoralstat capsules TID

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Avoralstat    |
| Investigational medicinal product code |               |
| Other name                             | BCX4161       |
| Pharmaceutical forms                   | Capsule, soft |
| Routes of administration               | Oral use      |

Dosage and administration details:

5 × 100-mg avoralstat capsules for oral administration 3 times per day (total daily dose of 1500 mg) for 12 weeks

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Avoralstat 300mg |
|------------------|------------------|

Arm description:

3x 100 mg Avoralstat capsules + 2 matched placebo capsules TID

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Avoralstat    |
| Investigational medicinal product code |               |
| Other name                             | BCX4161       |
| Pharmaceutical forms                   | Capsule, soft |
| Routes of administration               | Oral use      |

Dosage and administration details:

3 × 100-mg avoralstat capsules for oral administration 3 times per day (total daily dose of 900 mg) for 12 weeks. At each dose, subjects received 2 placebo capsules together with avoralstat capsules to maintain dose blind.

|  |               |
|--|---------------|
| Investigational medicinal product name | Placebo       |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, soft |
| Routes of administration               | Oral use      |

Dosage and administration details:

The matching placebo contained the excipients polyethylene glycol 600, polyethylene glycol 400, alpha tocopherol and Vitamin E-TPGS. Subjects received 2 placebo capsules QID for 12 weeks together with avoralstat capsules to maintain dose blind.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

5x Placebo capsules TID

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

Dosage and administration details:

The matching placebo contained the excipients polyethylene glycol 600, polyethylene glycol 400, alpha tocopherol and Vitamin E-TPGS. Subjects received 5 capsules, 3 times a day for 12 weeks.

| <b>Number of subjects in period 1</b> | Avoralstat 500mg | Avoralstat 300mg | Placebo |
|---------------------------------------|------------------|------------------|---------|
| Started                               | 38               | 36               | 36      |
| Completed                             | 35               | 35               | 33      |
| Not completed                         | 3                | 1                | 3       |
| Consent withdrawn by subject          | -                | -                | 1       |
| Adverse event, non-fatal              | 2                | -                | -       |
| Pregnancy                             | -                | -                | 1       |
| Protocol deviation                    | 1                | -                | -       |
| Lack of efficacy                      | -                | 1                | 1       |

## Baseline characteristics

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Treatment period |
|-----------------------|------------------|

Reporting group description: -

| Reporting group values                    | Treatment period | Total |  |
|---|------------------|-------|--|
| Number of subjects                        | 110              | 110   |  |
| Age categorical                           |                  |       |  |
| Units: Subjects                           |                  |       |  |
| Adults (18-64 years)                      | 103              | 103   |  |
| From 65-84 years                          | 7                | 7     |  |
| Age continuous                            |                  |       |  |
| Units: years                              |                  |       |  |
| arithmetic mean                           | 41.2             |       |  |
| standard deviation                        | ± 13.3           | -     |  |
| Gender categorical                        |                  |       |  |
| Units: Subjects                           |                  |       |  |
| Female                                    | 85               | 85    |  |
| Male                                      | 25               | 25    |  |
| Race                                      |                  |       |  |
| Units: Subjects                           |                  |       |  |
| American Indian or Alaska Native          | 1                | 1     |  |
| Asian                                     | 2                | 2     |  |
| Black or African American                 | 0                | 0     |  |
| White                                     | 102              | 102   |  |
| Other                                     | 3                | 3     |  |
| Native Hawaiian or Other Pacific Islander | 2                | 2     |  |
| HAE attack rate                           |                  |       |  |
| Units: Subjects                           |                  |       |  |
| ≥ 1 attack/week                           | 65               | 65    |  |
| < 1 attack/week                           | 45               | 45    |  |

## End points

### End points reporting groups

|  |                  |
|--|------------------|
| Reporting group title  | Avoralstat 500mg |
| Reporting group description:                                   |                  |
| 5x 100 mg Avoralstat capsules TID                              |                  |
| Reporting group title  | Avoralstat 300mg |
| Reporting group description:                                   |                  |
| 3x 100 mg Avoralstat capsules + 2 matched placebo capsules TID |                  |
| Reporting group title  | Placebo          |
| Reporting group description:                                   |                  |
| 5x Placebo capsules TID  |                  |

### Primary: Weekly Rate of Confirmed HAE Attacks

|  |                                      |
|--|--------------------------------------|
| End point title  | Weekly Rate of Confirmed HAE Attacks |
| End point description:   |                                      |
| Subjects completed an electronic study diary (e-diary) to record details of all HAE attacks that occurred. Each e-diary recorded HAE attack was reviewed in real-time by the investigator and subjects contacted as needed to discuss any queries or for additional attack details. This information, in conjunction with the e-Diary record, was used by the Investigator to verify or reject the record as an HAE attack. Subject-reported attacks were further adjudicated by the independent Clinical Endpoint Adjudication Panel (CEAP); the CEAP members individually rated each attack as confirmed (C), confirmed with modification (CM) or rejected (R). Attacks confirmed by the adjudication committee were then included in efficacy analyses. |                                      |
| End point type   | Primary                              |
| End point timeframe:   |                                      |
| 12 weeks   |                                      |

| End point values                    | Avoralstat 500mg     | Avoralstat 300mg     | Placebo              |  |
|-------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type                  | Reporting group      | Reporting group      | Reporting group      |  |
| Number of subjects analysed         | 38                   | 36                   | 36                   |  |
| Units: HAE attacks/week             |                      |                      |                      |  |
| least squares mean (standard error) | 0.589 ( $\pm$ 0.086) | 0.675 ( $\pm$ 0.089) | 0.593 ( $\pm$ 0.088) |  |

### Statistical analyses

|                            |                                     |
|----------------------------|-------------------------------------|
| Statistical analysis title | HAE attack rate - 500 mg Avoralstat |
| Comparison groups          | Avoralstat 500mg v Placebo          |

|   |                              |
|---|------------------------------|
| Number of subjects included in analysis | 74                           |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | equivalence                  |
| P-value                                 | = 0.975 <sup>[1]</sup>       |
| Method                                  | ANCOVA                       |
| Parameter estimate                      | Difference Least Mean Square |
| Point estimate                          | -0.004                       |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | -0.248                       |
| upper limit                             | 0.24                         |

Notes:

[1] - ANCOVA Model includes terms of treatment and the randomization strata

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>       | HAE attack rate - 300 mg Avoralstat |
| Comparison groups                       | Placebo v Avoralstat 300mg          |
| Number of subjects included in analysis | 72                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | equivalence                         |
| P-value                                 | = 0.512 <sup>[2]</sup>              |
| Method                                  | ANCOVA                              |
| Parameter estimate                      | Difference Least Mean Square        |
| Point estimate                          | 0.082                               |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | -0.165                              |
| upper limit                             | 0.329                               |

Notes:

[2] - ANCOVA Model includes terms of treatment and the randomization strata

### Secondary: Number of Attack-Free Days

|                        |                            |
|------------------------|----------------------------|
| End point title        | Number of Attack-Free Days |
| End point description: |                            |
| End point type         | Secondary                  |
| End point timeframe:   |                            |
| 12 weeks               |                            |

| End point values                    | Avoralstat<br>500mg | Avoralstat<br>300mg | Placebo             |  |
|-------------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type                  | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed         | 38                  | 36                  | 36                  |  |
| Units: Attack-Free Days             |                     |                     |                     |  |
| least squares mean (standard error) | 67.174 (±<br>2.646) | 64.100 (±<br>2.720) | 64.217 (±<br>2.703) |  |



## Statistical analyses

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>       | Attack-Free Days - 500 mg Avoralstat |
| Comparison groups                       | Avoralstat 500mg v Placebo           |
| Number of subjects included in analysis | 74                                   |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | equivalence                          |
| P-value                                 | = 0.434 <sup>[3]</sup>               |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | Difference Least Mean Square         |
| Point estimate                          | 2.957                                |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -4.153                               |
| upper limit                             | 10.427                               |

Notes:

[3] - ANCOVA Model includes terms of treatment and the randomization strata

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>       | Attack-Free Days - 300 mg Avoralstat |
| Comparison groups                       | Avoralstat 300mg v Placebo           |
| Number of subjects included in analysis | 72                                   |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | equivalence                          |
| P-value                                 | = 0.976 <sup>[4]</sup>               |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | Difference Least Mean Square         |
| Point estimate                          | -0.117                               |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -7.688                               |
| upper limit                             | 7.455                                |

Notes:

[4] - ANCOVA Model includes terms of treatment and the randomization strata

## Secondary: HAE Disease Activity

|                 |                      |
|-----------------|----------------------|
| End point title | HAE Disease Activity |
|-----------------|----------------------|

End point description:

Disease activity was assessed using an Angioedema Activity Score (AAS) calculated from data entered in the eDiaries by the subject over 84 days. The AAS score was defined as the sum of the individual scores for 4 AAS domains (daily activities, appearance, physical discomfort, and overall severity) for all subject-reported attacks reported during the treatment period. Individual domain scores were based on answers to questions each of which had 4 possible responses scored 0-3 (0 - no impact; 1-3 - increasing levels of impact). The total AAS score per attack could range from 0 to 12; lower scores & higher scores represent lower & higher disease activities, respectively. However, the overall total AAS score reported

for this study included the total scores for all subject-reported attacks, therefore the upper limit of the range was subject-specific. The statistical analysis of the total modified AAS scores for the treatment period is presented below.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 84 days              |           |

| End point values                    | Avoralstat 500mg       | Avoralstat 300mg        | Placebo                |  |
|-------------------------------------|------------------------|-------------------------|------------------------|--|
| Subject group type                  | Reporting group        | Reporting group         | Reporting group        |  |
| Number of subjects analysed         | 38                     | 36                      | 36                     |  |
| Units: AAS Score                    |                        |                         |                        |  |
| least squares mean (standard error) | 83.938 ( $\pm$ 14.131) | 109.081 ( $\pm$ 14.524) | 94.841 ( $\pm$ 14.434) |  |

## Statistical analyses

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>       | Disease Activity - 500 mg Avoralstat |
| Comparison groups                       | Avoralstat 500mg v Placebo           |
| Number of subjects included in analysis | 74                                   |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | equivalence                          |
| P-value                                 | = 0.589 <sup>[5]</sup>               |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | Difference Least Mean Square         |
| Point estimate                          | -10.903                              |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -50.789                              |
| upper limit                             | 28.983                               |

Notes:

[5] - ANCOVA Model includes terms of treatment and the randomization strata

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>       | Disease Activity - 300 mg Avoralstat |
| Comparison groups                       | Avoralstat 300mg v Placebo           |
| Number of subjects included in analysis | 72                                   |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | equivalence                          |
| P-value                                 | = 0.487 <sup>[6]</sup>               |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | Difference Least Mean Square         |
| Point estimate                          | 14.24                                |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -26.189 |
| upper limit         | 54.669  |

Notes:

[6] - ANCOVA Model includes terms of treatment and the randomization strata

## Secondary: Angioedema Quality of Life (AE-QoL)

|                 |                                     |
|-----------------|-------------------------------------|
| End point title | Angioedema Quality of Life (AE-QoL) |
|-----------------|-------------------------------------|

End point description:

Quality of Life (QoL) specific to hereditary angioedema (HAE) was assessed via AE-QoL, which consists of 17 questions that spanned 4 domains (functioning, fatigue/mood, fear/shame, and nutrition). Each AE-QoL question had 5 answer options (scored 1-5), with lower and higher scores indicting less and more adverse impact, respectively. Per-subject scores for each domain were computed using the appropriate scoring algorithm applied to the question response scores for each domain. Per-subject total scores (including all 4 domains) were similarly computed using the question response scores for all 17 questions. The outputs from the scoring algorithm were normalized on a scale ranging from 0 (less adverse impact) to 100 (most adverse impact). The statistical analysis of the AE-QoL total score change from baseline to Week 12 is presented below.

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

End point timeframe:

Angioedema Quality of Life questionnaire (AE QoL) was completed during clinic visits, prior to dosing on Day 1, and on Days 29, 57 & 85 (Weeks 4, 8 & 12) during the treatment period.

| End point values                    | Avoralstat 500mg     | Avoralstat 300mg    | Placebo              |  |
|-------------------------------------|----------------------|---------------------|----------------------|--|
| Subject group type                  | Reporting group      | Reporting group     | Reporting group      |  |
| Number of subjects analysed         | 38                   | 36                  | 36                   |  |
| Units: AE-QoL Score                 |                      |                     |                      |  |
| least squares mean (standard error) | -17.45 ( $\pm$ 2.66) | -9.89 ( $\pm$ 3.11) | -12.14 ( $\pm$ 2.64) |  |

## Statistical analyses

|   |                                   |
|---|-----------------------------------|
| Statistical analysis title              | AE-QoL - 500 mg Avoralstat        |
| Comparison groups                       | Avoralstat 500mg v Placebo        |
| Number of subjects included in analysis | 74                                |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | equivalence                       |
| P-value                                 | = 0.162 <sup>[7]</sup>            |
| Method                                  | Mixed Model for Repeated Measures |
| Parameter estimate                      | Difference Least Mean Square      |
| Point estimate                          | -5.31                             |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -12.8                             |
| upper limit                             | 2.2                               |

Notes:

[7] - Mixed model for repeated measures includes terms for baseline value, visit, treatment and visit by treatment interaction.

|   |                                   |
|---|-----------------------------------|
| <b>Statistical analysis title</b>       | AE-QoL - 300 mg Avoralstat        |
| Comparison groups                       | Avoralstat 300mg v Placebo        |
| Number of subjects included in analysis | 72                                |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | equivalence                       |
| P-value                                 | = 0.585 <sup>[8]</sup>            |
| Method                                  | Mixed Model for Repeated Measures |
| Parameter estimate                      | Difference Least Mean Square      |
| Point estimate                          | 2.25                              |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -5.9                              |
| upper limit                             | 10.4                              |

Notes:

[8] - Mixed model for repeated measures includes terms for baseline value, visit, treatment and visit by treatment interaction.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) reported from informed consent signature until the follow-up visit (week 14) or until the AE is resolved or the subject is in a clinically stable condition with regards to the AE.

Adverse event reporting additional description:

Symptoms of HAE were not considered an AE unless they qualify as an SAE.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Avoralstat 500mg |
|-----------------------|------------------|

Reporting group description:

5x 100 mg Avoralstat capsules TID

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Avoralstat 300mg |
|-----------------------|------------------|

Reporting group description:

3x 100 mg Avoralstat capsules + 2 matched placebo capsules TID

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

Reporting group description:

5x Placebo capsules TID

| Serious adverse events                            | Avoralstat 500mg | Avoralstat 300mg | Placebo        |
|---|------------------|------------------|----------------|
| Total subjects affected by serious adverse events |                  |                  |                |
| subjects affected / exposed                       | 3 / 38 (7.89%)   | 2 / 36 (5.56%)   | 3 / 36 (8.33%) |
| number of deaths (all causes)                     | 0                | 0                | 0              |
| number of deaths resulting from adverse events    | 0                | 0                | 0              |
| Congenital, familial and genetic disorders        |                  |                  |                |
| HAE   |                  |                  |                |
| subjects affected / exposed                       | 1 / 38 (2.63%)   | 2 / 36 (5.56%)   | 1 / 36 (2.78%) |
| occurrences causally related to treatment / all   | 0 / 1            | 0 / 2            | 0 / 1          |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0            | 0 / 0          |
| Surgical and medical procedures                   |                  |                  |                |
| abortion, induced                                 |                  |                  |                |
| subjects affected / exposed                       | 0 / 38 (0.00%)   | 0 / 36 (0.00%)   | 1 / 36 (2.78%) |
| occurrences causally related to treatment / all   | 0 / 0            | 0 / 0            | 0 / 1          |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0            | 0 / 0          |
| Nervous system disorders                          |                  |                  |                |
| Migraine  |                  |                  |                |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 38 (0.00%) | 1 / 36 (2.78%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| chest discomfort                                     |                |                |                |
| subjects affected / exposed                          | 1 / 38 (2.63%) | 0 / 36 (0.00%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Chest pain   |                |                |                |
| subjects affected / exposed                          | 1 / 38 (2.63%) | 0 / 36 (0.00%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders      |                |                |                |
| Back pain  |                |                |                |
| subjects affected / exposed                          | 0 / 38 (0.00%) | 0 / 36 (0.00%) | 1 / 36 (2.78%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |

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

| <b>Non-serious adverse events</b>                     | Avoralstat 500mg | Avoralstat 300mg | Placebo          |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events |                  |                  |                  |
| subjects affected / exposed                           | 35 / 38 (92.11%) | 31 / 36 (86.11%) | 32 / 36 (88.89%) |
| Investigations  |                  |                  |                  |
| Blood alkaline phosphatase increased                  |                  |                  |                  |
| subjects affected / exposed                           | 0 / 38 (0.00%)   | 3 / 36 (8.33%)   | 0 / 36 (0.00%)   |
| occurrences (all)                                     | 0                | 3                | 0                |
| Blood urine present                                   |                  |                  |                  |
| subjects affected / exposed                           | 0 / 38 (0.00%)   | 3 / 36 (8.33%)   | 0 / 36 (0.00%)   |
| occurrences (all)                                     | 0                | 3                | 0                |
| Gamma-glutamyltransferase increased                   |                  |                  |                  |
| subjects affected / exposed                           | 0 / 38 (0.00%)   | 3 / 36 (8.33%)   | 0 / 36 (0.00%)   |
| occurrences (all)                                     | 0                | 3                | 0                |
| Injury, poisoning and procedural complications        |                  |                  |                  |

|  |                        |                      |                      |
|--|------------------------|----------------------|----------------------|
| Contusion<br>subjects affected / exposed<br>occurrences (all)            | 2 / 38 (5.26%)<br>2    | 0 / 36 (0.00%)<br>0  | 0 / 36 (0.00%)<br>0  |
| Nervous system disorders   |                        |                      |                      |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)            | 0 / 38 (0.00%)<br>0    | 2 / 36 (5.56%)<br>2  | 0 / 36 (0.00%)<br>0  |
| Headache<br>subjects affected / exposed<br>occurrences (all)             | 7 / 38 (18.42%)<br>7   | 4 / 36 (11.11%)<br>4 | 6 / 36 (16.67%)<br>6 |
| Somnolence<br>subjects affected / exposed<br>occurrences (all)           | 1 / 38 (2.63%)<br>1    | 0 / 36 (0.00%)<br>0  | 2 / 36 (5.56%)<br>2  |
| Gastrointestinal disorders   |                        |                      |                      |
| Abdominal distension<br>subjects affected / exposed<br>occurrences (all) | 2 / 38 (5.26%)<br>2    | 3 / 36 (8.33%)<br>3  | 2 / 36 (5.56%)<br>2  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 4 / 38 (10.53%)<br>4   | 0 / 36 (0.00%)<br>0  | 2 / 36 (5.56%)<br>2  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | 0 / 38 (0.00%)<br>0    | 3 / 36 (8.33%)<br>3  | 0 / 36 (0.00%)<br>0  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)            | 2 / 38 (5.26%)<br>2    | 0 / 36 (0.00%)<br>0  | 1 / 36 (2.78%)<br>1  |
| Faeces soft<br>subjects affected / exposed<br>occurrences (all)          | 1 / 38 (2.63%)<br>1    | 1 / 36 (2.78%)<br>1  | 3 / 36 (8.33%)<br>3  |
| Flatulence<br>subjects affected / exposed<br>occurrences (all)           | 10 / 38 (26.32%)<br>10 | 5 / 36 (13.89%)<br>5 | 9 / 36 (25.00%)<br>9 |
| Nausea<br>subjects affected / exposed<br>occurrences (all)               | 3 / 38 (7.89%)<br>3    | 4 / 36 (11.11%)<br>4 | 3 / 36 (8.33%)<br>3  |
| Diarrhoea  |                        |                      |                      |

|   |                  |                 |                  |
|---|------------------|-----------------|------------------|
| subjects affected / exposed                     | 16 / 38 (42.11%) | 8 / 36 (22.22%) | 12 / 36 (33.33%) |
| occurrences (all)                               | 16               | 8               | 12               |
| Frequent bowel movements                        |                  |                 |                  |
| subjects affected / exposed                     | 0 / 38 (0.00%)   | 2 / 36 (5.56%)  | 0 / 36 (0.00%)   |
| occurrences (all)                               | 0                | 2               | 0                |
| Constipation                                    |                  |                 |                  |
| subjects affected / exposed                     | 1 / 38 (2.63%)   | 0 / 36 (0.00%)  | 3 / 36 (8.33%)   |
| occurrences (all)                               | 1                | 0               | 3                |
| Gastrooesophageal reflux disease                |                  |                 |                  |
| subjects affected / exposed                     | 0 / 38 (0.00%)   | 1 / 36 (2.78%)  | 2 / 36 (5.56%)   |
| occurrences (all)                               | 0                | 1               | 2                |
| Reproductive system and breast disorders        |                  |                 |                  |
| Ovarian cyst                                    |                  |                 |                  |
| subjects affected / exposed                     | 1 / 38 (2.63%)   | 0 / 36 (0.00%)  | 2 / 36 (5.56%)   |
| occurrences (all)                               | 1                | 0               | 2                |
| Respiratory, thoracic and mediastinal disorders |                  |                 |                  |
| Oropharyngeal pain                              |                  |                 |                  |
| subjects affected / exposed                     | 0 / 38 (0.00%)   | 2 / 36 (5.56%)  | 0 / 36 (0.00%)   |
| occurrences (all)                               | 0                | 2               | 0                |
| Skin and subcutaneous tissue disorders          |                  |                 |                  |
| Acne  |                  |                 |                  |
| subjects affected / exposed                     | 2 / 38 (5.26%)   | 0 / 36 (0.00%)  | 1 / 36 (2.78%)   |
| occurrences (all)                               | 2                | 0               | 1                |
| Musculoskeletal and connective tissue disorders |                  |                 |                  |
| Arthralgia                                      |                  |                 |                  |
| subjects affected / exposed                     | 0 / 38 (0.00%)   | 2 / 36 (5.56%)  | 1 / 36 (2.78%)   |
| occurrences (all)                               | 0                | 2               | 1                |
| Back pain                                       |                  |                 |                  |
| subjects affected / exposed                     | 1 / 38 (2.63%)   | 1 / 36 (2.78%)  | 2 / 36 (5.56%)   |
| occurrences (all)                               | 1                | 1               | 2                |
| Myalgia   |                  |                 |                  |
| subjects affected / exposed                     | 1 / 38 (2.63%)   | 2 / 36 (5.56%)  | 0 / 36 (0.00%)   |
| occurrences (all)                               | 1                | 2               | 0                |
| Infections and infestations                     |                  |                 |                  |



|                                   |                 |                 |                 |
|-----------------------------------|-----------------|-----------------|-----------------|
| Cystitis                          |                 |                 |                 |
| subjects affected / exposed       | 2 / 38 (5.26%)  | 1 / 36 (2.78%)  | 0 / 36 (0.00%)  |
| occurrences (all)                 | 2               | 1               | 0               |
| Gastroenteritis                   |                 |                 |                 |
| subjects affected / exposed       | 1 / 38 (2.63%)  | 1 / 36 (2.78%)  | 2 / 36 (5.56%)  |
| occurrences (all)                 | 1               | 1               | 2               |
| Influenza                         |                 |                 |                 |
| subjects affected / exposed       | 2 / 38 (5.26%)  | 0 / 36 (0.00%)  | 0 / 36 (0.00%)  |
| occurrences (all)                 | 2               | 0               | 0               |
| Nasopharyngitis                   |                 |                 |                 |
| subjects affected / exposed       | 8 / 38 (21.05%) | 5 / 36 (13.89%) | 7 / 36 (19.44%) |
| occurrences (all)                 | 8               | 5               | 7               |
| Oral herpes                       |                 |                 |                 |
| subjects affected / exposed       | 0 / 38 (0.00%)  | 1 / 36 (2.78%)  | 2 / 36 (5.56%)  |
| occurrences (all)                 | 0               | 1               | 2               |
| Sinusitis                         |                 |                 |                 |
| subjects affected / exposed       | 1 / 38 (2.63%)  | 1 / 36 (2.78%)  | 3 / 36 (8.33%)  |
| occurrences (all)                 | 1               | 1               | 3               |
| Tonsillitis                       |                 |                 |                 |
| subjects affected / exposed       | 2 / 38 (5.26%)  | 0 / 36 (0.00%)  | 0 / 36 (0.00%)  |
| occurrences (all)                 | 2               | 0               | 0               |
| Upper respiratory tract infection |                 |                 |                 |
| subjects affected / exposed       | 2 / 38 (5.26%)  | 1 / 36 (2.78%)  | 1 / 36 (2.78%)  |
| occurrences (all)                 | 2               | 1               | 1               |
| Viral infection                   |                 |                 |                 |
| subjects affected / exposed       | 2 / 38 (5.26%)  | 1 / 36 (2.78%)  | 0 / 36 (0.00%)  |
| occurrences (all)                 | 2               | 1               | 0               |
| Vulvovaginal candidiasis          |                 |                 |                 |
| subjects affected / exposed       | 2 / 38 (5.26%)  | 0 / 36 (0.00%)  | 0 / 36 (0.00%)  |
| occurrences (all)                 | 2               | 0               | 0               |
| Pharyngitis                       |                 |                 |                 |
| subjects affected / exposed       | 0 / 38 (0.00%)  | 1 / 36 (2.78%)  | 2 / 36 (5.56%)  |
| occurrences (all)                 | 0               | 1               | 2               |
| Urinary tract infection           |                 |                 |                 |
| subjects affected / exposed       | 2 / 38 (5.26%)  | 2 / 36 (5.56%)  | 1 / 36 (2.78%)  |
| occurrences (all)                 | 2               | 2               | 1               |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| Tooth infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 38 (0.00%)<br>0 | 1 / 36 (2.78%)<br>1 | 2 / 36 (5.56%)<br>2 |
|---|---------------------|---------------------|---------------------|

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 23 December 2014 | <p>UK-Specific Amendment:</p> <ul style="list-style-type: none"><li>- Inclusion criterion 4a was modified to indicate that 2 highly effective contraceptive methods must be used by females of childbearing potential. Two or more of the following methods were identified as acceptable and had to include at least one barrier method: surgical sterilization (i.e. bilateral tubal ligation); placement of an intrauterine device or intrauterine system; hormonal contraception (implantable, patch, oral, vaginal ring); or barrier methods (either their partner's use of a condom or the subject's use of an occlusive cap [diaphragm, or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository). Estrogen- and progestin-containing hormonal contraception was only permitted if it had been initiated within 60 days prior to screening or expected to be initiated at any time through the end of the study (follow-up); IUDs with progestin were permitted to be placed at any time prior to or during screening.</li><li>- Inclusion criteria 4c (females) and 5a (males) was modified to include a clear definition of abstinence as true abstinence when in line with the preferred and usual lifestyle of the subject.</li><li>- Inclusion criterion 5a was modified to indicate that male participants were required to utilize a highly effective contraceptive method with female partners of childbearing potential (defined as postmenopausal <math>\leq 2</math> years or a non-menopausal female who had not had a hysterectomy, bilateral oophorectomy, or documented ovarian failure). The term "highly effective contraceptive method" was defined as having had a vasectomy, or utilizing 2 forms of contraception, 1 of which must have been a condom, during intercourse, for the study duration and for 90 days after the last dose of the study drug.</li></ul> |
| 15 April 2015    | Canada-specific Amendment: Canada was added to the list of countries in which study centers were located.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported