



Clinical trial results:

PROTOCOL RET-D-001: EFFICACY AND SAFETY OF SPARSENTAN (RE-021), A DUAL ENDOTHELIN RECEPTOR AND ANGIOTENSIN RECEPTOR BLOCKER, IN PATIENTS WITH FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS): A RANDOMIZED, DOUBLE-BLIND, ACTIVE-CONTROL, DOSE-ESCALATION STUDY

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-002358-38 |
| Trial protocol | CZ IT BE |
| Global end of trial date | 25 March 2024 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 30 March 2025 |
| First version publication date | 25 September 2024 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set• Addition of final Open-Label Extension data |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | RET-D-001 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01613118 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Travere Therapeutics, Inc. |
| Sponsor organisation address | 3611 Valley Centre Drive, Suite 300, San Diego, United States, 92130 |
| Public contact | Medical Information, Travere Call Center, 001 877.659.5518, medinfo@travere.com |
| Scientific contact | Medical Information, Travere Call Center, 001 877.659.5518, medinfo@travere.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001984-PIP02-20 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No | No |

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 08 May 2024 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 09 June 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 March 2024 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine the change in urine protein/creatinine (Up/C) after 8 weeks of treatment in FSGS patients receiving Sparsentan, a novel dual endothelin receptor and angiotensin receptor blocker, over a range of dose levels (200 mg, 400 mg, and 800 mg) compared to treatment with Irbesartan as active control.

Protection of trial subjects:

Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The Institutional Review Board (IRB) or Independent Ethics Committee (IEC) at each investigational site reviewed and approved the protocol and informed consent form (ICF)/assent form for the study prior to site initiation in accordance with ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

Ethical Conduct of the Study

The study was conducted and monitored in accordance with the individual vendor/contractor procedures and SOPs. All procedures and SOPs comply with the ethical principles of GCP, as required by regulatory authorities, and are in accordance with the Declaration of Helsinki.

Subject Information and Consent

The Investigator was responsible for documenting the consent process within the source documents, and for obtaining consent using an IRB/IEC approved consent form. Subjects and/or their parent/legal guardian signed informed consent/assent at Visit 1 (beginning of the Screening period) prior to undergoing any protocol-related procedures. A signed and dated copy of the consent/assent form(s) was given to the subject.

Background therapy:

None

Evidence for comparator:

While there are currently no approved medicinal products indicated for the treatment of FSGS, an important part of treatment is rigorous blood pressure control using renin-angiotensin-aldosterone system (RAAS) inhibitor therapy (angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin receptor blockers [ARBs]) to target blood pressure values <130/80 mmHg in order to reduce hemodynamic stress and proteinuria and, thereby, slow the progression of renal disease. Randomized, placebo-controlled trials have shown long-term benefit of RAAS inhibitor treatment, which is universally considered to be first-line standard-of-care, as outlined in the KDIGO Clinical Practice Guideline.

| | |
|---|------------------|
| Actual start date of recruitment | 07 March 2014 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 10 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 89 |
| Country: Number of subjects enrolled | Czechia: 4 |
| Country: Number of subjects enrolled | Italy: 16 |
| Worldwide total number of subjects | 109 |
| EEA total number of subjects | 20 |

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) | 6 |
| Adolescents (12-17 years) | 12 |
| Adults (18-64 years) | 85 |
| From 65 to 84 years | 6 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

185 patients screened, 76 excluded, 109 enrolled

Pre-assignment

Screening details:

Screening was performed between 2 to 4 weeks before Washout began. Patients who failed screening for any reason were allowed to re-screen up to two times. In addition to confirming inclusion and exclusion criteria and repeating any necessary assessment, the following procedures were required: blood pressure, S-potassium, eGFR, and urine Up/C.

Period 1

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

Blinding implementation details:

Irbesartan 150 mg tablets were over-encapsulated (blinded) with size 00 gray opaque hard gelatin capsules (Capsugel) and backfilled with Avicel. Patients randomized to the irbesartan active control may also have received placebo capsules, to maintain the blind by keeping the number of capsules taken consistent with that of sparsentan-treated patients in the same cohort. The placebo product used was a size 00 gray opaque capsule (Capsugel) containing microcrystalline cellulose.

Arms

| | |
|------------------------------|-----------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Investigational medicinal product |

Arm description:

Investigational medicinal product

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Sparsentan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The doses to be administered in the double-blind period (200, 400, or 800 mg) were dispensed as 100 mg size 00 sparsentan capsules. In the open-label period, doses were dispensed as either 100 mg (size 00 or 0) sparsentan capsules or as 400 mg scored sparsentan tablets. Patients were instructed to take the appropriate quantity of capsules or tablets for the assigned cohort, orally once daily prior to the morning meal, with the exception of the day of a study visit as the patient took their study medication in the clinic.

| | |
|------------------|----------------|
| Arm title | Active Control |
|------------------|----------------|

Arm description:

Active control

| | |
|--|------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Irbesartan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard + tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The irbesartan doses administered in the study (150 and 300 mg) were supplied as double-blinded

over-encapsulated tablets. Patients were instructed to take the appropriate quantity of capsules or tablets for the assigned cohort, orally once daily prior to the morning meal, with the exception of the day of a study visit as the patient took their study medication in the clinic.

| Number of subjects in period 1 | Investigational medicinal product | Active Control |
|--------------------------------|-----------------------------------|----------------|
| Started | 73 | 36 |
| Completed | 68 | 35 |
| Not completed | 5 | 1 |
| Adverse event, non-fatal | 3 | 1 |
| Discontinued | 1 | - |
| Protocol deviation | 1 | - |

Period 2

| | |
|------------------------------|----------------------|
| Period 2 title | Open-label Extension |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|--|-----------------------------------|
| Arm title | Investigational medicinal product |
| Arm description: | |
| Investigational medicinal product | |
| Arm type | Experimental |
| Investigational medicinal product name | Sparsentan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet, Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

In the open-label period, doses may be dispensed as either 100 mg (size 00 or 0) sparsentan capsules or as 400 mg scored sparsentan tablets. Patients were instructed to take the appropriate quantity of capsules or tablets for the assigned cohort, orally once daily prior to the morning meal, with the exception of the day of a study visit as the patient took their study medication in the clinic.

| Number of subjects in period 2 | Investigational medicinal product |
|--|--|
| Started | 103 |
| Completed | 1 |
| Not completed | 102 |
| Consent withdrawn by subject | 18 |
| Physician decision | 16 |
| Adverse event, non-fatal | 21 |
| Other | 5 |
| Termination by sponsor | 30 |
| Pregnancy | 4 |
| Non-compliance with study intervention | 2 |
| Lost to follow-up | 5 |
| Protocol deviation | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------------------|-----------------------------------|
| Reporting group title | Investigational medicinal product |
| Reporting group description: | |
| Investigational medicinal product | |
| Reporting group title | Active Control |
| Reporting group description: | |
| Active control | |

| Reporting group values | Investigational medicinal product | Active Control | Total |
|---------------------------|-----------------------------------|----------------|-------|
| Number of subjects | 73 | 36 | 109 |
| Age categorical | | | |
| Age (years) at screening | | | |
| Units: Subjects | | | |
| Children (2-11 years) | 4 | 2 | 6 |
| Adolescents (12-17 years) | 7 | 5 | 12 |
| Adults (18-64 years) | 57 | 28 | 85 |
| From 65-84 years | 5 | 1 | 6 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 38 | 34.1 | |
| standard deviation | ± 16.78 | ± 15.96 | - |
| Gender categorical | | | |
| Male or Female | | | |
| Units: Subjects | | | |
| Female | 32 | 17 | 49 |
| Male | 41 | 19 | 60 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 14 | 6 | 20 |
| Not Hispanic or Latino | 59 | 30 | 89 |
| Race | | | |
| Race | | | |
| Units: Subjects | | | |
| Asian | 5 | 1 | 6 |
| Black | 8 | 7 | 15 |
| White | 57 | 26 | 83 |
| Other | 3 | 2 | 5 |
| Weight | | | |
| Weight in kilograms | | | |
| Units: Kilograms | | | |
| arithmetic mean | 81 | 82 | |
| standard deviation | ± 22.48 | ± 22.19 | - |
| Height | | | |
| Height in centimeters | | | |
| Units: centimetre | | | |
| arithmetic mean | 168 | 168 | |

| | | | |
|--------------------|---------|---------|---|
| standard deviation | ± 12.77 | ± 14.22 | - |
| BMI | | | |
| Body Mass Index | | | |
| Units: kg/m2 | | | |
| arithmetic mean | 28 | 29 | |
| standard deviation | ± 6.139 | ± 6.404 | - |

End points

End points reporting groups

| | |
|---|-----------------------------------|
| Reporting group title | Investigational medicinal product |
| Reporting group description: Investigational medicinal product | |
| Reporting group title | Active Control |
| Reporting group description: Active control | |
| Reporting group title | Investigational medicinal product |
| Reporting group description: Investigational medicinal product | |

Primary: Primary endpoint 1

| | |
|---|--------------------|
| End point title | Primary endpoint 1 |
| End point description: Percent change from baseline to Week 8 in urine protein to creatinine ratio in the 200, 400 and 800 mg sparsentan groups combined and the 300 mg irbesartan group | |
| End point type | Primary |
| End point timeframe: baseline to week 8 | |

| End point values | Investigational medicinal product | Active Control | | |
|----------------------------------|-----------------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 64 | 32 | | |
| Units: percent change | | | | |
| number (confidence interval 95%) | | | | |
| week 8 | -44.8 (-52.7 to -35.7) | -18.5 (-34.6 to 1.7) | | |

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Primary Endpoint Chart/Primary Endpoint Chart.pdf |
|-----------------------------------|---|

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Primary endpoint 1 |
| Comparison groups | Investigational medicinal product v Active Control |

| | |
|---|----------------------|
| Number of subjects included in analysis | 96 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| P-value | = 0.006 |
| Method | ANCOVA |

Notes:

[1] - percent change

Primary: Primary endpoint 2

| | |
|--|--------------------|
| End point title | Primary endpoint 2 |
| End point description: Percent change from baseline to Week 8 in urine protein to creatinine ratio in the 400 and 800 mg sparsentan groups combined and 300 mg irbesartan group | |
| End point type | Primary |
| End point timeframe: baseline to week 8 | |

| End point values | Investigational medicinal product | Active Control | | |
|----------------------------------|-----------------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 51 | 25 | | |
| Units: Percent change | | | | |
| number (confidence interval 95%) | | | | |
| Week 8 | -47.4 (-56.3 to -36.9) | -19.0 (-38.0 to 5.9) | | |

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Primary Endpoint Chart/Primary Endpoint Chart.pdf |
|-----------------------------------|---|

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Primary endpoint 2 |
| Comparison groups | Investigational medicinal product v Active Control |
| Number of subjects included in analysis | 76 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| P-value | = 0.011 |
| Method | ANCOVA |

Notes:

[2] - percent change

Primary: Primary endpoint 3

| | |
|--|--------------------|
| End point title | Primary endpoint 3 |
| End point description: Percent change from baseline to Week 8 in urine protein to creatinine ratio in the 400 mg sparsentan group and the 300 mg irbesartan group | |

| | |
|--|---------|
| End point type | Primary |
| End point timeframe: baseline to week 8 | |

| End point values | Investigational medicinal product | Active Control | | |
|----------------------------------|-----------------------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 17 | | |
| Units: percent change | | | | |
| number (confidence interval 95%) | | | | |
| Week 8 | -52.7 (-64.3 to -37.2) | -28.1 (-47.5 to -1.6) | | |

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Primary Endpoint Chart/Primary Endpoint Chart.pdf |
|-----------------------------------|---|

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Primary endpoint 3 |
| Comparison groups | Investigational medicinal product v Active Control |
| Number of subjects included in analysis | 38 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| P-value | = 0.056 |
| Method | ANCOVA |

Notes:

[3] - percent change

Primary: Primary endpoint 4

| | |
|---|--------------------|
| End point title | Primary endpoint 4 |
| End point description: Percent change from baseline to Week 8 in urine protein to creatinine ratio in the 800 mg group and the 300 mg irbesartan group | |
| End point type | Primary |
| End point timeframe: Week 8 | |

| End point values | Investigational medicinal product | Active Control | | |
|----------------------------------|-----------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 8 | | |
| Units: percent change | | | | |
| number (confidence interval 95%) | | | | |

| | | | | |
|--------|------------------------|----------------------|--|--|
| Week 8 | -41.3 (-54.4 to -24.4) | -9.3 (-45.3 to 50.3) | | |
|--------|------------------------|----------------------|--|--|

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Primary Endpoint Chart/Primary Endpoint Chart.pdf |
|-----------------------------------|---|

Statistical analyses

| | |
|-----------------------------------|--------------------|
| Statistical analysis title | Primary endpoint 4 |
|-----------------------------------|--------------------|

Statistical analysis description:

percent change from baseline to week 8

| | |
|---|--|
| Comparison groups | Investigational medicinal product v Active Control |
| Number of subjects included in analysis | 38 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[4] |
| P-value | = 0.127 |
| Method | ANCOVA |
| Parameter estimate | least squares |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| Variability estimate | Standard deviation |

Notes:

[4] - percent change

Primary: Primary endpoint 5

| | |
|-----------------|--------------------|
| End point title | Primary endpoint 5 |
|-----------------|--------------------|

End point description:

Percent change from baseline to Week 8 in urine protein to creatinine ratio in the 200 mg group and the 300 mg irbesartan group

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

End point timeframe:

baseline to week 8

| End point values | Investigational medicinal product | Active Control | | |
|----------------------------------|-----------------------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 7 | | |
| Units: percent change | | | | |
| number (confidence interval 95%) | | | | |
| Week 8 | -33.1 (-49.3 to -11.6) | -15.0 (-41.8 to 24.2) | | |

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Primary Endpoint Chart/Primary Endpoint Chart.pdf |
|-----------------------------------|---|

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Primary endpoint 5 |
| Comparison groups | Active Control v Investigational medicinal product |
| Number of subjects included in analysis | 20 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[5] |
| P-value | = 0.298 |
| Method | ANCOVA |

Notes:

[5] - percent change from baseline

Secondary: Secondary endpoint 1

| | |
|-----------------|----------------------|
| End point title | Secondary endpoint 1 |
|-----------------|----------------------|

End point description:

Percent difference in subjects achieving FSGS Partial Remission Endpoint (FPRE – patients experiencing a UP/C ratio ≤ 1.5 g/g and $>40\%$ reduction from baseline in UP/C) at Week 8 in the 200, 400, and 800 mg sparsentan groups combined vs. the 300 mg irbesartan group

Percentage of subjects achieving FPRE

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

End point timeframe:

Week 8

| End point values | Investigational medicinal product | Active Control | | |
|-----------------------------|-----------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 64 | 32 | | |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Week 8 | 28.13 | 9.38 | | |

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Secondary Endpoint Chart/Secondary Endpoint Chart.pdf |
|-----------------------------------|---|

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Secondary endpoint 1 |
| Statistical analysis description: | |
| Percent difference in subjects achieving FPRE at Week 8 in the 200, 400, and 800 mg sparsentan groups combined vs. the 300 mg irbesartan group | |
| Comparison groups | Investigational medicinal product v Active Control |

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 96 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[6] |
| P-value | = 0.04 |
| Method | Fisher exact |
| Parameter estimate | % Difference (Sparsentan-Irbesartan) |
| Point estimate | 18.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.46 |
| upper limit | 36.04 |

Notes:

[6] - Percent difference (Sparsentan - Irbesartan)

Secondary: Secondary endpoint 2

| | |
|--|----------------------|
| End point title | Secondary endpoint 2 |
| End point description: | |
| Percent difference in subjects achieving FPPE at Week 8 in the 400 and 800 mg sparsentan groups combined vs. the 300 mg irbesartan group | |
| Percentage of subjects achieving FPPE | |
| End point type | Secondary |
| End point timeframe: | |
| Week 8 | |

| End point values | Investigational medicinal product | Active Control | | |
|-----------------------------|-----------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 51 | 25 | | |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Week 8 | 31.37 | 12 | | |

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Secondary Endpoint Chart/Secondary Endpoint Chart.pdf |
|-----------------------------------|---|

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Secondary endpoint 2 |
| Statistical analysis description: | |
| Percent difference in subjects achieving FPPE at Week 8 in the 400 and 800 mg sparsentan groups combined vs. the 300 mg irbesartan group | |
| Percentage Difference (Sparsentan-Irbesartan) | |
| Comparison groups | Investigational medicinal product v Active Control |

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 76 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[7] |
| P-value | = 0.092 |
| Method | Fisher exact |
| Parameter estimate | % Difference (Sparsentan-Irbesartan) |
| Point estimate | 19.37 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.62 |
| upper limit | 40.37 |

Notes:

[7] - Percentage Difference (Sparsentan-Irbesartan)

Secondary: Secondary endpoint 3

| | |
|--|----------------------|
| End point title | Secondary endpoint 3 |
| End point description: | |
| Percent difference in subjects achieving FPPE at Week 8 in the 400 mg sparsentan group vs. the 300 mg irbesartan group | |
| Percentage of subjects achieving FPPE | |
| End point type | Secondary |
| End point timeframe: | |
| Week 8 | |

| End point values | Investigational medicinal product | Active Control | | |
|-----------------------------|-----------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 17 | | |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Week 8 | 38.10 | 17.65 | | |

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Secondary Endpoint Chart/Secondary Endpoint Chart.pdf |
|-----------------------------------|---|

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Secondary endpoint 3 |
| Statistical analysis description: | |
| Percent difference in subjects achieving FPPE at Week 8 in the 400 mg sparsentan groups combined vs. the 300 mg irbesartan group | |
| Percentage Difference (Sparsentan-Irbesartan) | |
| Comparison groups | Investigational medicinal product v Active Control |

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 38 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[8] |
| P-value | = 0.282 |
| Method | Fisher exact |
| Parameter estimate | % Difference (Sparsentan-Irbesartan) |
| Point estimate | 20.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.44 |
| upper limit | 53.33 |

Notes:

[8] - Percentage Difference (Sparsentan-Irbesartan)

Secondary: Secondary endpoint 4

| | |
|---------------------------------------|--|
| End point title | Secondary endpoint 4 |
| End point description: | Percent difference in subjects achieving FPPE at Week 8 in the 800 mg sparsentan group vs. the 300 mg irbesartan group |
| Percentage of subjects achieving FPPE | |
| End point type | Secondary |
| End point timeframe: | Week 8 |

| End point values | Investigational medicinal product | Active Control | | |
|-----------------------------|-----------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 8 | | |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Week 8 | 26.67 | 0 | | |

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Secondary Endpoint Chart/Secondary Endpoint Chart.pdf |
|-----------------------------------|---|

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Secondary endpoint 4 |
| Statistical analysis description: | Percent difference in subjects achieving FPPE at Week 8 in the 800 mg sparsentan groups combined vs. the 300 mg irbesartan group |
| Percentage Difference (Sparsentan-Irbesartan) | |
| Comparison groups | Investigational medicinal product v Active Control |

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 38 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[9] |
| P-value | = 0.164 |
| Method | Fisher exact |
| Parameter estimate | % Difference (Sparsentan-Irbesartan) |
| Point estimate | 26.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.93 |
| upper limit | 50.41 |

Notes:

[9] - Percentage Difference (Sparsentan-Irbesartan)

Secondary: Secondary endpoint 5

| | |
|---------------------------------------|--|
| End point title | Secondary endpoint 5 |
| End point description: | Percent difference in subjects achieving FPPE at Week 8 in the 200 mg sparsentan group vs. the 300 mg irbesartan group |
| Percentage of subjects achieving FPPE | |
| End point type | Secondary |
| End point timeframe: | Week 8 |

| End point values | Investigational medicinal product | Active Control | | |
|-----------------------------|-----------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 7 | | |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Week 8 | 15.38 | 0 | | |

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Secondary Endpoint Chart/Secondary Endpoint Chart.pdf |
|-----------------------------------|---|

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Secondary endpoint 5 |
| Statistical analysis description: | Percent difference in subjects achieving FPPE at Week 8 in the 200 mg sparsentan group vs. the 300 mg irbesartan group |
| Percentage Difference (Sparsentan-Irbesartan) | |
| Comparison groups | Investigational medicinal product v Active Control |

| | |
|---|--------------------------------------|
| Number of subjects included in analysis | 20 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[10] |
| P-value | = 0.521 |
| Method | Fisher exact |
| Parameter estimate | % Difference (Sparsentan-Irbesartan) |
| Point estimate | 15.38 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15.22 |
| upper limit | 45.99 |

Notes:

[10] - Percentage Difference (Sparsentan-Irbesartan)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Period 1 + Period 2

Adverse event reporting additional description:

Included all subjects who were randomized and took at least 1 dose of sparsentan during either the Double Blind Period (those randomized to sparsentan in Period 1) or OLE Period (all subjects who entered the OLE [Period 2]) were included in the All Sparsentan Analysis Set.

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

Dictionary used

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

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|--------------------|------|
| Dictionary version | 27.0 |
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Reporting groups

| | |
|-----------------------|-----------------------------|
| Reporting group title | All Sparsentan Analysis Set |
|-----------------------|-----------------------------|

Reporting group description:

The All Sparsentan Analysis Set was included all subjects who were randomized and took at least 1 dose of sparsentan during either the Double Blind Period (those randomized to sparsentan in Period 1) or OLE Period (all subjects who entered the OLE [Period 2]) were included in the All Sparsentan Analysis Set.

| Serious adverse events | All Sparsentan Analysis Set | | |
|---|-----------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 48 / 108 (44.44%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Angioimmunoblastic T-cell lymphoma | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal cell carcinoma | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |

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|--|-----------------|--|--|
| Deep vein thrombosis | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angiopathy | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertensive urgency | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 4 / 108 (3.70%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oedema | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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|---|-----------------|--|--|
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug withdrawal syndrome | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Generalised oedema | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Endometrial hyperplasia | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Apnoea | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depression | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Glomerular filtration rate decreased | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulse absent | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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|---|-----------------|--|--|
| Jaw fracture | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular pseudoaneurysm | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Conduction disorder | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Supraventricular extrasystolesn | | | |

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|---|-----------------|--|--|
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 3 / 108 (2.78%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Anal fistula | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|------------------|--|--|
| Erosive oesophagitis | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Melaena | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Liver injury | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 10 / 108 (9.26%) | | |
| occurrences causally related to treatment / all | 5 / 11 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Proteinuria | | | |

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|---|-----------------|--|--|
| subjects affected / exposed | 3 / 108 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| End stage renal disease | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subcapsular renal haematoma | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Hyperaldosteronism | | | |

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|---|------------------|--|--|
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Bone infarction | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Flank pain | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteonecrosis | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 10 / 108 (9.26%) | | |
| occurrences causally related to treatment / all | 0 / 11 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 108 (3.70%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abscess limb | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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|---|-----------------|--|--|
| Appendicitis | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hypervolaemia | | | |
| subjects affected / exposed | 3 / 108 (2.78%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 2 / 108 (1.85%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 108 (0.93%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | All Sparsentan Analysis Set | | |
|--|--------------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 104 / 108 (96.30%) | | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 23 / 108 (21.30%) | | |
| occurrences (all) | 38 | | |
| Hypertension | | | |
| subjects affected / exposed | 19 / 108 (17.59%) | | |
| occurrences (all) | 30 | | |
| General disorders and administration site conditions | | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 30 / 108 (27.78%) | | |
| occurrences (all) | 45 | | |
| Pyrexia | | | |
| subjects affected / exposed | 16 / 108 (14.81%) | | |
| occurrences (all) | 19 | | |
| Fatigue | | | |
| subjects affected / exposed | 12 / 108 (11.11%) | | |
| occurrences (all) | 15 | | |
| Chest pain | | | |
| subjects affected / exposed | 10 / 108 (9.26%) | | |
| occurrences (all) | 14 | | |
| Asthenia | | | |
| subjects affected / exposed | 6 / 108 (5.56%) | | |
| occurrences (all) | 8 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 13 / 108 (12.04%) | | |
| occurrences (all) | 18 | | |
| Nasal congestion | | | |
| subjects affected / exposed | 12 / 108 (11.11%) | | |
| occurrences (all) | 17 | | |

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|---|-------------------------|--|--|
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 11 / 108 (10.19%) 18 | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 8 / 108 (7.41%) 8 | | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 11 / 108 (10.19%) 11 | | |
| Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) | 17 / 108 (15.74%) 21 | | |
| Blood creatine increased subjects affected / exposed occurrences (all) | 16 / 108 (14.81%) 23 | | |
| Glomerular filtration rate decreased subjects affected / exposed occurrences (all) | 11 / 108 (10.19%) 15 | | |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 7 / 108 (6.48%) 7 | | |
| N-terminal prohormone brain natriuretic peptide increased subjects affected / exposed occurrences (all) | 6 / 108 (5.56%) 8 | | |
| Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) | 7 / 108 (6.48%) 8 | | |
| Skin laceration subjects affected / exposed occurrences (all) | 6 / 108 (5.56%) 9 | | |
| Nervous system disorders | | | |

| | | | |
|--|-------------------|--|--|
| Headache | | | |
| subjects affected / exposed | 32 / 108 (29.63%) | | |
| occurrences (all) | 43 | | |
| Dizziness | | | |
| subjects affected / exposed | 19 / 108 (17.59%) | | |
| occurrences (all) | 28 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 19 / 108 (17.59%) | | |
| occurrences (all) | 20 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 27 / 108 (25.00%) | | |
| occurrences (all) | 36 | | |
| Nausea | | | |
| subjects affected / exposed | 26 / 108 (24.07%) | | |
| occurrences (all) | 37 | | |
| Vomiting | | | |
| subjects affected / exposed | 19 / 108 (17.59%) | | |
| occurrences (all) | 30 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 7 / 108 (6.48%) | | |
| occurrences (all) | 10 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 6 / 108 (5.56%) | | |
| occurrences (all) | 7 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 6 / 108 (5.56%) | | |
| occurrences (all) | 6 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 7 / 108 (6.48%) | | |
| occurrences (all) | 9 | | |
| Pruritus | | | |
| subjects affected / exposed | 6 / 108 (5.56%) | | |
| occurrences (all) | 6 | | |
| Renal and urinary disorders | | | |

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|---|-------------------------|--|--|
| Acute kidney injury subjects affected / exposed occurrences (all) | 15 / 108 (13.89%) 22 | | |
| Proteinuria subjects affected / exposed occurrences (all) | 15 / 108 (13.89%) 21 | | |
| Renal impairment subjects affected / exposed occurrences (all) | 6 / 108 (5.56%) 7 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 19 / 108 (17.59%) 28 | | |
| Back pain subjects affected / exposed occurrences (all) | 14 / 108 (12.96%) 15 | | |
| Muscle spasms subjects affected / exposed occurrences (all) | 11 / 108 (10.19%) 13 | | |
| Pain in extremity subjects affected / exposed occurrences (all) | 10 / 108 (9.26%) 15 | | |
| Osteoarthritis subjects affected / exposed occurrences (all) | 7 / 108 (6.48%) 8 | | |
| Flank pain subjects affected / exposed occurrences (all) | 6 / 108 (5.56%) 7 | | |
| Myalgia subjects affected / exposed occurrences (all) | 6 / 108 (5.56%) 6 | | |
| Infections and infestations | | | |
| COVID-19 subjects affected / exposed occurrences (all) | 17 / 108 (15.74%) 19 | | |
| Upper respiratory tract infection | | | |

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|------------------------------------|-------------------|--|--|
| subjects affected / exposed | 17 / 108 (15.74%) | | |
| occurrences (all) | 43 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 13 / 108 (12.04%) | | |
| occurrences (all) | 23 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 11 / 108 (10.19%) | | |
| occurrences (all) | 22 | | |
| Influenza | | | |
| subjects affected / exposed | 9 / 108 (8.33%) | | |
| occurrences (all) | 10 | | |
| Sinusitis | | | |
| subjects affected / exposed | 8 / 108 (7.41%) | | |
| occurrences (all) | 11 | | |
| Bronchitis | | | |
| subjects affected / exposed | 7 / 108 (6.48%) | | |
| occurrences (all) | 10 | | |
| Cellulitis | | | |
| subjects affected / exposed | 6 / 108 (5.56%) | | |
| occurrences (all) | 6 | | |
| Pneumonia | | | |
| subjects affected / exposed | 6 / 108 (5.56%) | | |
| occurrences (all) | 6 | | |
| Metabolism and nutrition disorders | | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 22 / 108 (20.37%) | | |
| occurrences (all) | 41 | | |
| Gout | | | |
| subjects affected / exposed | 15 / 108 (13.89%) | | |
| occurrences (all) | 29 | | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 10 / 108 (9.26%) | | |
| occurrences (all) | 12 | | |
| Dehydration | | | |
| subjects affected / exposed | 6 / 108 (5.56%) | | |
| occurrences (all) | 7 | | |

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|--|----------------------|--|--|
| Vitamin D deficiency subjects affected / exposed occurrences (all) | 6 / 108 (5.56%) 6 | | |
|--|----------------------|--|--|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--------------|
| 30 July 2012 | Amendment 1 |
| 11 July 2013 | Amendment 2 |
| 20 September 2013 | Amendment 3 |
| 25 November 2013 | Amendment 4 |
| 21 May 2014 | Amendment 5 |
| 22 December 2014 | Amendment 6 |
| 05 December 2016 | Amendment 7 |
| 20 December 2017 | Amendment 8 |
| 24 October 2018 | Amendment 9 |
| 25 July 2019 | Amendment 10 |
| 27 February 2020 | Amendment 11 |
| 01 November 2021 | Amendment 12 |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported