



## Clinical trial results:

### A Phase 3 Multi-center, Open-label Study to Evaluate the Efficacy and Safety of Lanadelumab (SHP643) in Japanese Subjects with Hereditary Angioedema

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2022-002621-98 |
| Trial protocol           | Outside EU/EEA |
| Global end of trial date | 26 August 2021 |

#### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v1 (current)      |
| This version publication date  | 07 September 2022 |
| First version publication date | 07 September 2022 |

#### Trial information

##### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | SHP643-302 |
|-----------------------|------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04180163 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### Sponsors

|                              |                                                       |
|------------------------------|-------------------------------------------------------|
| Sponsor organisation name    | Shire                                                 |
| Sponsor organisation address | 300 Shire Way, Lexington, United States, MA 02421     |
| Public contact               | Study Director, Shire, ClinicalTransparency@shire.com |
| Scientific contact           | Study Director, Shire, ClinicalTransparency@shire.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? | Yes |

Notes:

## Results analysis stage

|                                                      |                |
|------------------------------------------------------|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 26 August 2021 |
| Is this the analysis of the primary completion data? | No             |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 26 August 2021 |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the safety and efficacy of lanadelumab in Japanese participants with HAE Type I or II.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 12 December 2019 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |           |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Japan: 12 |
| Worldwide total number of subjects   | 12        |
| EEA total number of subjects         | 0         |

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)                 | 1  |
| Adults (18-64 years)                      | 11 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 12 participants took part in the study at 10 investigative sites in Japan from 12 December 2019 to 26 August 2021. Participants who rolled over to TAK-743-5007 (NCT04687137) had a 2-week follow-up while others had 4 weeks of follow-up.

### Pre-assignment

Screening details:

Subjects were observed in 4-week Baseline Run-in that could be extended upto 8 weeks. Subjects experiencing  $\geq 1.0$  angioedema attacks per 4 weeks during Run-in Period, who remained eligible per inclusion criteria entered 52-week lanadelumab Treatment Period (TP) [TP:A + TP:B], followed by upto 4-week Safety Follow-up. Lanadelumab was given only during TPs.

### Period 1

|                              |                                    |
|------------------------------|------------------------------------|
| Period 1 title               | Run-in Period (4 or up to 8 Weeks) |
| Is this the baseline period? | Yes                                |
| Allocation method            | Not applicable                     |
| Blinding used                | Not blinded                        |

### Arms

|           |                               |
|-----------|-------------------------------|
| Arm title | Lanadelumab 300 mg q2w or q4w |
|-----------|-------------------------------|

Arm description:

Lanadelumab 300 mg solution, subcutaneously (SC), once every 2 weeks (q2w) for 26 weeks in Treatment Period A. This was followed by Treatment Period B (additional 26 weeks, total of 52 weeks including Treatment Period A) during which participants remained on Treatment Period A regimen or received 300 mg lanadelumab solution once every 4 weeks (q4w) for 26 weeks if well-controlled (attack-free) for 26 consecutive weeks with lanadelumab treatment. The dose frequency change was based on the Investigator's discretion and approval by the Sponsor's Medical Monitor.

|                                        |                          |
|----------------------------------------|--------------------------|
| Arm type                               | Experimental             |
| Investigational medicinal product name | Lanadelumab              |
| Investigational medicinal product code |                          |
| Other name                             | DX-2930, TAK-743, SHP643 |
| Pharmaceutical forms                   | Solution for injection   |
| Routes of administration               | Subcutaneous use         |

Dosage and administration details:

Lanadelumab solution, SC

|                                       |                               |
|---------------------------------------|-------------------------------|
| <b>Number of subjects in period 1</b> | Lanadelumab 300 mg q2w or q4w |
| Started                               | 12                            |
| Completed                             | 12                            |

**Period 2**

|                              |                                    |
|------------------------------|------------------------------------|
| Period 2 title               | Treatment Period A (Weeks 1 to 26) |
| Is this the baseline period? | No                                 |
| Allocation method            | Not applicable                     |
| Blinding used                | Not blinded                        |

**Arms**

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | Lanadelumab 300 mg q2w or q4w |
|------------------|-------------------------------|

## Arm description:

Lanadelumab 300 mg solution, subcutaneously (SC), once every 2 weeks (q2w) for 26 weeks in Treatment Period A. This was followed by Treatment Period B (additional 26 weeks, total of 52 weeks including Treatment Period A) during which participants remained on Treatment Period A regimen or received 300 mg lanadelumab solution once every 4 weeks (q4w) for 26 weeks if well-controlled (attack-free) for 26 consecutive weeks with lanadelumab treatment. The dose frequency change was based on the Investigator's discretion and approval by the Sponsor's Medical Monitor.

|                                        |                          |
|----------------------------------------|--------------------------|
| Arm type                               | Experimental             |
| Investigational medicinal product name | Lanadelumab              |
| Investigational medicinal product code |                          |
| Other name                             | DX-2930, TAK-743, SHP643 |
| Pharmaceutical forms                   | Solution for injection   |
| Routes of administration               | Subcutaneous use         |

## Dosage and administration details:

Lanadelumab solution, SC

|                                       |                               |
|---------------------------------------|-------------------------------|
| <b>Number of subjects in period 2</b> | Lanadelumab 300 mg q2w or q4w |
| Started                               | 12                            |
| Completed                             | 12                            |

**Period 3**

|                              |                                     |
|------------------------------|-------------------------------------|
| Period 3 title               | Treatment Period B (Weeks 27 to 52) |
| Is this the baseline period? | No                                  |
| Allocation method            | Not applicable                      |
| Blinding used                | Not blinded                         |

**Arms**

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | Lanadelumab 300 mg q2w or q4w |
|------------------|-------------------------------|

## Arm description:

Lanadelumab 300 mg solution, subcutaneously (SC), once every 2 weeks (q2w) for 26 weeks in Treatment Period A. This was followed by Treatment Period B (additional 26 weeks, total of 52 weeks including Treatment Period A) during which participants remained on Treatment Period A regimen or received 300 mg lanadelumab solution once every 4 weeks (q4w) for 26 weeks if well-controlled (attack-free) for 26 consecutive weeks with lanadelumab treatment. The dose frequency change was based on the Investigator's discretion and approval by the Sponsor's Medical Monitor.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|                                        |                          |
|----------------------------------------|--------------------------|
| Investigational medicinal product name | Lanadelumab              |
| Investigational medicinal product code |                          |
| Other name                             | DX-2930, TAK-743, SHP643 |
| Pharmaceutical forms                   | Solution for injection   |
| Routes of administration               | Subcutaneous use         |
| Dosage and administration details:     |                          |
| Lanadelumab solution, SC               |                          |

|                                       |                               |
|---------------------------------------|-------------------------------|
| <b>Number of subjects in period 3</b> | Lanadelumab 300 mg q2w or q4w |
| Started                               | 12                            |
| Completed                             | 12                            |

#### Period 4

|                              |                                          |
|------------------------------|------------------------------------------|
| Period 4 title               | Safety Follow-up Period (Weeks 53 to 56) |
| Is this the baseline period? | No                                       |
| Allocation method            | Not applicable                           |
| Blinding used                | Not blinded                              |

#### Arms

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | Lanadelumab 300 mg q2w or q4w |
|------------------|-------------------------------|

Arm description:

Lanadelumab 300 mg solution, subcutaneously (SC), once every 2 weeks (q2w) for 26 weeks in Treatment Period A. This was followed by Treatment Period B (additional 26 weeks, total of 52 weeks including Treatment Period A) during which participants remained on Treatment Period A regimen or received 300 mg lanadelumab solution once every 4 weeks (q4w) for 26 weeks if well-controlled (attack-free) for 26 consecutive weeks with lanadelumab treatment. The dose frequency change was based on the Investigator's discretion and approval by the Sponsor's Medical Monitor.

|                                        |                          |
|----------------------------------------|--------------------------|
| Arm type                               | Experimental             |
| Investigational medicinal product name | Lanadelumab              |
| Investigational medicinal product code |                          |
| Other name                             | DX-2930, TAK-743, SHP643 |
| Pharmaceutical forms                   | Solution for injection   |
| Routes of administration               | Subcutaneous use         |

Dosage and administration details:

Lanadelumab solution, SC

|                                       |                               |
|---------------------------------------|-------------------------------|
| <b>Number of subjects in period 4</b> | Lanadelumab 300 mg q2w or q4w |
| Started                               | 12                            |
| Completed                             | 12                            |

## Baseline characteristics

### Reporting groups

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Lanadelumab 300 mg q2w or q4w |
|-----------------------|-------------------------------|

Reporting group description:

Lanadelumab 300 mg solution, subcutaneously (SC), once every 2 weeks (q2w) for 26 weeks in Treatment Period A. This was followed by Treatment Period B (additional 26 weeks, total of 52 weeks including Treatment Period A) during which participants remained on Treatment Period A regimen or received 300 mg lanadelumab solution once every 4 weeks (q4w) for 26 weeks if well-controlled (attack-free) for 26 consecutive weeks with lanadelumab treatment. The dose frequency change was based on the Investigator's discretion and approval by the Sponsor's Medical Monitor.

| Reporting group values | Lanadelumab 300 mg q2w or q4w | Total |  |
|------------------------|-------------------------------|-------|--|
| Number of subjects     | 12                            | 12    |  |
| Age Categorical        |                               |       |  |
| Units: Subjects        |                               |       |  |

|                                           |          |    |  |
|-------------------------------------------|----------|----|--|
| Age continuous                            |          |    |  |
| Units: years                              |          |    |  |
| arithmetic mean                           | 41.9     |    |  |
| standard deviation                        | ± 12.36  | -  |  |
| Gender categorical                        |          |    |  |
| Units: Subjects                           |          |    |  |
| Male                                      | 3        | 3  |  |
| Female                                    | 9        | 9  |  |
| Race                                      |          |    |  |
| Units: Subjects                           |          |    |  |
| American Indian or Alaska Native          | 0        | 0  |  |
| Asian                                     | 12       | 12 |  |
| Native Hawaiian or Other Pacific Islander | 0        | 0  |  |
| Black or African American                 | 0        | 0  |  |
| White                                     | 0        | 0  |  |
| More than one race                        | 0        | 0  |  |
| Unknown or Not Reported                   | 0        | 0  |  |
| Ethnicity                                 |          |    |  |
| Units: Subjects                           |          |    |  |
| Hispanic or Latino                        | 0        | 0  |  |
| Not Hispanic or Latino                    | 12       | 12 |  |
| Unknown or Not Reported                   | 0        | 0  |  |
| Weight                                    |          |    |  |
| Units: kg                                 |          |    |  |
| arithmetic mean                           | 61.24    |    |  |
| standard deviation                        | ± 10.346 | -  |  |
| Height                                    |          |    |  |
| Units: cm                                 |          |    |  |
| arithmetic mean                           | 161.08   |    |  |
| standard deviation                        | ± 9.379  | -  |  |
| Body Mass Index (BMI)                     |          |    |  |
| BMI= weight(kg) / height(meter)^2         |          |    |  |

|                          |         |   |  |
|--------------------------|---------|---|--|
| Units: kg/m <sup>2</sup> |         |   |  |
| arithmetic mean          | 23.80   |   |  |
| standard deviation       | ± 5.065 | - |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                               |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Lanadelumab 300 mg q2w or q4w |
| Reporting group description:<br>Lanadelumab 300 mg solution, subcutaneously (SC), once every 2 weeks (q2w) for 26 weeks in Treatment Period A. This was followed by Treatment Period B (additional 26 weeks, total of 52 weeks including Treatment Period A) during which participants remained on Treatment Period A regimen or received 300 mg lanadelumab solution once every 4 weeks (q4w) for 26 weeks if well-controlled (attack-free) for 26 consecutive weeks with lanadelumab treatment. The dose frequency change was based on the Investigator's discretion and approval by the Sponsor's Medical Monitor. |                               |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Lanadelumab 300 mg q2w or q4w |
| Reporting group description:<br>Lanadelumab 300 mg solution, subcutaneously (SC), once every 2 weeks (q2w) for 26 weeks in Treatment Period A. This was followed by Treatment Period B (additional 26 weeks, total of 52 weeks including Treatment Period A) during which participants remained on Treatment Period A regimen or received 300 mg lanadelumab solution once every 4 weeks (q4w) for 26 weeks if well-controlled (attack-free) for 26 consecutive weeks with lanadelumab treatment. The dose frequency change was based on the Investigator's discretion and approval by the Sponsor's Medical Monitor. |                               |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Lanadelumab 300 mg q2w or q4w |
| Reporting group description:<br>Lanadelumab 300 mg solution, subcutaneously (SC), once every 2 weeks (q2w) for 26 weeks in Treatment Period A. This was followed by Treatment Period B (additional 26 weeks, total of 52 weeks including Treatment Period A) during which participants remained on Treatment Period A regimen or received 300 mg lanadelumab solution once every 4 weeks (q4w) for 26 weeks if well-controlled (attack-free) for 26 consecutive weeks with lanadelumab treatment. The dose frequency change was based on the Investigator's discretion and approval by the Sponsor's Medical Monitor. |                               |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Lanadelumab 300 mg q2w or q4w |
| Reporting group description:<br>Lanadelumab 300 mg solution, subcutaneously (SC), once every 2 weeks (q2w) for 26 weeks in Treatment Period A. This was followed by Treatment Period B (additional 26 weeks, total of 52 weeks including Treatment Period A) during which participants remained on Treatment Period A regimen or received 300 mg lanadelumab solution once every 4 weeks (q4w) for 26 weeks if well-controlled (attack-free) for 26 consecutive weeks with lanadelumab treatment. The dose frequency change was based on the Investigator's discretion and approval by the Sponsor's Medical Monitor. |                               |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Treatment Period A: Non-HAE   |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Safety analysis               |
| Subject analysis set description:<br>Lanadelumab 300 mg solution, SC, q2w for 26 weeks in Treatment Period A. Non-HAE attack (subset identified in case report form [CRF] as not reported HAE attack) subset participants were included in this arm.                                                                                                                                                                                                                                                                                                                                                                  |                               |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Treatment Period A: HAE       |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Safety analysis               |
| Subject analysis set description:<br>Lanadelumab 300 mg solution, SC, q2w for 26 weeks in Treatment Period A. HAE attack (subset of AEs identified in CRF as reported HAE attack) subset participants were included in this arm.                                                                                                                                                                                                                                                                                                                                                                                      |                               |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Treatment Period B: Non-HAE   |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Safety analysis               |
| Subject analysis set description:<br>Lanadelumab 300 mg solution, SC, q2w for 26 weeks or lanadelumab 300 mg solution, SC, q4w for 26 weeks in Treatment Period B if well tolerated (attack-free) for 26 consecutive weeks with lanadelumab treatment during Treatment Period A. Non-HAE attack (subset identified in CRF as not reported HAE attack) subset participants were included in this arm.                                                                                                                                                                                                                  |                               |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Treatment Period B: HAE       |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Safety analysis               |
| Subject analysis set description:<br>Lanadelumab 300 mg solution, SC, q2w for 26 weeks or lanadelumab 300 mg solution, SC, q4w for 26 weeks in Treatment Period B if well tolerated (attack-free) for 26 consecutive weeks with lanadelumab                                                                                                                                                                                                                                                                                                                                                                           |                               |

treatment during Treatment Period A. HAE attack (subset of AEs identified in CRF as reported HAE attack) subset participants were included in this arm.

|                            |                                  |
|----------------------------|----------------------------------|
| Subject analysis set title | Safety Follow-up Period: Non-HAE |
|----------------------------|----------------------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Participants who completed the lanadelumab 300 mg regimen in Treatment Period B returned on Day 378 (for participants who chose to roll over into study TAK-743-5007 [NCT04687137]) or Day 392 as follow-up visit for final assessment in the Safety Follow-up Period. Non-HAE attack (subset identified in CRF as not reported HAE attack) subset participants were included in this arm.

|                            |                              |
|----------------------------|------------------------------|
| Subject analysis set title | Safety Follow-up Period: HAE |
|----------------------------|------------------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Participants who completed the lanadelumab 300 mg regimen in Treatment Period B returned on Day 378 (for participants who chose to roll over into study TAK-743-5007) or Day 392 as follow-up visit for final assessment in the Safety Follow-up Period. HAE attack (subset of AEs identified in CRF as reported HAE attack) subset participants were included in this arm.

### **Primary: Number of Participants Achieving Attack-Free Status for the Efficacy Evaluation Period of Day 0 Through Day 182**

|                 |                                                                                                                                |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants Achieving Attack-Free Status for the Efficacy Evaluation Period of Day 0 Through Day 182 <sup>[1]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------|

End point description:

A participant was considered as attack free during an efficacy evaluation period if the participant had no investigator-confirmed hereditary angioedema (HAE) attacks during that efficacy evaluation period. A HAE attack was defined as the symptoms or signs consistent with an attack in at least 1 of the following locations: peripheral angioedema (cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region), abdominal angioedema (abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea), laryngeal angioedema (stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx). Number of participants achieving attack-free status for the efficacy evaluation period of Day 0 through Day 182 were assessed. Full Analysis Set (FAS) included all participants who received at least 1 dose of investigational medicinal product (IMP).

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 0 through Day 182

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics was planned to be reported for this endpoint.

|                             |                               |  |  |  |
|-----------------------------|-------------------------------|--|--|--|
| <b>End point values</b>     | Lanadelumab 300 mg q2w or q4w |  |  |  |
| Subject group type          | Reporting group               |  |  |  |
| Number of subjects analysed | 12                            |  |  |  |
| Units: participants         | 5                             |  |  |  |

### **Statistical analyses**

No statistical analyses for this end point

### **Secondary: Number of Investigator-Confirmed Hereditary Angioedema (HAE) Attacks During Each of the Efficacy Evaluation Periods**

|                 |                                                                                                                     |
|-----------------|---------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Investigator-Confirmed Hereditary Angioedema (HAE) Attacks During Each of the Efficacy Evaluation Periods |
|-----------------|---------------------------------------------------------------------------------------------------------------------|

End point description:

Efficacy evaluation period consisted of four periods: Day 0 (after study drug administration) through Day 182 (the end of Treatment Period A), Day 0 (after study drug administration) through Day 364 (the end of Treatment Period B), presumed steady-state period from Day 70 through Day 182, presumed steady-state period from Day 70 through Day 364. Number of investigator-confirmed HAE attacks during each of the efficacy evaluation periods were assessed. FAS included all participants who received at least 1 dose of IMP.

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

End point timeframe:

Day 0 through Day 182, Day 0 through Day 364, Day 70 through Day 182, Day 70 through Day 364

|                             |                                     |  |  |  |
|-----------------------------|-------------------------------------|--|--|--|
| <b>End point values</b>     | Lanadelumab<br>300 mg q2w or<br>q4w |  |  |  |
| Subject group type          | Reporting group                     |  |  |  |
| Number of subjects analysed | 12                                  |  |  |  |
| Units: HAE attacks          |                                     |  |  |  |
| Day 0 Through Day 182       | 92                                  |  |  |  |
| Day 0 Through Day 364       | 189                                 |  |  |  |
| Day 70 Through Day 182      | 55                                  |  |  |  |
| Day 70 Through Day 364      | 152                                 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Investigator-Confirmed Hereditary Angioedema (HAE) Attacks Requiring Acute Treatment During Each of the Efficacy Evaluation Periods

|                 |                                                                                                                                               |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Investigator-Confirmed Hereditary Angioedema (HAE) Attacks Requiring Acute Treatment During Each of the Efficacy Evaluation Periods |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Efficacy evaluation period consisted of four periods: Day 0 (after study drug administration) through Day 182 (the end of Treatment Period A), Day 0 (after study drug administration) through Day 364 (the end of Treatment Period B), presumed steady-state period from Day 70 through Day 182, presumed steady-state period from Day 70 through Day 364. Number of investigator-confirmed HAE attacks requiring acute treatment during each of the efficacy evaluation periods were assessed. FAS included all participants who received at least 1 dose of IMP.

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

End point timeframe:

Day 0 through Day 182, Day 0 through Day 364, Day 70 through Day 182, Day 70 through Day 364

|                             |                                     |  |  |  |
|-----------------------------|-------------------------------------|--|--|--|
| <b>End point values</b>     | Lanadelumab<br>300 mg q2w or<br>q4w |  |  |  |
| Subject group type          | Reporting group                     |  |  |  |
| Number of subjects analysed | 12                                  |  |  |  |
| Units: HAE attacks          |                                     |  |  |  |
| Day 0 Through Day 182       | 79                                  |  |  |  |
| Day 0 Through Day 364       | 168                                 |  |  |  |
| Day 70 Through Day 182      | 46                                  |  |  |  |
| Day 70 Through Day 364      | 135                                 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Moderate or Severe Investigator-Confirmed Hereditary Angioedema (HAE) Attacks During Each of the Efficacy Evaluation Periods

|                 |                                                                                                                                        |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Moderate or Severe Investigator-Confirmed Hereditary Angioedema (HAE) Attacks During Each of the Efficacy Evaluation Periods |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Severe attack was defined as Grade 3 (some assistance usually required, medical intervention/therapy required, hospitalizations possible), moderate attack was defined as Grade 2 (some assistance may be needed, no or minimal medical intervention/therapy required). Number of investigator-confirmed moderate or severe HAE attacks during the each of efficacy evaluation periods was assessed. Efficacy evaluation period consisted of four periods: Day 0 (after study drug administration) through Day 182 (the end of Treatment Period A), Day 0 (after study drug administration) through Day 364 (the end of Treatment Period B), presumed steady-state period from Day 70 through Day 182, presumed steady-state period from Day 70 through Day 364. FAS included all participants who received at least 1 dose of IMP.

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

End point timeframe:

Day 0 through Day 182, Day 0 through Day 364, Day 70 through Day 182, Day 70 through Day 364

|                             |                                     |  |  |  |
|-----------------------------|-------------------------------------|--|--|--|
| <b>End point values</b>     | Lanadelumab<br>300 mg q2w or<br>q4w |  |  |  |
| Subject group type          | Reporting group                     |  |  |  |
| Number of subjects analysed | 12                                  |  |  |  |
| Units: HAE attacks          |                                     |  |  |  |
| Day 0 Through Day 182       | 72                                  |  |  |  |
| Day 0 Through Day 364       | 153                                 |  |  |  |
| Day 70 Through Day 182      | 41                                  |  |  |  |
| Day 70 Through Day 364      | 122                                 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Maximum Hereditary Angioedema (HAE) Attack Severity During Each of the Efficacy Evaluation Periods

|                 |                                                                                                                                |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Maximum Hereditary Angioedema (HAE) Attack Severity During Each of the Efficacy Evaluation Periods |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------|

End point description:

Efficacy evaluation period consisted of four periods: Day 0 (after study drug administration) through Day 182 (the end of Treatment Period A), Day 0 (after study drug administration) through Day 364 (the end of Treatment Period B), presumed steady-state period from Day 70 through Day 182, presumed steady-state period from Day 70 through Day 364. Number of participants with maximum HAE attack severity during each of the efficacy evaluation periods was assessed. HAE attack severity was calculated per participant based on the severity categories as follows: No attack, Mild, Moderate, and Severe. FAS included all participants who received at least 1 dose of IMP.

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

End point timeframe:

Day 0 through Day 182, Day 0 through Day 364, Day 70 through Day 182, Day 70 through Day 364

|                                   |                                     |  |  |  |
|-----------------------------------|-------------------------------------|--|--|--|
| <b>End point values</b>           | Lanadelumab<br>300 mg q2w or<br>q4w |  |  |  |
| Subject group type                | Reporting group                     |  |  |  |
| Number of subjects analysed       | 12                                  |  |  |  |
| Units: participants               |                                     |  |  |  |
| Day 0 Through Day 182: No Attack  | 5                                   |  |  |  |
| Day 0 Through Day 182: Mild       | 2                                   |  |  |  |
| Day 0 Through Day 182: Moderate   | 4                                   |  |  |  |
| Day 0 Through Day 182: Severe     | 1                                   |  |  |  |
| Day 0 Through Day 364: No Attack  | 2                                   |  |  |  |
| Day 0 Through Day 364: Mild       | 1                                   |  |  |  |
| Day 0 Through Day 364: Moderate   | 8                                   |  |  |  |
| Day 0 Through Day 364: Severe     | 1                                   |  |  |  |
| Day 70 Through Day 182: No Attack | 5                                   |  |  |  |
| Day 70 Through Day 182: Mild      | 4                                   |  |  |  |
| Day 70 Through Day 182: Moderate  | 2                                   |  |  |  |
| Day 70 Through Day 182: Severe    | 1                                   |  |  |  |
| Day 70 Through Day 364: No Attack | 2                                   |  |  |  |
| Day 70 Through Day 364: Mild      | 2                                   |  |  |  |
| Day 70 Through Day 364: Moderate  | 7                                   |  |  |  |
| Day 70 Through Day 364: Severe    | 1                                   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of High-Morbidity Investigator-Confirmed Hereditary Angioedema (HAE) Attacks During Each of the Efficacy Evaluation Periods

|                 |                                                            |
|-----------------|------------------------------------------------------------|
| End point title | Number of High-Morbidity Investigator-Confirmed Hereditary |
|-----------------|------------------------------------------------------------|

End point description:

A high morbidity HAE attack was defined as any attack that has at least 1 of the following characteristics: severe, results in hospitalization (except hospitalization for observation <24 hours), hemodynamically significant (systolic blood pressure <90, requires intravenous (IV) hydration, or associated with syncope or near syncope) or laryngeal. Number of high-morbidity investigator-confirmed HAE attacks during each of the 4 efficacy evaluation periods (Treatment Period A, Overall Treatment Period, Presumed Steady-state Period for Treatment Period A and Overall Presumed Steady-state Period) were assessed. FAS included all participants who received at least 1 dose of IMP.

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

End point timeframe:

Day 0 through Day 182, Day 0 through Day 364, Day 70 through Day 182, Day 70 through Day 364

| End point values            | Lanadelumab<br>300 mg q2w or<br>q4w |  |  |  |
|-----------------------------|-------------------------------------|--|--|--|
| Subject group type          | Reporting group                     |  |  |  |
| Number of subjects analysed | 12                                  |  |  |  |
| Units: HAE attacks          |                                     |  |  |  |
| Day 0 Through Day 182       | 5                                   |  |  |  |
| Day 0 Through Day 364       | 11                                  |  |  |  |
| Day 70 Through Day 182      | 4                                   |  |  |  |
| Day 70 Through Day 364      | 10                                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to First Hereditary Angioedema (HAE) Attack After Day 0 for the Efficacy Evaluation Period

|                 |                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------|
| End point title | Time to First Hereditary Angioedema (HAE) Attack After Day 0 for the Efficacy Evaluation Period |
|-----------------|-------------------------------------------------------------------------------------------------|

End point description:

The time to the first HAE attack (days) after Day 0 for the efficacy evaluation period of Day 0 through Day 182 was calculated from the date and time of the first dose of lanadelumab for the efficacy evaluation period (Day 0 through Day 182) to the date and time of the first in HAE attack after the first open-label dose for the efficacy evaluation period of Day 0 through Day 182. Kaplan-Meier Method was used for analysis and the Kaplan Meier estimate expressed as time (in days) to first HAE attack After Day 0 for Treatment Period A (Day 0 through Day 182) is presented. FAS included all participants who received at least 1 dose of IMP. 99999= The upper limit of 95% confidence interval (CI) was not evaluable due to low number of participants with events.

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

End point timeframe:

Day 0 through Day 182

|                                  |                                     |  |  |  |
|----------------------------------|-------------------------------------|--|--|--|
| <b>End point values</b>          | Lanadelumab<br>300 mg q2w or<br>q4w |  |  |  |
| Subject group type               | Reporting group                     |  |  |  |
| Number of subjects analysed      | 12                                  |  |  |  |
| Units: days                      |                                     |  |  |  |
| median (confidence interval 95%) | 97.2 (4.2 to<br>99999)              |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to First Hereditary Angioedema (HAE) Attack After Day 0 for the Efficacy Evaluation Period

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Time to First Hereditary Angioedema (HAE) Attack After Day 0 for the Efficacy Evaluation Period |
| End point description:<br>The time to the first HAE attack (days) after Day 0 for the efficacy evaluation period of Day 70 through Day 182 was calculated from the date and time of the first dose of lanadelumab for the efficacy evaluation period (Day 70 through Day 182) to the date and time of the first in HAE attack after the first open-label dose for the efficacy evaluation period of Day 70 through Day 182. Kaplan-Meier Method was used for analysis and the Kaplan Meier estimate expressed as time (in days) to first HAE attack After Day 0 for presumed steady-state period for Treatment Period A (Day 70 through Day 182) is presented. FAS included all participants who received at least 1 dose of IMP. 99999= The upper limit of 95% CI was not evaluable due to low number of participants with events. |                                                                                                 |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Secondary                                                                                       |
| End point timeframe:<br>Day 70 through Day 182                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                 |

|                                  |                                     |  |  |  |
|----------------------------------|-------------------------------------|--|--|--|
| <b>End point values</b>          | Lanadelumab<br>300 mg q2w or<br>q4w |  |  |  |
| Subject group type               | Reporting group                     |  |  |  |
| Number of subjects analysed      | 12                                  |  |  |  |
| Units: days                      |                                     |  |  |  |
| median (confidence interval 95%) | 91.0 (4.6 to<br>99999)              |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants Achieving at Least 50%, 70% and 90% Reduction in the Investigator-Confirmed Normalized Number of Attacks (NNA) per 4 Weeks Relative to the Run-in Period NNA for Each of Efficacy Evaluation Periods

|                 |                                                                                                                                                                                     |  |  |  |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|
| End point title | Number of Participants Achieving at Least 50%, 70% and 90% Reduction in the Investigator-Confirmed Normalized Number of Attacks (NNA) per 4 Weeks Relative to the Run-in Period NNA |  |  |  |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|

End point description:

Run- in Period was 4 weeks and may have been extended up to 8 weeks to determine participants' Baseline attack rate.period attack rate, multiplied by 100.

End point type Secondary

End point timeframe:

Day 0 through Day 182, Day 0 through Day 364, Day 70 through Day 182, Day 70 through Day 364

| End point values                                 | Lanadelumab<br>300 mg q2w or<br>q4w |  |  |  |
|--------------------------------------------------|-------------------------------------|--|--|--|
| Subject group type                               | Reporting group                     |  |  |  |
| Number of subjects analysed                      | 12                                  |  |  |  |
| Units: participants                              |                                     |  |  |  |
| Day 0 Through Day 182: $\geq 50\%$<br>Reduction  | 10                                  |  |  |  |
| Day 0 Through Day 182: $\geq 70\%$<br>Reduction  | 8                                   |  |  |  |
| Day 0 Through Day 182: $\geq 90\%$<br>Reduction  | 6                                   |  |  |  |
| Day 0 Through Day 364: $\geq 50\%$<br>Reduction  | 10                                  |  |  |  |
| Day 0 Through Day 364: $\geq 70\%$<br>Reduction  | 8                                   |  |  |  |
| Day 0 Through Day 364: $\geq 90\%$<br>Reduction  | 6                                   |  |  |  |
| Day 70 Through Day 182: $\geq 50\%$<br>Reduction | 11                                  |  |  |  |
| Day 70 Through Day 182: $\geq 70\%$<br>Reduction | 10                                  |  |  |  |
| Day 70 Through Day 182: $\geq 90\%$<br>Reduction | 6                                   |  |  |  |
| Day 70 Through Day 364: $\geq 50\%$<br>Reduction | 10                                  |  |  |  |
| Day 70 Through Day 364: $\geq 70\%$<br>Reduction | 8                                   |  |  |  |
| Day 70 Through Day 364: $\geq 90\%$<br>Reduction | 7                                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants Achieving Normalized Number of Attacks (NNA) <1.0 per 4 Weeks, <0.75 per 4 Weeks, <0.50 per 4 Weeks and <0.25 per 4 Weeks for Each of the Efficacy Evaluation Periods

|                 |                                                                                                                                                                                              |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants Achieving Normalized Number of Attacks (NNA) <1.0 per 4 Weeks, <0.75 per 4 Weeks, <0.50 per 4 Weeks and <0.25 per 4 Weeks for Each of the Efficacy Evaluation Periods |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The NNA (investigator-confirmed) during each efficacy evaluation period was expressed as a monthly (28 days) HAE attack rate. Number of participants achieving NNA <1.0 per 4 weeks, <0.75 per 4 weeks,

<0.50 per 4 weeks, and <0.25 per 4 weeks for each of the 4 efficacy evaluation periods (Treatment Period A, Overall Treatment Period, Presumed Steady-state Period for Treatment Period A, and Overall Presumed Steady-state Period) were assessed. The responder categories were not mutually exclusive, participants may appear in more than one category as applicable based on their HAE attack rate. FAS included all participants who received at least 1 dose of IMP.

|                                                                                              |           |
|----------------------------------------------------------------------------------------------|-----------|
| End point type                                                                               | Secondary |
| End point timeframe:                                                                         |           |
| Day 0 through Day 182, Day 0 through Day 364, Day 70 through Day 182, Day 70 through Day 364 |           |

|                                         |                                     |  |  |  |
|-----------------------------------------|-------------------------------------|--|--|--|
| <b>End point values</b>                 | Lanadelumab<br>300 mg q2w or<br>q4w |  |  |  |
| Subject group type                      | Reporting group                     |  |  |  |
| Number of subjects analysed             | 12                                  |  |  |  |
| Units: participants                     |                                     |  |  |  |
| Day 0 Through Day 182: <1.0 per Month   | 9                                   |  |  |  |
| Day 0 Through Day 182: <0.75 per Month  | 9                                   |  |  |  |
| Day 0 Through Day 182: <0.50 per Month  | 6                                   |  |  |  |
| Day 0 Through Day 182: <0.25 per Month  | 6                                   |  |  |  |
| Day 0 Through Day 364: <1.0 per Month   | 9                                   |  |  |  |
| Day 0 Through Day 364: <0.75 per Month  | 8                                   |  |  |  |
| Day 0 Through Day 364: <0.50 per Month  | 7                                   |  |  |  |
| Day 0 Through Day 364: <0.25 per Month  | 6                                   |  |  |  |
| Day 70 Through Day 182: <1.0 per Month  | 9                                   |  |  |  |
| Day 70 Through Day 182: <0.75 per Month | 9                                   |  |  |  |
| Day 70 Through Day 182: <0.50 per Month | 8                                   |  |  |  |
| Day 70 Through Day 182: <0.25 per Month | 6                                   |  |  |  |
| Day 70 Through Day 364: <1.0 per Month  | 9                                   |  |  |  |
| Day 70 Through Day 364: <0.75 per Month | 8                                   |  |  |  |
| Day 70 Through Day 364: <0.50 per Month | 7                                   |  |  |  |
| Day 70 Through Day 364: <0.25 per Month | 6                                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants Achieving Attack-Free Status for the Efficacy

**Evaluation Period Day 0 Through Day 364, Day 70 Through Day 182, and Day 70 Through Day 364**

|                 |                                                                                                                                                                  |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants Achieving Attack-Free Status for the Efficacy Evaluation Period Day 0 Through Day 364, Day 70 Through Day 182, and Day 70 Through Day 364 |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|

## End point description:

A participant was considered as attack free during an efficacy evaluation period if the participant had no investigator-confirmed HAE attacks during that efficacy evaluation period. A HAE attack was defined as the symptoms or signs consistent with an attack in at least 1 of the following locations: peripheral angioedema (cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region), abdominal angioedema (abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea), laryngeal angioedema (stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx). Number of participants achieving attack-free status for the 4 efficacy evaluation periods (Overall Treatment Period, Presumed Steady-state Period for Treatment Period A, and Overall Presumed Steady-state Period) were assessed. FAS included all participants who received at least 1 dose of IMP.

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

## End point timeframe:

Day 0 through Day 364, Day 70 through Day 182, and Day 70 through Day 364

|                             |                                     |  |  |  |
|-----------------------------|-------------------------------------|--|--|--|
| <b>End point values</b>     | Lanadelumab<br>300 mg q2w or<br>q4w |  |  |  |
| Subject group type          | Reporting group                     |  |  |  |
| Number of subjects analysed | 9                                   |  |  |  |
| Units: participants         |                                     |  |  |  |
| Day 0 Through Day 364       | 2                                   |  |  |  |
| Day 70 Through Day 182      | 5                                   |  |  |  |
| Day 70 Through Day 364      | 2                                   |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Number of Participants Achieving Attack-Free Status for Monthly Increments**

|                 |                                                                            |
|-----------------|----------------------------------------------------------------------------|
| End point title | Number of Participants Achieving Attack-Free Status for Monthly Increments |
|-----------------|----------------------------------------------------------------------------|

## End point description:

A participant was considered as attack free during an efficacy evaluation period if the participant had no investigator-confirmed HAE attacks during that efficacy evaluation period. A HAE attack was defined as the symptoms or signs consistent with an attack in at least 1 of the following locations: peripheral angioedema (cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region), abdominal angioedema (abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea), laryngeal angioedema (stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx). FAS included all participants who received at least 1 dose of IMP.

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

## End point timeframe:

At Months 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13

|                             |                                     |  |  |  |
|-----------------------------|-------------------------------------|--|--|--|
| <b>End point values</b>     | Lanadelumab<br>300 mg q2w or<br>q4w |  |  |  |
| Subject group type          | Reporting group                     |  |  |  |
| Number of subjects analysed | 12                                  |  |  |  |
| Units: participants         |                                     |  |  |  |
| Month 1                     | 7                                   |  |  |  |
| Month 2                     | 8                                   |  |  |  |
| Month 3                     | 9                                   |  |  |  |
| Month 4                     | 7                                   |  |  |  |
| Month 5                     | 9                                   |  |  |  |
| Month 6                     | 7                                   |  |  |  |
| Month 7                     | 8                                   |  |  |  |
| Month 8                     | 6                                   |  |  |  |
| Month 9                     | 7                                   |  |  |  |
| Month 10                    | 9                                   |  |  |  |
| Month 11                    | 8                                   |  |  |  |
| Month 12                    | 7                                   |  |  |  |
| Month 13                    | 8                                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants Achieving Investigator-Confirmed Hereditary Angioedema (HAE) Attack-Free Intervals

|                 |                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants Achieving Investigator-Confirmed Hereditary Angioedema (HAE) Attack-Free Intervals |
|-----------------|-----------------------------------------------------------------------------------------------------------|

End point description:

A participant was considered as attack free during a time period if the participant had no investigator-confirmed HAE attacks during that time period. Participants who discontinued during a time period were considered as non-responders for that time period. Number of participants achieving investigator-confirmed HAE attack free intervals from Day 0 through Day 182 were assessed. FAS included all participants who received at least 1 dose of IMP.

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

End point timeframe:

Day 0 through Day 182

|                             |                                     |  |  |  |
|-----------------------------|-------------------------------------|--|--|--|
| <b>End point values</b>     | Lanadelumab<br>300 mg q2w or<br>q4w |  |  |  |
| Subject group type          | Reporting group                     |  |  |  |
| Number of subjects analysed | 12                                  |  |  |  |
| Units: participants         | 5                                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Attack Free Days During Each of the Efficacy Evaluation Periods

|                 |                                                                               |
|-----------------|-------------------------------------------------------------------------------|
| End point title | Percentage of Attack Free Days During Each of the Efficacy Evaluation Periods |
|-----------------|-------------------------------------------------------------------------------|

End point description:

An attack-free day was defined as a calendar day with no investigator-confirmed HAE attack. HAE attack free days were calculated by counting the number of days in the efficacy evaluation period without an HAE attack and dividing by the number of days the participant contributed to the efficacy evaluation period. Percentage of investigator-confirmed HAE attack free days during each of the efficacy evaluation periods (Treatment Period A, Overall Treatment Period, Presumed Steady-state Period for Treatment Period A, and Overall Presumed Steady-state Period) were assessed. FAS included all participants who received at least 1 dose of IMP.

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

End point timeframe:

Day 0 through Day 182, Day 0 through Day 364, Day 70 through Day 182, Day 70 through Day 364

|                                       |                                     |  |  |  |
|---------------------------------------|-------------------------------------|--|--|--|
| <b>End point values</b>               | Lanadelumab<br>300 mg q2w or<br>q4w |  |  |  |
| Subject group type                    | Reporting group                     |  |  |  |
| Number of subjects analysed           | 12                                  |  |  |  |
| Units: percentage of attack-free days |                                     |  |  |  |
| arithmetic mean (standard deviation)  |                                     |  |  |  |
| Day 0 Through Day 182                 | 88.53 (±<br>27.146)                 |  |  |  |
| Day 0 Through Day 364                 | 89.04 (±<br>27.015)                 |  |  |  |
| Day 70 Through Day 182                | 90.34 (±<br>21.952)                 |  |  |  |
| Day 70 Through Day 364                | 89.85 (±<br>25.015)                 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Treatment Emergent Adverse Events (TEAEs) Including Adverse Events of Special Interest (AESI) and Serious Adverse Events (SAEs)

|                 |                                                        |
|-----------------|--------------------------------------------------------|
| End point title | Number of Participants with Treatment Emergent Adverse |
|-----------------|--------------------------------------------------------|

End point description:

TEAE=any event emerging at or after initiation of treatment with investigational product (IP) or any existing event that worsens in intensity/frequency on exposure to IP. Serious TEAE=any untoward clinical manifestation of signs, symptoms, outcomes (related to IP or not) at any dose: results in death, was life-threatening, requires inpatient/prolongation of hospitalization, resulted in persistent/significant disability/incapacity, congenital abnormality/birth defect, important medical event. AESI=investigator-reported hypersensitivity reactions, events of disordered coagulation as bleeding/hypercoagulable AESI. Adverse events (AEs) were classified as HAE attack and non-HAE attack reported AEs and are categorized accordingly. As Pre-specified in the protocol, TEAEs, SAEs and AESIs were collected per Period i.e., Treatment Period A, B and Safety follow-up Period and data is reported accordingly. FAS included all participants who received at least 1 dose of IMP.

End point type Secondary

End point timeframe:

From first dose of the study drug up to end of study (EOS) (up to Day 392)

| End point values            | Treatment Period A: Non-HAE | Treatment Period A: HAE | Treatment Period B: Non-HAE | Treatment Period B: HAE |
|-----------------------------|-----------------------------|-------------------------|-----------------------------|-------------------------|
| Subject group type          | Subject analysis set        | Subject analysis set    | Subject analysis set        | Subject analysis set    |
| Number of subjects analysed | 12                          | 12                      | 12                          | 12                      |
| Units: participants         |                             |                         |                             |                         |
| Any TEAEs                   | 10                          | 8                       | 9                           | 8                       |
| AESI                        | 3                           | 0                       | 0                           | 0                       |
| Any Serious TEAEs           | 1                           | 1                       | 1                           | 0                       |

| End point values            | Safety Follow-up Period: Non-HAE | Safety Follow-up Period: HAE |  |  |
|-----------------------------|----------------------------------|------------------------------|--|--|
| Subject group type          | Subject analysis set             | Subject analysis set         |  |  |
| Number of subjects analysed | 12                               | 12                           |  |  |
| Units: participants         |                                  |                              |  |  |
| Any TEAEs                   | 0                                | 3                            |  |  |
| AESI                        | 0                                | 0                            |  |  |
| Any Serious TEAEs           | 0                                | 0                            |  |  |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Lanadelumab

End point title Plasma Concentrations of Lanadelumab

End point description:

Pharmacokinetic (PK) Set included all participants in the FAS who had at least 1 evaluable post dose PK concentration value. n= number analysed indicates the number of participants with data available for analysis at a specific time point.

End point type Secondary

End point timeframe:

Predose on Days 0, 56, 98, 140, 182, 266, 350, 364, and at any time on Day 378 or 392

|                                         |                                     |  |  |  |
|-----------------------------------------|-------------------------------------|--|--|--|
| <b>End point values</b>                 | Lanadelumab<br>300 mg q2w or<br>q4w |  |  |  |
| Subject group type                      | Reporting group                     |  |  |  |
| Number of subjects analysed             | 12                                  |  |  |  |
| Units: nanograms per milliliter (ng/mL) |                                     |  |  |  |
| arithmetic mean (standard deviation)    |                                     |  |  |  |
| Day 0 (n=12)                            | 25.584 (±<br>50.2034)               |  |  |  |
| Day 56 (n=12)                           | 23630.973 (±<br>8665.1099)          |  |  |  |
| Day 98 (n=12)                           | 24142.776 (±<br>9575.7596)          |  |  |  |
| Day 140 (n=11)                          | 24613.885 (±<br>9319.6672)          |  |  |  |
| Day 182 (n=12)                          | 23679.526 (±<br>6793.3003)          |  |  |  |
| Day 266 (n=12)                          | 19269.249 (±<br>8870.0355)          |  |  |  |
| Day 350 (n=3)                           | 13225.533 (±<br>2538.8239)          |  |  |  |
| Day 364 (n=10)                          | 22329.820 (±<br>7527.7165)          |  |  |  |
| Day 378/392 (n=12)                      | 19308.033 (±<br>7708.1882)          |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Angioedema Quality of Life (AE-QoL) Questionnaire Total Score

|                 |                                                                                       |
|-----------------|---------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Angioedema Quality of Life (AE-QoL) Questionnaire Total Score |
|-----------------|---------------------------------------------------------------------------------------|

End point description:

The AE-QoL questionnaire is a self-administered validated instrument to assess health related (HR)QoL among participants with recurrent angioedema (including HAE). The AE-QoL consists of 17 disease-specific quality-of-life items, to produce a total AE-QoL score and 4 domain scores (functioning, fatigue/mood, fear/shame, and nutrition) and each of the 17 items had a five-point response scale ranging from 1 (Never) to 5 (Very Often). The questionnaire was scored according to the developers' guidelines to produce 4 domain scores (functioning, fatigue/mood, fear/shame, nutrition) yielding a total score. The raw total score (mean of all item scores) was rescaled using linear transformations into final percentage scores ranging 0 to 100, based on the maximum possible score, where higher the score, greater the QoL impairment. FAS included all participants who received at least 1 dose of IMP.

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

End point timeframe:

Days 0, 28, 56, 98, 126, 154, 182, 266, 364, 378 or 392

|                                      |                                     |  |  |  |
|--------------------------------------|-------------------------------------|--|--|--|
| <b>End point values</b>              | Lanadelumab<br>300 mg q2w or<br>q4w |  |  |  |
| Subject group type                   | Reporting group                     |  |  |  |
| Number of subjects analysed          | 12                                  |  |  |  |
| Units: score on a scale              |                                     |  |  |  |
| arithmetic mean (standard deviation) |                                     |  |  |  |
| Day 0                                | 46.57 (±<br>20.885)                 |  |  |  |
| Day 28                               | 26.35 (±<br>31.129)                 |  |  |  |
| Day 56                               | 28.43 (±<br>28.255)                 |  |  |  |
| Day 98                               | 26.96 (±<br>30.926)                 |  |  |  |
| Day 126                              | 32.60 (±<br>33.999)                 |  |  |  |
| Day 154                              | 21.69 (±<br>28.750)                 |  |  |  |
| Day 182                              | 26.10 (±<br>33.978)                 |  |  |  |
| Day 266                              | 26.96 (±<br>29.951)                 |  |  |  |
| Day 364                              | 26.59 (±<br>34.428)                 |  |  |  |
| Day 378/392                          | 28.55 (±<br>31.934)                 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Kallikrein (pKal) Activity

|                                                                                                                                                                                                                                                                                                                                                                                |                                   |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                | Plasma Kallikrein (pKal) Activity |
| End point description:                                                                                                                                                                                                                                                                                                                                                         |                                   |
| pKal activity was measured by biomarker cleaved high molecular weight kininogen (cHMWK) level to assess pharmacodynamics (PD) of lanadelumab. Pharmacodynamic (PD) Set included all participants in the FAS who had at least 1 evaluable post dose PD value. n= number analysed indicates the number of participants with data available for analysis at the given time point. |                                   |
| End point type                                                                                                                                                                                                                                                                                                                                                                 | Secondary                         |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                           |                                   |
| Predose on Days 0, 56, 98, 140, 182, 266, 350, 364, and at any time on Day 378 or 392                                                                                                                                                                                                                                                                                          |                                   |

|                                      |                                     |  |  |  |
|--------------------------------------|-------------------------------------|--|--|--|
| <b>End point values</b>              | Lanadelumab<br>300 mg q2w or<br>q4w |  |  |  |
| Subject group type                   | Reporting group                     |  |  |  |
| Number of subjects analysed          | 12                                  |  |  |  |
| Units: percentage of cHMWK           |                                     |  |  |  |
| arithmetic mean (standard deviation) |                                     |  |  |  |
| Day 0 (n=12)                         | 63.04 (±<br>22.096)                 |  |  |  |
| Day 56 (n=12)                        | 30.88 (±<br>17.090)                 |  |  |  |
| Day 98 (n=12)                        | 32.40 (±<br>18.829)                 |  |  |  |
| Day 140 (n=11)                       | 35.67 (±<br>13.787)                 |  |  |  |
| Day 182 (n=12)                       | 30.31 (±<br>17.344)                 |  |  |  |
| Day 266 (n=12)                       | 21.69 (±<br>11.221)                 |  |  |  |
| Day 350 (n=3)                        | 39.83 (±<br>12.407)                 |  |  |  |
| Day 364 (n=10)                       | 27.51 (±<br>12.901)                 |  |  |  |
| Day 378/392 (n=12)                   | 40.65 (±<br>15.828)                 |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Positive Anti-drug Antibody (ADA) in Plasma

|                 |                                                                         |
|-----------------|-------------------------------------------------------------------------|
| End point title | Number of Participants With Positive Anti-drug Antibody (ADA) in Plasma |
|-----------------|-------------------------------------------------------------------------|

End point description:

Baseline was defined as the last non-missing value prior to first dose of study drug (based on date or date/time). FAS included all participants who received at least 1 dose of IMP. n= number analysed indicates the number of participants with data available for analysis at the given time point.

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

End point timeframe:

Predose on Days 0 (or Baseline), 56, 98, 140, 182, 266, 350, 364, and at any time on Day 378 or 392

|                             |                                     |  |  |  |
|-----------------------------|-------------------------------------|--|--|--|
| <b>End point values</b>     | Lanadelumab<br>300 mg q2w or<br>q4w |  |  |  |
| Subject group type          | Reporting group                     |  |  |  |
| Number of subjects analysed | 12                                  |  |  |  |
| Units: participants         |                                     |  |  |  |
| Day 0 [or Baseline] (n=12)  | 0                                   |  |  |  |
| Day 56 (n=12)               | 0                                   |  |  |  |
| Day 98 (n=12)               | 0                                   |  |  |  |
| Day 140 (n=11)              | 0                                   |  |  |  |

|                    |   |  |  |  |
|--------------------|---|--|--|--|
| Day 182 (n=12)     | 0 |  |  |  |
| Day 266 (n=12)     | 0 |  |  |  |
| Day 350 (n=3)      | 0 |  |  |  |
| Day 364 (n=10)     | 0 |  |  |  |
| Day 378/392 (n=12) | 0 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With TEAEs Related to Clinical Laboratory Tests

|                 |                                                                        |
|-----------------|------------------------------------------------------------------------|
| End point title | Number of Participants With TEAEs Related to Clinical Laboratory Tests |
|-----------------|------------------------------------------------------------------------|

End point description:

A TEAE was defined as any event emerging or manifesting at or after the initiation of treatment with an IP or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the IP or medicinal product. As Pre-specified in the protocol, the TEAEs were collected per Period i.e., Treatment Period A, B and Safety follow-up Period. The data is reported as per HAE attack and non-HAE attack per Period. Number of participants with TEAEs related to clinical laboratory tests (hematology, clinical chemistry, coagulation, and urinalysis) were assessed. FAS included all participants who received at least 1 dose of IMP.

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

End point timeframe:

From first dose of the study drug up to end of study (EOS) (up to Day 392)

| End point values            | Treatment Period A: Non-HAE | Treatment Period A: HAE | Treatment Period B: Non-HAE | Treatment Period B: HAE |
|-----------------------------|-----------------------------|-------------------------|-----------------------------|-------------------------|
| Subject group type          | Subject analysis set        | Subject analysis set    | Subject analysis set        | Subject analysis set    |
| Number of subjects analysed | 12                          | 12                      | 12                          | 12                      |
| Units: participants         | 0                           | 0                       | 0                           | 0                       |

| End point values            | Safety Follow-up Period: Non-HAE | Safety Follow-up Period: HAE |  |  |
|-----------------------------|----------------------------------|------------------------------|--|--|
| Subject group type          | Subject analysis set             | Subject analysis set         |  |  |
| Number of subjects analysed | 12                               | 12                           |  |  |
| Units: participants         | 0                                | 0                            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With TEAEs Related to Vital Signs

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                          |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Number of Participants With TEAEs Related to Vital Signs |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                          |
| A TEAE was defined as any event emerging or manifesting at or after the initiation of treatment with an IP or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the IP or medicinal product. As Pre-specified in the protocol, the TEAEs were collected per Period i.e., Treatment Period A, B and Safety follow-up Period. The data is reported as per HAE attack and non-HAE attack per Period. Number of participants with TEAEs related to vital signs (blood pressure (BP), heart rate (HR), body temperature, and respiratory rate) were assessed. FAS included all participants who received at least 1 dose of IMP. |                                                          |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Secondary                                                |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                          |
| From first dose of the study drug up to end of study (EOS) (up to Day 392)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                          |

| End point values            | Treatment Period A: Non-HAE | Treatment Period A: HAE | Treatment Period B: Non-HAE | Treatment Period B: HAE |
|-----------------------------|-----------------------------|-------------------------|-----------------------------|-------------------------|
| Subject group type          | Subject analysis set        | Subject analysis set    | Subject analysis set        | Subject analysis set    |
| Number of subjects analysed | 12                          | 12                      | 12                          | 12                      |
| Units: participants         | 0                           | 0                       | 0                           | 0                       |

| End point values            | Safety Follow-up Period: Non-HAE | Safety Follow-up Period: HAE |  |  |
|-----------------------------|----------------------------------|------------------------------|--|--|
| Subject group type          | Subject analysis set             | Subject analysis set         |  |  |
| Number of subjects analysed | 12                               | 12                           |  |  |
| Units: participants         | 0                                | 0                            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With TEAEs Related to Electrocardiogram (ECG)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Number of Participants With TEAEs Related to Electrocardiogram (ECG) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                      |
| A TEAE was defined as any event emerging or manifesting at or after the initiation of treatment with an IP or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the IP or medicinal product. As Pre-specified in the protocol, the TEAEs were collected per Period i.e., Treatment Period A, B and Safety follow-up Period. The data is reported as per HAE attack and non-HAE attack per Period. Number of participants with TEAEs related to 12 lead-ECG were assessed. FAS included all participants who received at least 1 dose of IMP. |                                                                      |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Secondary                                                            |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                      |
| From first dose of the study drug up to end of study (EOS) (up to Day 392)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                      |

| <b>End point values</b>     | Treatment<br>Period A: Non-<br>HAE | Treatment<br>Period A: HAE | Treatment<br>Period B: Non-<br>HAE | Treatment<br>Period B: HAE |
|-----------------------------|------------------------------------|----------------------------|------------------------------------|----------------------------|
| Subject group type          | Subject analysis set               | Subject analysis set       | Subject analysis set               | Subject analysis set       |
| Number of subjects analysed | 12                                 | 12                         | 12                                 | 12                         |
| Units: participants         | 0                                  | 0                          | 0                                  | 0                          |

| <b>End point values</b>     | Safety Follow-<br>up Period:<br>Non-HAE | Safety Follow-<br>up Period: HAE |  |  |
|-----------------------------|-----------------------------------------|----------------------------------|--|--|
| Subject group type          | Subject analysis set                    | Subject analysis set             |  |  |
| Number of subjects analysed | 12                                      | 12                               |  |  |
| Units: participants         | 0                                       | 0                                |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of the study drug up to end of study (EOS) (up to Day 392)

Adverse event reporting additional description:

FAS included all participants who received at least 1 dose of IMP. As Pre-specified in the protocol, the TEAEs were collected per Period i.e., Treatment Period A, B and Safety follow-up Period. The data is reported as per HAE attack and non-HAE attack per Period.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

### Reporting groups

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Treatment Period A: Non-HAE |
|-----------------------|-----------------------------|

Reporting group description:

Lanadelumab 300 mg solution, SC, q2w for 26 weeks in Treatment Period A. Non-HAE attack (subset identified in case report form [CRF] as not reported HAE attack) subset participants were included in this arm.

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Treatment Period A: HAE |
|-----------------------|-------------------------|

Reporting group description:

Lanadelumab 300 mg solution, SC, q2w for 26 weeks in Treatment Period A. HAE attack (subset of AEs identified in CRF as reported HAE attack) subset participants were included in this arm.

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Treatment Period B: Non-HAE |
|-----------------------|-----------------------------|

Reporting group description:

Lanadelumab 300 mg solution, SC, q2w for 26 weeks or lanadelumab 300 mg solution, SC, q4w for 26 weeks in Treatment Period B if well tolerated (attack-free) for 26 consecutive weeks with lanadelumab treatment during Treatment Period A. Non-HAE attack (subset identified in CRF as not reported HAE attack) subset participants were included in this arm.

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Treatment Period B: HAE |
|-----------------------|-------------------------|

Reporting group description:

Lanadelumab 300 mg solution, SC, q2w for 26 weeks or lanadelumab 300 mg solution, SC, q4w for 26 weeks in Treatment Period B if well tolerated (attack-free) for 26 consecutive weeks with lanadelumab treatment during Treatment Period A. HAE attack (subset of AEs identified in CRF as reported HAE attack) subset participants were included in this arm.

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Safety Follow-up Period: Non-HAE |
|-----------------------|----------------------------------|

Reporting group description:

Participants who completed the lanadelumab 300 mg regimen in Treatment Period B returned on Day 378 (for participants who chose to roll over into study TAK-743-5007 [NCT04687137]) or Day 392 as follow-up visit for final assessment in the Safety Follow-up Period. Non-HAE attack (subset identified in CRF as not reported HAE attack) subset participants were included in this arm.

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Safety Follow-up Period: HAE |
|-----------------------|------------------------------|

Reporting group description:

Participants who completed the lanadelumab 300 mg regimen in Treatment Period B returned on Day 378 (for participants who chose to roll over into study TAK-743-5007) or Day 392 as follow-up visit for final assessment in the Safety Follow-up Period. HAE attack (subset of AEs identified in CRF as reported HAE attack) subset participants were included in this arm.

| Serious adverse events                            | Treatment Period A: Non-HAE | Treatment Period A: HAE | Treatment Period B: Non-HAE |
|---------------------------------------------------|-----------------------------|-------------------------|-----------------------------|
| Total subjects affected by serious adverse events |                             |                         |                             |
| subjects affected / exposed                       | 1 / 12 (8.33%)              | 1 / 12 (8.33%)          | 1 / 12 (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      |                |                |                |
| Hereditary angioedema                           |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (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          |
| Psychiatric disorders                           |                |                |                |
| Anxiety disorder                                |                |                |                |
| subjects affected / exposed                     | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (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          |
| Infections and infestations                     |                |                |                |
| Device related infection                        |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                     | Treatment Period B:<br>HAE | Safety Follow-up<br>Period: Non-HAE | Safety Follow-up<br>Period: HAE |
|---------------------------------------------------|----------------------------|-------------------------------------|---------------------------------|
| Total subjects affected by serious adverse events |                            |                                     |                                 |
| subjects affected / exposed                       | 0 / 12 (0.00%)             | 0 / 12 (0.00%)                      | 0 / 12 (0.00%)                  |
| number of deaths (all causes)                     | 0                          | 0                                   | 0                               |
| number of deaths resulting from adverse events    | 0                          | 0                                   | 0                               |
| Congenital, familial and genetic disorders        |                            |                                     |                                 |
| Hereditary angioedema                             |                            |                                     |                                 |
| subjects affected / exposed                       | 0 / 12 (0.00%)             | 0 / 12 (0.00%)                      | 0 / 12 (0.00%)                  |
| occurrences causally related to treatment / all   | 0 / 0                      | 0 / 0                               | 0 / 0                           |
| deaths causally related to treatment / all        | 0 / 0                      | 0 / 0                               | 0 / 0                           |
| Psychiatric disorders                             |                            |                                     |                                 |
| Anxiety disorder                                  |                            |                                     |                                 |
| subjects affected / exposed                       | 0 / 12 (0.00%)             | 0 / 12 (0.00%)                      | 0 / 12 (0.00%)                  |
| occurrences causally related to treatment / all   | 0 / 0                      | 0 / 0                               | 0 / 0                           |
| deaths causally related to treatment / all        | 0 / 0                      | 0 / 0                               | 0 / 0                           |
| Infections and infestations                       |                            |                                     |                                 |
| Device related infection                          |                            |                                     |                                 |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                                   | Treatment Period A:<br>Non-HAE                                                                                      | Treatment Period A:<br>HAE | Treatment Period B:<br>Non-HAE |
|---------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|----------------------------|--------------------------------|
| Total subjects affected by non-serious adverse events               |                                                                                                                     |                            |                                |
| subjects affected / exposed                                         | 10 / 12 (83.33%)                                                                                                    | 7 / 12 (58.33%)            | 9 / 12 (75.00%)                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                                                                                                     |                            |                                |
| Uterine leiomyoma                                                   | Additional description: Number of participants at risk in each arm is based on the female population in this study. |                            |                                |
| subjects affected / exposed <sup>[1]</sup>                          | 0 / 9 (0.00%)                                                                                                       | 0 / 9 (0.00%)              | 1 / 9 (11.11%)                 |
| occurrences (all)                                                   | 0                                                                                                                   | 0                          | 1                              |
| General disorders and administration site conditions                |                                                                                                                     |                            |                                |
| Injection site reaction                                             |                                                                                                                     |                            |                                |
| subjects affected / exposed                                         | 6 / 12 (50.00%)                                                                                                     | 0 / 12 (0.00%)             | 0 / 12 (0.00%)                 |
| occurrences (all)                                                   | 37                                                                                                                  | 0                          | 0                              |
| Injection site erythema                                             |                                                                                                                     |                            |                                |
| subjects affected / exposed                                         | 1 / 12 (8.33%)                                                                                                      | 0 / 12 (0.00%)             | 2 / 12 (16.67%)                |
| occurrences (all)                                                   | 4                                                                                                                   | 0                          | 5                              |
| Injection site pruritus                                             |                                                                                                                     |                            |                                |
| subjects affected / exposed                                         | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%)             | 2 / 12 (16.67%)                |
| occurrences (all)                                                   | 0                                                                                                                   | 0                          | 2                              |
| Pyrexia                                                             |                                                                                                                     |                            |                                |
| subjects affected / exposed                                         | 2 / 12 (16.67%)                                                                                                     | 0 / 12 (0.00%)             | 1 / 12 (8.33%)                 |
| occurrences (all)                                                   | 2                                                                                                                   | 0                          | 1                              |
| Chest pain                                                          |                                                                                                                     |                            |                                |
| subjects affected / exposed                                         | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%)             | 1 / 12 (8.33%)                 |
| occurrences (all)                                                   | 0                                                                                                                   | 0                          | 1                              |
| Infusion site pruritus                                              |                                                                                                                     |                            |                                |
| subjects affected / exposed                                         | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%)             | 1 / 12 (8.33%)                 |
| occurrences (all)                                                   | 0                                                                                                                   | 0                          | 1                              |
| Injection site pain                                                 |                                                                                                                     |                            |                                |

|                                                 |                                                                                                                     |                |                |
|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 12 (8.33%)                                                                                                      | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                               | 1                                                                                                                   | 0              | 0              |
| Injection site swelling                         |                                                                                                                     |                |                |
| subjects affected / exposed                     | 1 / 12 (8.33%)                                                                                                      | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                               | 1                                                                                                                   | 0              | 0              |
| Malaise                                         |                                                                                                                     |                |                |
| subjects affected / exposed                     | 1 / 12 (8.33%)                                                                                                      | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                               | 2                                                                                                                   | 0              | 0              |
| Non-cardiac chest pain                          |                                                                                                                     |                |                |
| subjects affected / exposed                     | 1 / 12 (8.33%)                                                                                                      | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                               | 1                                                                                                                   | 0              | 0              |
| Immune system disorders                         |                                                                                                                     |                |                |
| Allergy to chemicals                            |                                                                                                                     |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all)                               | 0                                                                                                                   | 0              | 1              |
| Anaphylactic shock                              |                                                                                                                     |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all)                               | 0                                                                                                                   | 0              | 1              |
| Contrast media allergy                          |                                                                                                                     |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all)                               | 0                                                                                                                   | 0              | 1              |
| Drug hypersensitivity                           |                                                                                                                     |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all)                               | 0                                                                                                                   | 0              | 1              |
| Reproductive system and breast disorders        |                                                                                                                     |                |                |
| Dysmenorrhoea                                   | Additional description: Number of participants at risk in each arm is based on the female population in this study. |                |                |
| subjects affected / exposed <sup>[2]</sup>      | 0 / 9 (0.00%)                                                                                                       | 0 / 9 (0.00%)  | 1 / 9 (11.11%) |
| occurrences (all)                               | 0                                                                                                                   | 0              | 1              |
| Respiratory, thoracic and mediastinal disorders |                                                                                                                     |                |                |
| Oropharyngeal pain                              |                                                                                                                     |                |                |
| subjects affected / exposed                     | 2 / 12 (16.67%)                                                                                                     | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                               | 2                                                                                                                   | 0              | 0              |
| Psychiatric disorders                           |                                                                                                                     |                |                |
| Anxiety disorder                                |                                                                                                                     |                |                |

|                                                  |                     |                     |                     |
|--------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 1 / 12 (8.33%)<br>1 | 0 / 12 (0.00%)<br>0 | 1 / 12 (8.33%)<br>1 |
| Injury, poisoning and procedural complications   |                     |                     |                     |
| Contusion                                        |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      | 1 / 12 (8.33%)      |
| occurrences (all)                                | 0                   | 0                   | 1                   |
| Fall                                             |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      | 1 / 12 (8.33%)      |
| occurrences (all)                                | 0                   | 0                   | 1                   |
| Heat illness                                     |                     |                     |                     |
| subjects affected / exposed                      | 1 / 12 (8.33%)      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      |
| occurrences (all)                                | 1                   | 0                   | 0                   |
| Procedural pain                                  |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      | 1 / 12 (8.33%)      |
| occurrences (all)                                | 0                   | 0                   | 1                   |
| Skin abrasion                                    |                     |                     |                     |
| subjects affected / exposed                      | 1 / 12 (8.33%)      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      |
| occurrences (all)                                | 1                   | 0                   | 0                   |
| Thermal burn                                     |                     |                     |                     |
| subjects affected / exposed                      | 1 / 12 (8.33%)      | 0 / 12 (0.00%)      | 1 / 12 (8.33%)      |
| occurrences (all)                                | 1                   | 0                   | 1                   |
| Tooth fracture                                   |                     |                     |                     |
| subjects affected / exposed                      | 1 / 12 (8.33%)      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      |
| occurrences (all)                                | 1                   | 0                   | 0                   |
| Congenital, familial and genetic disorders       |                     |                     |                     |
| Hereditary angioedema                            |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 7 / 12 (58.33%)     | 0 / 12 (0.00%)      |
| occurrences (all)                                | 0                   | 92                  | 0                   |
| Cardiac disorders                                |                     |                     |                     |
| Palpitations                                     |                     |                     |                     |
| subjects affected / exposed                      | 1 / 12 (8.33%)      | 0 / 12 (0.00%)      | 1 / 12 (8.33%)      |
| occurrences (all)                                | 12                  | 0                   | 9                   |
| Nervous system disorders                         |                     |                     |                     |
| Headache                                         |                     |                     |                     |
| subjects affected / exposed                      | 2 / 12 (16.67%)     | 0 / 12 (0.00%)      | 2 / 12 (16.67%)     |
| occurrences (all)                                | 8                   | 0                   | 5                   |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| Hypoaesthesia               |                |                |                 |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 1 / 12 (8.33%)  |
| occurrences (all)           | 1              | 0              | 1               |
| Intercostal neuralgia       |                |                |                 |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Ear and labyrinth disorders |                |                |                 |
| Vertigo                     |                |                |                 |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 1 / 12 (8.33%)  |
| occurrences (all)           | 2              | 0              | 1               |
| Gastrointestinal disorders  |                |                |                 |
| Vomiting                    |                |                |                 |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all)           | 1              | 0              | 2               |
| Abdominal pain lower        |                |                |                 |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%)  |
| occurrences (all)           | 0              | 0              | 2               |
| Abdominal pain upper        |                |                |                 |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Constipation                |                |                |                 |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%)  |
| occurrences (all)           | 0              | 0              | 1               |
| Dental caries               |                |                |                 |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%)  |
| occurrences (all)           | 0              | 0              | 1               |
| Diarrhoea                   |                |                |                 |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%)  |
| occurrences (all)           | 0              | 0              | 1               |
| Gingival bleeding           |                |                |                 |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Hyperaesthesia teeth        |                |                |                 |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%)  |
| occurrences (all)           | 0              | 0              | 1               |
| Large intestine polyp       |                |                |                 |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Nausea                                          |                |                |                |
| subjects affected / exposed                     | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all)                               | 10             | 0              | 10             |
| Toothache                                       |                |                |                |
| subjects affected / exposed                     | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Skin and subcutaneous tissue disorders          |                |                |                |
| Alopecia areata                                 |                |                |                |
| subjects affected / exposed                     | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Angioedema                                      |                |                |                |
| subjects affected / exposed                     | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Dermatitis contact                              |                |                |                |
| subjects affected / exposed                     | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Eczema                                          |                |                |                |
| subjects affected / exposed                     | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Eczema asteatotic                               |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Pruritus                                        |                |                |                |
| subjects affected / exposed                     | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Urticaria                                       |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Arthralgia                                      |                |                |                |
| subjects affected / exposed                     | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Back pain                                       |                |                |                |

|                                            |                                                                                                                     |                |                |
|--------------------------------------------|---------------------------------------------------------------------------------------------------------------------|----------------|----------------|
| subjects affected / exposed                | 1 / 12 (8.33%)                                                                                                      | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                          | 1                                                                                                                   | 0              | 0              |
| Neck pain                                  |                                                                                                                     |                |                |
| subjects affected / exposed                | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all)                          | 0                                                                                                                   | 0              | 1              |
| Infections and infestations                |                                                                                                                     |                |                |
| Cystitis                                   |                                                                                                                     |                |                |
| subjects affected / exposed                | 2 / 12 (16.67%)                                                                                                     | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                          | 2                                                                                                                   | 0              | 0              |
| Nasopharyngitis                            |                                                                                                                     |                |                |
| subjects affected / exposed                | 2 / 12 (16.67%)                                                                                                     | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                          | 4                                                                                                                   | 0              | 0              |
| Furuncle                                   |                                                                                                                     |                |                |
| subjects affected / exposed                | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all)                          | 0                                                                                                                   | 0              | 1              |
| Gingivitis                                 |                                                                                                                     |                |                |
| subjects affected / exposed                | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all)                          | 0                                                                                                                   | 0              | 1              |
| Laryngopharyngitis                         |                                                                                                                     |                |                |
| subjects affected / exposed                | 1 / 12 (8.33%)                                                                                                      | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all)                          | 3                                                                                                                   | 0              | 2              |
| Oral herpes                                |                                                                                                                     |                |                |
| subjects affected / exposed                | 1 / 12 (8.33%)                                                                                                      | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                          | 1                                                                                                                   | 0              | 0              |
| Vulvitis                                   | Additional description: Number of participants at risk in each arm is based on the female population in this study. |                |                |
| subjects affected / exposed <sup>[3]</sup> | 0 / 9 (0.00%)                                                                                                       | 0 / 9 (0.00%)  | 1 / 9 (11.11%) |
| occurrences (all)                          | 0                                                                                                                   | 0              | 1              |
| Metabolism and nutrition disorders         |                                                                                                                     |                |                |
| Decreased appetite                         |                                                                                                                     |                |                |
| subjects affected / exposed                | 1 / 12 (8.33%)                                                                                                      | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                          | 1                                                                                                                   | 0              | 0              |
| Dehydration                                |                                                                                                                     |                |                |
| subjects affected / exposed                | 1 / 12 (8.33%)                                                                                                      | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                          | 1                                                                                                                   | 0              | 0              |
| Diabetes mellitus                          |                                                                                                                     |                |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |

| <b>Non-serious adverse events</b>                                   | Treatment Period B:<br>HAE                                                                                          | Safety Follow-up<br>Period: Non-HAE | Safety Follow-up<br>Period: HAE |
|---------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|-------------------------------------|---------------------------------|
| Total subjects affected by non-serious adverse events               |                                                                                                                     |                                     |                                 |
| subjects affected / exposed                                         | 8 / 12 (66.67%)                                                                                                     | 0 / 12 (0.00%)                      | 3 / 12 (25.00%)                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                                                                                                     |                                     |                                 |
| Uterine leiomyoma                                                   | Additional description: Number of participants at risk in each arm is based on the female population in this study. |                                     |                                 |
| subjects affected / exposed <sup>[1]</sup>                          | 0 / 9 (0.00%)                                                                                                       | 0 / 9 (0.00%)                       | 0 / 9 (0.00%)                   |
| occurrences (all)                                                   | 0                                                                                                                   | 0                                   | 0                               |
| General disorders and administration site conditions                |                                                                                                                     |                                     |                                 |
| Injection site reaction                                             |                                                                                                                     |                                     |                                 |
| subjects affected / exposed                                         | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%)                      | 0 / 12 (0.00%)                  |
| occurrences (all)                                                   | 0                                                                                                                   | 0                                   | 0                               |
| Injection site erythema                                             |                                                                                                                     |                                     |                                 |
| subjects affected / exposed                                         | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%)                      | 0 / 12 (0.00%)                  |
| occurrences (all)                                                   | 0                                                                                                                   | 0                                   | 0                               |
| Injection site pruritus                                             |                                                                                                                     |                                     |                                 |
| subjects affected / exposed                                         | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%)                      | 0 / 12 (0.00%)                  |
| occurrences (all)                                                   | 0                                                                                                                   | 0                                   | 0                               |
| Pyrexia                                                             |                                                                                                                     |                                     |                                 |
| subjects affected / exposed                                         | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%)                      | 0 / 12 (0.00%)                  |
| occurrences (all)                                                   | 0                                                                                                                   | 0                                   | 0                               |
| Chest pain                                                          |                                                                                                                     |                                     |                                 |
| subjects affected / exposed                                         | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%)                      | 0 / 12 (0.00%)                  |
| occurrences (all)                                                   | 0                                                                                                                   | 0                                   | 0                               |
| Infusion site pruritus                                              |                                                                                                                     |                                     |                                 |
| subjects affected / exposed                                         | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%)                      | 0 / 12 (0.00%)                  |
| occurrences (all)                                                   | 0                                                                                                                   | 0                                   | 0                               |
| Injection site pain                                                 |                                                                                                                     |                                     |                                 |
| subjects affected / exposed                                         | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%)                      | 0 / 12 (0.00%)                  |
| occurrences (all)                                                   | 0                                                                                                                   | 0                                   | 0                               |
| Injection site swelling                                             |                                                                                                                     |                                     |                                 |
| subjects affected / exposed                                         | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%)                      | 0 / 12 (0.00%)                  |
| occurrences (all)                                                   | 0                                                                                                                   | 0                                   | 0                               |

|                                                                            |                                                                                                                     |                     |                     |
|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|---------------------|---------------------|
| Malaise<br>subjects affected / exposed<br>occurrences (all)                | 0 / 12 (0.00%)<br>0                                                                                                 | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |
| Non-cardiac chest pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0                                                                                                 | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |
| Immune system disorders                                                    |                                                                                                                     |                     |                     |
| Allergy to chemicals<br>subjects affected / exposed<br>occurrences (all)   | 0 / 12 (0.00%)<br>0                                                                                                 | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |
| Anaphylactic shock<br>subjects affected / exposed<br>occurrences (all)     | 0 / 12 (0.00%)<br>0                                                                                                 | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |
| Contrast media allergy<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0                                                                                                 | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |
| Drug hypersensitivity<br>subjects affected / exposed<br>occurrences (all)  | 0 / 12 (0.00%)<br>0                                                                                                 | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |
| Reproductive system and breast disorders                                   |                                                                                                                     |                     |                     |
| Dysmenorrhoea                                                              | Additional description: Number of participants at risk in each arm is based on the female population in this study. |                     |                     |
| subjects affected / exposed <sup>[2]</sup><br>occurrences (all)            | 0 / 9 (0.00%)<br>0                                                                                                  | 0 / 9 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  |
| Respiratory, thoracic and mediastinal disorders                            |                                                                                                                     |                     |                     |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)     | 0 / 12 (0.00%)<br>0                                                                                                 | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |
| Psychiatric disorders                                                      |                                                                                                                     |                     |                     |
| Anxiety disorder<br>subjects affected / exposed<br>occurrences (all)       | 0 / 12 (0.00%)<br>0                                                                                                 | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |
| Injury, poisoning and procedural complications                             |                                                                                                                     |                     |                     |
| Contusion<br>subjects affected / exposed<br>occurrences (all)              | 0 / 12 (0.00%)<br>0                                                                                                 | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |
| Fall                                                                       |                                                                                                                     |                     |                     |

|                                            |                 |                |                 |
|--------------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed                | 0 / 12 (0.00%)  | 0 / 12 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)                          | 0               | 0              | 0               |
| Heat illness                               |                 |                |                 |
| subjects affected / exposed                | 0 / 12 (0.00%)  | 0 / 12 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)                          | 0               | 0              | 0               |
| Procedural pain                            |                 |                |                 |
| subjects affected / exposed                | 0 / 12 (0.00%)  | 0 / 12 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)                          | 0               | 0              | 0               |
| Skin abrasion                              |                 |                |                 |
| subjects affected / exposed                | 0 / 12 (0.00%)  | 0 / 12 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)                          | 0               | 0              | 0               |
| Thermal burn                               |                 |                |                 |
| subjects affected / exposed                | 0 / 12 (0.00%)  | 0 / 12 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)                          | 0               | 0              | 0               |
| Tooth fracture                             |                 |                |                 |
| subjects affected / exposed                | 0 / 12 (0.00%)  | 0 / 12 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)                          | 0               | 0              | 0               |
| Congenital, familial and genetic disorders |                 |                |                 |
| Hereditary angioedema                      |                 |                |                 |
| subjects affected / exposed                | 8 / 12 (66.67%) | 0 / 12 (0.00%) | 3 / 12 (25.00%) |
| occurrences (all)                          | 97              | 0              | 11              |
| Cardiac disorders                          |                 |                |                 |
| Palpitations                               |                 |                |                 |
| subjects affected / exposed                | 0 / 12 (0.00%)  | 0 / 12 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)                          | 0               | 0              | 0               |
| Nervous system disorders                   |                 |                |                 |
| Headache                                   |                 |                |                 |
| subjects affected / exposed                | 0 / 12 (0.00%)  | 0 / 12 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)                          | 0               | 0              | 0               |
| Hypoaesthesia                              |                 |                |                 |
| subjects affected / exposed                | 0 / 12 (0.00%)  | 0 / 12 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)                          | 0               | 0              | 0               |
| Intercostal neuralgia                      |                 |                |                 |
| subjects affected / exposed                | 0 / 12 (0.00%)  | 0 / 12 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)                          | 0               | 0              | 0               |
| Ear and labyrinth disorders                |                 |                |                 |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Vertigo                     |                |                |                |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Gastrointestinal disorders  |                |                |                |
| Vomiting                    |                |                |                |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Abdominal pain lower        |                |                |                |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Abdominal pain upper        |                |                |                |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Constipation                |                |                |                |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Dental caries               |                |                |                |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Diarrhoea                   |                |                |                |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Gingival bleeding           |                |                |                |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Hyperaesthesia teeth        |                |                |                |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Large intestine polyp       |                |                |                |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Nausea                      |                |                |                |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Toothache                   |                |                |                |

|                                                  |                     |                     |                     |
|--------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |
| Skin and subcutaneous tissue disorders           |                     |                     |                     |
| Alopecia areata                                  |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Angioedema                                       |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Dermatitis contact                               |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Eczema                                           |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Eczema asteatotic                                |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Pruritus                                         |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Urticaria                                        |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Musculoskeletal and connective tissue disorders  |                     |                     |                     |
| Arthralgia                                       |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Back pain                                        |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Neck pain                                        |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      | 0 / 12 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Infections and infestations                      |                     |                     |                     |

|                                            |                                                                                                                     |                |                |
|--------------------------------------------|---------------------------------------------------------------------------------------------------------------------|----------------|----------------|
| Cystitis                                   |                                                                                                                     |                |                |
| subjects affected / exposed                | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                          | 0                                                                                                                   | 0              | 0              |
| Nasopharyngitis                            |                                                                                                                     |                |                |
| subjects affected / exposed                | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                          | 0                                                                                                                   | 0              | 0              |
| Furuncle                                   |                                                                                                                     |                |                |
| subjects affected / exposed                | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                          | 0                                                                                                                   | 0              | 0              |
| Gingivitis                                 |                                                                                                                     |                |                |
| subjects affected / exposed                | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                          | 0                                                                                                                   | 0              | 0              |
| Laryngopharyngitis                         |                                                                                                                     |                |                |
| subjects affected / exposed                | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                          | 0                                                                                                                   | 0              | 0              |
| Oral herpes                                |                                                                                                                     |                |                |
| subjects affected / exposed                | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                          | 0                                                                                                                   | 0              | 0              |
| Vulvitis                                   | Additional description: Number of participants at risk in each arm is based on the female population in this study. |                |                |
| subjects affected / exposed <sup>[3]</sup> | 0 / 9 (0.00%)                                                                                                       | 0 / 9 (0.00%)  | 0 / 9 (0.00%)  |
| occurrences (all)                          | 0                                                                                                                   | 0              | 0              |
| Metabolism and nutrition disorders         |                                                                                                                     |                |                |
| Decreased appetite                         |                                                                                                                     |                |                |
| subjects affected / exposed                | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                          | 0                                                                                                                   | 0              | 0              |
| Dehydration                                |                                                                                                                     |                |                |
| subjects affected / exposed                | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                          | 0                                                                                                                   | 0              | 0              |
| Diabetes mellitus                          |                                                                                                                     |                |                |
| subjects affected / exposed                | 0 / 12 (0.00%)                                                                                                      | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                          | 0                                                                                                                   | 0              | 0              |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Number of subjects exposed to this adverse event is based on the female population in this study.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects

exposed for the reporting group. These numbers are expected to be equal.

Justification: Number of subjects exposed to this adverse event is based on the female population in this study.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Number of subjects exposed to this adverse event is based on the female population in this study.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 29 July 2019    | The changes implemented based on Amendment 1 were: -Added the requirement to exclude participants with a known hypersensitivity to the IMP or its components as a new exclusion criterion. -Corrected text regarding the number of days for reporting non-serious AEs that are reported as HAE attacks for consistency.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 05 October 2020 | The changes implemented based on Amendment 2 were: -Revised Sponsor approval -Added that participants may elect to roll over into an expanded access study (Study TAK-743-5007). -Revised interim analysis to include 2 interim analyses: first analysis was to be performed when the first 6 participants enrolled in the study had reached Day 182 or discontinued in Treatment Period A (26 weeks of treatment) and second analysis was to be performed when the first 4 participants enrolled in the study had reached Day 364 or discontinued. -Corrected error that screening visit was also Visit 1. -Corrected error on collection of prior treatment to reflect that prior treatments should be collected prior to screening visit. -Corrected investigator-confirmed HAE attacks to state: 3 or more than 3 investigator-confirmed HAE attacks. -Removed body weight from physical exams at Visit 26 and Visit 27. -Removed pregnancy tests at Visit 26 and Visit 27. -Removed following sentence: Overall attack rates will be estimated using a Poisson general linear model adjusting for run-in period attack rate and accounting for potential overdispersion. -Added 'if applicable' to analysis of efficacy endpoints at 4 efficacy evaluation periods. -Other efficacy endpoints along with statistical methods for their analysis were added. -Added language that subgroup analyses may be performed. -Corrected carbon dioxide to bicarbonate. |

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported