



## Clinical trial results:

### MOSAIC - A Phase 2b, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study Evaluating the Efficacy and Safety of Selonsertib in Subjects with Moderate to Advanced Diabetic Kidney Disease

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2018-003951-39    |
| Trial protocol           | GB ES IT          |
| Global end of trial date | 03 September 2021 |

#### Results information

|                                |                                                                                                                                                         |
|--------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| Result version number          | v3 (current)                                                                                                                                            |
| This version publication date  | 15 December 2022                                                                                                                                        |
| First version publication date | 16 September 2022                                                                                                                                       |
| Version creation reason        | <ul style="list-style-type: none"><li>• Correction of full data set</li><li>Update to Ethnicity data in the baseline characteristics section.</li></ul> |

#### Trial information

##### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | GS-US-223-1017 |
|-----------------------|----------------|

##### Additional study identifiers

|                                    |                                                          |
|------------------------------------|----------------------------------------------------------|
| ISRCTN number                      | -                                                        |
| ClinicalTrials.gov id (NCT number) | NCT04026165                                              |
| WHO universal trial number (UTN)   | -                                                        |
| Other trial identifiers            | Japan Pharmaceutical Information Center: JapicCTI-194911 |

Notes:

#### Sponsors

|                              |                                                                                            |
|------------------------------|--------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Gilead Sciences                                                                            |
| Sponsor organisation address | 333 Lakeside Drive, Foster City, CA, United States, 94404                                  |
| Public contact               | Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com |
| Scientific contact           | Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|                                                      |                   |
|------------------------------------------------------|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 03 September 2021 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 03 September 2021 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 03 September 2021 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate whether selonsertib (SEL) can slow the decline in kidney function in participants with moderate to advanced diabetic kidney disease (DKD).

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements. This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 24 July 2019 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Australia: 6       |
| Country: Number of subjects enrolled | Canada: 32         |
| Country: Number of subjects enrolled | Japan: 79          |
| Country: Number of subjects enrolled | New Zealand: 16    |
| Country: Number of subjects enrolled | United States: 251 |
| Worldwide total number of subjects   | 384                |
| 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          | 0 |

|                           |     |
|---------------------------|-----|
| months)                   |     |
| Children (2-11 years)     | 0   |
| Adolescents (12-17 years) | 0   |
| Adults (18-64 years)      | 155 |
| From 65 to 84 years       | 229 |
| 85 years and over         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States, Japan, Canada, New Zealand, and Australia.

### Pre-assignment

Screening details:

961 participants were screened.

### Period 1

|                              |                       |
|------------------------------|-----------------------|
| Period 1 title               | Run-in Placebo Period |
| Is this the baseline period? | No                    |
| Allocation method            | Not applicable        |
| Blinding used                | Not blinded           |

### Arms

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

Arm description:

Participants received placebo to match selonsertib (SEL) tablet orally once daily for at least one week.

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Placebo            |
| Investigational medicinal product name | Placebo            |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Placebo to match SEL administered once daily for at least one week

| Number of subjects in period 1             | Run-in Placebo |
|--------------------------------------------|----------------|
| Started                                    | 384            |
| Completed                                  | 362            |
| Not completed                              | 22             |
| Withdrew Consent                           | 2              |
| Enrollment Error                           | 13             |
| Significant Non-compliance with Study Drug | 1              |
| Protocol Violation                         | 2              |
| Run-in Failure                             | 4              |

**Period 2**

|                              |                   |
|------------------------------|-------------------|
| Period 2 title               | Run-in SEL Period |
| Is this the baseline period? | No                |
| Allocation method            | Not applicable    |
| Blinding used                | Not blinded       |

**Arms**

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Run-in SEL 18 mg |
|------------------|------------------|

Arm description:

Participants received SEL 18 mg tablet orally once daily for at least 4 weeks.

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | SEL                |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

18 mg administered once daily

| <b>Number of subjects in period 2<sup>[1]</sup></b> | Run-in SEL 18 mg |
|-----------------------------------------------------|------------------|
| Started                                             | 357              |
| Completed                                           | 311              |
| Not completed                                       | 46               |
| Withdrew Consent                                    | 10               |
| Enrollment Error                                    | 4                |
| Death                                               | 1                |
| Investigator's Discretion                           | 2                |
| Protocol Violation                                  | 3                |
| Run-in Failure                                      | 26               |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Five participants discontinued the study after completing the Run-in Placebo (Period 1) and didn't enter the Run-in SEL period (Period 2).

**Period 3**

|                              |                         |
|------------------------------|-------------------------|
| Period 3 title               | Randomised Period       |
| Is this the baseline period? | Yes <sup>[2]</sup>      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Double blind            |
| Roles blinded                | Subject, Investigator   |

**Arms**

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

|                                                                                                                                                                                                  |                      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| <b>Arm title</b>                                                                                                                                                                                 | Randomised SEL 18 mg |
| Arm description:                                                                                                                                                                                 |                      |
| Participants received SEL 18 mg tablet orally once daily for at least 4 weeks in the Run-in period, were then randomised, and received SEL 18 mg tablet orally once daily for at least 48 weeks. |                      |
| Arm type                                                                                                                                                                                         | Experimental         |
| Investigational medicinal product name                                                                                                                                                           | SEL                  |
| Investigational medicinal product code                                                                                                                                                           |                      |
| Other name                                                                                                                                                                                       |                      |
| Pharmaceutical forms                                                                                                                                                                             | Film-coated tablet   |
| Routes of administration                                                                                                                                                                         | Oral use             |
| Dosage and administration details:                                                                                                                                                               |                      |
| 18 mg administered once daily                                                                                                                                                                    |                      |

|                                                                                                                                                                                                             |                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| <b>Arm title</b>                                                                                                                                                                                            | Randomised Placebo |
| Arm description:                                                                                                                                                                                            |                    |
| Participants received SEL 18 mg tablet orally once daily for at least 4 weeks in the Run-in period, were then randomised, and received placebo-to-match SEL tablet orally once daily for at least 48 weeks. |                    |
| Arm type                                                                                                                                                                                                    | Placebo            |
| Investigational medicinal product name                                                                                                                                                                      | Placebo            |
| Investigational medicinal product code                                                                                                                                                                      |                    |
| Other name                                                                                                                                                                                                  |                    |
| Pharmaceutical forms                                                                                                                                                                                        | Film-coated tablet |
| Routes of administration                                                                                                                                                                                    | Oral use           |
| Dosage and administration details:                                                                                                                                                                          |                    |
| Placebo to match SEL was administered once daily                                                                                                                                                            |                    |

Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The baseline characteristics were measured in Period 1. However, baseline characteristics are presented for the Safety analysis set (n=667) by Randomisation status and Randomised treatment group. Therefore, period 3 was selected as the Baseline period due to system constraints so the treatment groups are correctly populated in the system.

| <b>Number of subjects in period 3<sup>[3]</sup>[4]</b> | Randomised SEL 18 mg | Randomised Placebo |
|--------------------------------------------------------|----------------------|--------------------|
| Started                                                | 154                  | 156                |
| Completed                                              | 140                  | 137                |
| Not completed                                          | 14                   | 19                 |
| Withdrew Consent                                       | 5                    | 8                  |
| Death                                                  | 5                    | 7                  |
| Lost to Follow-up                                      | 2                    | 2                  |
| Investigator's Discretion                              | 2                    | 2                  |

Notes:

[3] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics were reported for the Safety Analysis Set only, which included participants who received at least one dose of Run-in SEL.

[4] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Following the Run-in period, eligible participants were randomised to receive either SEL (18 mg) or placebo.

## Baseline characteristics

### Reporting groups

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Randomised SEL 18 mg |
|-----------------------|----------------------|

Reporting group description:

Participants received SEL 18 mg tablet orally once daily for at least 4 weeks in the Run-in period, were then randomised, and received SEL 18 mg tablet orally once daily for at least 48 weeks.

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

Reporting group description:

Participants received SEL 18 mg tablet orally once daily for at least 4 weeks in the Run-in period, were then randomised, and received placebo-to-match SEL tablet orally once daily for at least 48 weeks.

| Reporting group values             | Randomised SEL 18 mg | Randomised Placebo | Total |
|------------------------------------|----------------------|--------------------|-------|
| Number of subjects                 | 154                  | 156                | 310   |
| Age categorical<br>Units: Subjects |                      |                    |       |

|                                                                         |             |             |     |
|-------------------------------------------------------------------------|-------------|-------------|-----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 65<br>± 9.3 | 66<br>± 8.8 | -   |
| Gender categorical<br>Units: Subjects                                   |             |             |     |
| Female                                                                  | 48          | 51          | 99  |
| Male                                                                    | 106         | 105         | 211 |
| Race<br>Units: Subjects                                                 |             |             |     |
| American Indian or Alaska Native                                        | 2           | 0           | 2   |
| Asian                                                                   | 41          | 44          | 85  |
| Black or African American                                               | 26          | 22          | 48  |
| Native Hawaiian or Pacific Islander                                     | 5           | 4           | 9   |
| White                                                                   | 78          | 84          | 162 |
| Other                                                                   | 2           | 2           | 4   |
| Ethnicity<br>Units: Subjects                                            |             |             |     |
| Not Hispanic or Latino                                                  | 132         | 136         | 268 |
| Hispanic or Latino                                                      | 21          | 19          | 40  |
| Unknown or Not Reported                                                 | 1           | 1           | 2   |

### Subject analysis sets

|                            |                                  |
|----------------------------|----------------------------------|
| Subject analysis set title | Run-in SEL 18 mg, Not Randomised |
|----------------------------|----------------------------------|

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

Subject analysis set description:

The analysis set included all participants who took at least 1 dose of Run-in SEL and were not randomised.

|                                                                         |                                     |  |  |
|-------------------------------------------------------------------------|-------------------------------------|--|--|
| <b>Reporting group values</b>                                           | Run-in SEL 18 mg,<br>Not Randomised |  |  |
| Number of subjects                                                      | 47                                  |  |  |
| Age categorical<br>Units: Subjects                                      |                                     |  |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 65<br>± 9.7                         |  |  |
| Gender categorical<br>Units: Subjects                                   |                                     |  |  |
| Female                                                                  | 12                                  |  |  |
| Male                                                                    | 35                                  |  |  |
| Race<br>Units: Subjects                                                 |                                     |  |  |
| American Indian or Alaska Native                                        | 0                                   |  |  |
| Asian                                                                   | 4                                   |  |  |
| Black or African American                                               | 4                                   |  |  |
| Native Hawaiian or Pacific Islander                                     | 1                                   |  |  |
| White                                                                   | 36                                  |  |  |
| Other                                                                   | 2                                   |  |  |
| Ethnicity<br>Units: Subjects                                            |                                     |  |  |
| Not Hispanic or Latino                                                  | 39                                  |  |  |
| Hispanic or Latino                                                      | 8                                   |  |  |
| Unknown or Not Reported                                                 |                                     |  |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                             |                                  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| Reporting group title                                                                                                                                                                                                                       | Run-in Placebo                   |
| Reporting group description:<br>Participants received placebo to match selonsertib (SEL) tablet orally once daily for at least one week.                                                                                                    |                                  |
| Reporting group title                                                                                                                                                                                                                       | Run-in SEL 18 mg                 |
| Reporting group description:<br>Participants received SEL 18 mg tablet orally once daily for at least 4 weeks.                                                                                                                              |                                  |
| Reporting group title                                                                                                                                                                                                                       | Randomised SEL 18 mg             |
| Reporting group description:<br>Participants received SEL 18 mg tablet orally once daily for at least 4 weeks in the Run-in period, were then randomised, and received SEL 18 mg tablet orally once daily for at least 48 weeks.            |                                  |
| Reporting group title                                                                                                                                                                                                                       | Randomised Placebo               |
| Reporting group description:<br>Participants received SEL 18 mg tablet orally once daily for at least 4 weeks in the Run-in period, were then randomised, and received placebo-to-match SEL tablet orally once daily for at least 48 weeks. |                                  |
| Subject analysis set title                                                                                                                                                                                                                  | Run-in SEL 18 mg, Not Randomised |
| Subject analysis set type                                                                                                                                                                                                                   | Safety analysis                  |
| Subject analysis set description:<br>The analysis set included all participants who took at least 1 dose of Run-in SEL and were not randomised.                                                                                             |                                  |

### Primary: Treatment-specific Baseline Estimated Glomerular Filtration Rate Based on Creatinine (eGFRcr)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                              |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Treatment-specific Baseline Estimated Glomerular Filtration Rate Based on Creatinine (eGFRcr) <sup>[1]</sup> |
| End point description:<br>The values of eGFRcr were calculated using the Chronic Kidney Disease Epidemiology (CKD-EPI) Creatinine Equation (2009). $eGFRcr = 141 \cdot \min(\text{Standardized Serum Creatinine (Scr)}/\kappa, 1)^{\alpha} \cdot \max(\text{Scr}/\kappa, 1)^{-1.209} \cdot 0.993^{\text{Age}} \cdot 1.018[\text{if female}] \cdot 1.159[\text{if Black}]$ , where $\kappa=0.7(\text{females})$ or $0.9(\text{males})$ , $\alpha=-0.329(\text{females})$ or $-0.411(\text{males})$ . min indicates the minimum of Scr/ $\kappa$ or 1, max indicates the maximum of Scr/ $\kappa$ or 1, and age is in years. Treatment-specific Baselines = the average of Visits A and B values for Placebo, and the average of Visit C and Day 1 values for SEL. Visit A= enrollment, Visit B= 7-14 days after Visit A, Visit C= 21-28 days after Visit B, and Visit 1= 7-14 days after Visit C. The Full Analysis Set included all participants who were randomised in the study, and received at least one dose of study drug in the Randomisation Phase. |                                                                                                              |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Primary                                                                                                      |
| End point timeframe:<br>Treatment-specific Baselines (From enrollment (Visit A) up to 14 days after Visit A for placebo and from Visit C up to 14 days after Visit C for SEL)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                              |
| Notes:<br>[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.<br>Justification: No statistical analyses was planned for this endpoint.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                              |

| End point values                     | Randomised SEL 18 mg | Randomised Placebo |  |  |
|--------------------------------------|----------------------|--------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group    |  |  |
| Number of subjects analysed          | 154                  | 156                |  |  |
| Units: mL/min/1.73m <sup>2</sup>     |                      |                    |  |  |
| arithmetic mean (standard deviation) | 32.7 (± 10.59)       | 34.9 (± 10.81)     |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: eGFRcr Slope

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | eGFRcr Slope |
| End point description:<br>The values of eGFRcr were calculated using the CKD-EPI Creatinine Equation (2009). $eGFRcr = 141 * \min(Scr/kappa, 1)^\alpha * \max(Scr/kappa, 1)^{-1.209} * 0.993^{Age} * 1.018[\text{if female}] * 1.159[\text{if Black}]$ , where $kappa=0.7(\text{females})$ or $0.9(\text{males})$ , $\alpha=-0.329(\text{females})$ or $-0.411(\text{males})$ . min indicates the minimum of Scr/kappa or 1, max indicates the maximum of Scr/kappa or 1, and age is in years. Treatment specific baselines for eGFRcr: average of Visit A (enrollment) and Visit B (7-14 days after Visit A) values for Placebo, and average of Visit C (21-28 days after Visit B, and Visit 1 (7-14 days after Visit C) values for SEL. Participants in the Full Analysis Set with available data were analysed. |              |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Primary      |
| End point timeframe:<br>Treatment-specific Baselines through Week 84                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |              |

| End point values                       | Randomised SEL 18 mg | Randomised Placebo |  |  |
|----------------------------------------|----------------------|--------------------|--|--|
| Subject group type                     | Reporting group      | Reporting group    |  |  |
| Number of subjects analysed            | 153                  | 156                |  |  |
| Units: mL/min/1.73m <sup>2</sup> /year |                      |                    |  |  |
| least squares mean (standard error)    | -2.29 (± 0.58)       | -3.49 (± 0.58)     |  |  |

## Statistical analyses

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                           |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Randomised SEL 18 mg, Randomised Placebo  |
| Statistical analysis description:<br>Estimates were from a random slope model with change in eGFRcr from treatment-specific Baselines at Weeks 4, 8, 12, 24, 36, 48, 60, 72, and 84 as outcome, including terms for treatment-specific Baseline eGFRcr, pre-run-in urine albumin to creatinine ratio (UACR) category (< 1500 mg/g vs. ≥ 1500 mg/g), concomitant use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors at Randomisation, treatment group, week, and treatment-by-week interaction, where week has a random effect. |                                           |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Randomised SEL 18 mg v Randomised Placebo |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 309                                       |
| Analysis specification                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Pre-specified                             |
| Analysis type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | superiority                               |
| P-value                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | = 0.1439                                  |
| Method                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Random Slope Model                        |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Difference in Adjusted Mean               |
| Point estimate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 1.2                                       |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -0.41                      |
| upper limit          | 2.81                       |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.82                       |

## Secondary: Percentage of Participants with Kidney Clinical Events at Week 48

|                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                        | Percentage of Participants with Kidney Clinical Events at Week 48 |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                   |
| Kidney clinical events were defined as any of the following events: confirmed $\geq 40\%$ decline in eGFRcr from baseline, or kidney failure (dialysis performed for at least 4 weeks, kidney transplantation, or confirmed decrease in eGFRcr to $< 15$ mL/min/1.73 m <sup>2</sup> for participants without dialysis or kidney transplantation), or death due to kidney disease. Participants in the Full Analysis Set were analysed. |                                                                   |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                         | Secondary                                                         |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                   |
| Week 48                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                   |

| End point values                  | Randomised<br>SEL 18 mg | Randomised<br>Placebo |  |  |
|-----------------------------------|-------------------------|-----------------------|--|--|
| Subject group type                | Reporting group         | Reporting group       |  |  |
| Number of subjects analysed       | 154                     | 156                   |  |  |
| Units: percentage of participants |                         |                       |  |  |
| number (not applicable)           | 9.1                     | 9.0                   |  |  |

## Statistical analyses

|                                                                                                                              |                                           |
|------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| Statistical analysis title                                                                                                   | Randomised SEL 18 mg, Randomised Placebo  |
| Statistical analysis description:                                                                                            |                                           |
| 95% exact CI based on the Santner-Snell method was presented for the difference in proportions between SEL and placebo arms. |                                           |
| Comparison groups                                                                                                            | Randomised SEL 18 mg v Randomised Placebo |
| Number of subjects included in analysis                                                                                      | 310                                       |
| Analysis specification                                                                                                       | Pre-specified                             |
| Analysis type                                                                                                                | superiority                               |
| P-value                                                                                                                      | = 0.8353 <sup>[2]</sup>                   |
| Method                                                                                                                       | Cochran-Mantel-Haenszel                   |
| Parameter estimate                                                                                                           | Difference in Percentage                  |
| Point estimate                                                                                                               | 0.1                                       |
| Confidence interval                                                                                                          |                                           |
| level                                                                                                                        | 95 %                                      |
| sides                                                                                                                        | 2-sided                                   |
| lower limit                                                                                                                  | -10.9                                     |
| upper limit                                                                                                                  | 11.4                                      |

Notes:

[2] - p-value was based on Cochran-Mantel-Haenszel test stratified by Randomisation stratification factors. Randomisation stratification factors= pre-run-in eGFRcr stratum, pre-run-in UACR category and concomitant use of SGLT-2 inhibitors at Randomisation.

## Secondary: Time From Randomization to First Occurrence of a Kidney Clinical Event: Event Rate Per 100 Participant-years for First Occurrence of Kidney Clinical Event

|                 |                                                                                                                                                            |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Time From Randomization to First Occurrence of a Kidney Clinical Event: Event Rate Per 100 Participant-years for First Occurrence of Kidney Clinical Event |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Kidney clinical events were defined as any of the following events: confirmed  $\geq 40\%$  decline in eGFRcr from baseline, or kidney failure (dialysis performed for at least 4 weeks, kidney transplantation, or confirmed decrease in eGFRcr to  $< 15$  mL/min/1.73 m<sup>2</sup> for participants without dialysis or kidney transplantation), or death due to kidney disease. This outcome measure was analyzed using event rate per 100 participant-years for first occurrence of kidney clinical event. Participant year was calculated as total follow-up duration across all participants in a given group. Follow-up duration was defined as time from Randomization to the earliest of study completion, premature study discontinuation, death, or event of interest in each row. Participants in the Full Analysis Set were analysed.

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

End point timeframe:

From randomisation up to Week 101

| End point values                        | Randomised<br>SEL 18 mg | Randomised<br>Placebo |  |  |
|-----------------------------------------|-------------------------|-----------------------|--|--|
| Subject group type                      | Reporting group         | Reporting group       |  |  |
| Number of subjects analysed             | 154                     | 156                   |  |  |
| Units: events per 100 participant-years |                         |                       |  |  |
| number (not applicable)                 | 13.4                    | 9.8                   |  |  |

## Statistical analyses

|                            |                                          |
|----------------------------|------------------------------------------|
| Statistical analysis title | Randomised SEL 18 mg, Randomised Placebo |
|----------------------------|------------------------------------------|

Statistical analysis description:

Hazard ratio and 95% CI were estimated using a stratified Cox proportional hazard model, stratified by randomisation stratification factors and were reported only for outcomes with more than 10 events, and have at least 1 event in each treatment arm.

|                                         |                                           |
|-----------------------------------------|-------------------------------------------|
| Comparison groups                       | Randomised SEL 18 mg v Randomised Placebo |
| Number of subjects included in analysis | 310                                       |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | superiority                               |
| P-value                                 | = 0.201 <sup>[3]</sup>                    |
| Method                                  | Stratified Log-Rank                       |
| Parameter estimate                      | Hazard ratio (HR)                         |
| Point estimate                          | 1.48                                      |
| Confidence interval                     |                                           |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | 0.81                                      |
| upper limit                             | 2.72                                      |

Notes:

[3] - P-value was calculated using a stratified log-rank test, stratified by randomisation stratification factors.

### Secondary: Pre-run-in Baseline Estimated Glomerular Filtration Rate Based on Cystatin C (eGFRcys)

|                 |                                                                                        |
|-----------------|----------------------------------------------------------------------------------------|
| End point title | Pre-run-in Baseline Estimated Glomerular Filtration Rate Based on Cystatin C (eGFRcys) |
|-----------------|----------------------------------------------------------------------------------------|

End point description:

eGFRcys = Estimated Glomerular Filtration Rate calculated by CKD-EPI Cystatin C Equation (2012).  
$$eGFR = 133 * \min(\text{Standardized Serum Cystatin (Scys)}/0.8, 1) ^{(-0.499)} * \max(\text{Scys}/0.8, 1) ^{(-1.328)} * 0.996^{\text{Age}} * 0.932[\text{if female}]$$
. min indicates the minimum of Scys/0.8 or 1, max indicates the maximum of Scr/0.8 or 1, and age is in years. Participants in the Full Analysis Set were analysed.

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

End point timeframe:

Pre-run-in Baseline (Pre-run in Baseline = Average of visit A (Enrollment) and Visit B (7-14 days after Visit A) eGFRcys values)

| End point values                     | Randomised<br>SEL 18 mg | Randomised<br>Placebo |  |  |
|--------------------------------------|-------------------------|-----------------------|--|--|
| Subject group type                   | Reporting group         | Reporting group       |  |  |
| Number of subjects analysed          | 154                     | 156                   |  |  |
| Units: mL/min/1.73m <sup>2</sup>     |                         |                       |  |  |
| arithmetic mean (standard deviation) | 33.6 (± 11.81)          | 32.4 (± 10.94)        |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: eGFRcys Slope

|                 |               |
|-----------------|---------------|
| End point title | eGFRcys Slope |
|-----------------|---------------|

End point description:

eGFRcys = Estimated Glomerular Filtration Rate calculated by CKD-EPI Cystatin C Equation (2012).  
$$eGFR = 133 * \min(\text{Scys}/0.8, 1) ^{(-0.499)} * \max(\text{Scys}/0.8, 1) ^{(-1.328)} * 0.996^{\text{Age}} * 0.932[\text{if female}]$$
. min indicates the minimum of Scys/0.8 or 1, max indicates the maximum of Scr/0.8 or 1, and age is in years. Pre-run in Baseline = Average of Visit A (Enrollment) and Visit B (7-14 days after Visit A) eGFRcys values. Participants in the Full Analysis Set with available data were analysed.

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

End point timeframe:

Pre-run-in Baseline through Week 84

| End point values                       | Randomised<br>SEL 18 mg | Randomised<br>Placebo |  |  |
|----------------------------------------|-------------------------|-----------------------|--|--|
| Subject group type                     | Reporting group         | Reporting group       |  |  |
| Number of subjects analysed            | 153                     | 156                   |  |  |
| Units: mL/min/1.73m <sup>2</sup> /year |                         |                       |  |  |
| least squares mean (standard error)    | -3.79 (± 0.51)          | -4.23 (± 0.51)        |  |  |

## Statistical analyses

| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                                                            | Randomised SEL 18 mg, Randomised Placebo  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                                                                                                     |                                           |
| Estimates were from a random slope model with change in eGFR <sub>cys</sub> from pre-run-in Baseline at Weeks 4, 8, 12, 24, 36, 48, 60, 72, and 84 as outcome, including terms for pre-run-in Baseline eGFR <sub>cys</sub> , pre-run-in UACR category (< 1500 mg/g vs. ≥ 1500 mg/g), concomitant use of SGLT-2 inhibitors at Randomisation, treatment group, week, and treatment-by-week interaction, where week has a random effect. |                                           |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                     | Randomised SEL 18 mg v Randomised Placebo |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                                                                                               | 309                                       |
| Analysis specification                                                                                                                                                                                                                                                                                                                                                                                                                | Pre-specified                             |
| Analysis type                                                                                                                                                                                                                                                                                                                                                                                                                         | superiority                               |
| P-value                                                                                                                                                                                                                                                                                                                                                                                                                               | = 0.5399                                  |
| Method                                                                                                                                                                                                                                                                                                                                                                                                                                | Random Slope Model                        |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                                                                                                    | Difference in Adjusted Mean               |
| Point estimate                                                                                                                                                                                                                                                                                                                                                                                                                        | 0.44                                      |
| Confidence interval                                                                                                                                                                                                                                                                                                                                                                                                                   |                                           |
| level                                                                                                                                                                                                                                                                                                                                                                                                                                 | 95 %                                      |
| sides                                                                                                                                                                                                                                                                                                                                                                                                                                 | 2-sided                                   |
| lower limit                                                                                                                                                                                                                                                                                                                                                                                                                           | -0.97                                     |
| upper limit                                                                                                                                                                                                                                                                                                                                                                                                                           | 1.86                                      |
| Variability estimate                                                                                                                                                                                                                                                                                                                                                                                                                  | Standard error of the mean                |
| Dispersion value                                                                                                                                                                                                                                                                                                                                                                                                                      | 0.72                                      |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All-Cause Mortality: Enrollment up to maximum duration of 107.1 weeks; Adverse Events: First dose in Run-in

SEL phase up to last dose (maximum: 101 weeks) plus 30 days

Adverse event reporting additional description:

All-Cause Mortality: The All Enrolled Analysis Set included all participants who were enrolled in the study. There were no deaths in the Run-in Placebo period.

Adverse Events: The Safety Analysis Set included all participants who took at least 1 dose of Run-in SEL.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 24.1   |

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Run-in SEL 18 mg |
|-----------------------|------------------|

Reporting group description:

Participants received SEL 18 mg tablet orally once daily for at least 4 weeks.

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

Reporting group description:

Participants received placebo-to-match SEL tablet orally once daily for at least 48 weeks after randomisation.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Randomised SEL 18 mg |
|-----------------------|----------------------|

Reporting group description:

Participants received SEL 18 mg tablet orally once daily for at least 48 weeks after randomisation.

| Serious adverse events                                              | Run-in SEL 18 mg | Randomised Placebo | Randomised SEL 18 mg |
|---------------------------------------------------------------------|------------------|--------------------|----------------------|
| Total subjects affected by serious adverse events                   |                  |                    |                      |
| subjects affected / exposed                                         | 16 / 357 (4.48%) | 45 / 156 (28.85%)  | 45 / 154 (29.22%)    |
| number of deaths (all causes)                                       | 1                | 7                  | 5                    |
| number of deaths resulting from adverse events                      |                  |                    |                      |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                    |                      |
| Bladder cancer                                                      |                  |                    |                      |
| subjects affected / exposed                                         | 0 / 357 (0.00%)  | 0 / 156 (0.00%)    | 2 / 154 (1.30%)      |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 0              | 0 / 2                |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0              | 0 / 0                |
| Hepatic cancer metastatic                                           |                  |                    |                      |
| subjects affected / exposed                                         | 0 / 357 (0.00%)  | 0 / 156 (0.00%)    | 1 / 154 (0.65%)      |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 0              | 0 / 1                |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0              | 0 / 1                |

|                                                      |                 |                 |                 |
|------------------------------------------------------|-----------------|-----------------|-----------------|
| Lipoma                                               |                 |                 |                 |
| subjects affected / exposed                          | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Meningioma                                           |                 |                 |                 |
| subjects affected / exposed                          | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Vascular disorders                                   |                 |                 |                 |
| Orthostatic hypotension                              |                 |                 |                 |
| subjects affected / exposed                          | 0 / 357 (0.00%) | 2 / 156 (1.28%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood pressure inadequately ~ controlled             |                 |                 |                 |
| subjects affected / exposed                          | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertension                                         |                 |                 |                 |
| subjects affected / exposed                          | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Hypotension                                          |                 |                 |                 |
| subjects affected / exposed                          | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral artery occlusion                          |                 |                 |                 |
| subjects affected / exposed                          | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |
| Generalised oedema                                   |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Impaired healing                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Acute respiratory failure                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 357 (0.28%) | 1 / 156 (0.64%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Asthma                                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 357 (0.28%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic obstructive pulmonary ~ disease         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 2 / 154 (1.30%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute pulmonary oedema                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Dyspnoea                                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dyspnoea exertional                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Lung infiltration                               |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumothorax                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Pulmonary hypertension                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Product issues                                  |                 |                 |                 |
| Device end of service                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigations                                  |                 |                 |                 |
| Arteriogram coronary abnormal                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Carbon dioxide abnormal                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Electrocardiogram abnormal                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| International normalised ratio ~ increased      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Transaminases increased                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Fall                                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 2 / 154 (1.30%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Contusion                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Post procedural complication                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Rib fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subdural haematoma                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Tibia fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Congenital, familial and genetic disorders      |                 |                 |                 |
| Arteriovenous malformation                      |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Cardiac failure congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 3 / 357 (0.84%) | 5 / 156 (3.21%) | 3 / 154 (1.95%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 8           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute myocardial infarction                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 5 / 156 (3.21%) | 2 / 154 (1.30%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 5           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary artery disease                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 2 / 156 (1.28%) | 2 / 154 (1.30%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 357 (0.28%) | 1 / 156 (0.64%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute left ventricular failure                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 2 / 156 (1.28%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 2 / 156 (1.28%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure acute                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 357 (0.28%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina unstable                                 |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Arteriosclerosis coronary artery                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial fibrillation                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrioventricular block complete                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bradycardia                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac arrest                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Cardio-respiratory arrest                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Cardiogenic shock                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Cardiopulmonary failure                         |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 357 (0.28%) | 0 / 156 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Hypertensive heart disease                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Myocardial infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 357 (0.28%) | 0 / 156 (0.00%) | 0 / 154 (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           |
| Pulseless electrical activity                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Sinus node dysfunction                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 357 (0.28%) | 0 / 156 (0.00%) | 0 / 154 (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           |
| Ventricular fibrillation                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Nervous system disorders                        |                 |                 |                 |
| Syncope                                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 2 / 154 (1.30%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Headache                                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Carotid artery stenosis                         |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Cerebral haemorrhage                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Cerebrovascular accident                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hemiparesis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoglycaemic unconsciousness                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Transient ischaemic attack                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Anaemia                                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Leukocytosis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nephrogenic anaemia                             |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders                                   |                 |                 |                 |
| Retinopathy hypertensive                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Gastrointestinal haemorrhage                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 5 / 156 (3.21%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 5           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Abdominal pain                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diarrhoea                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 357 (0.28%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colitis ischaemic                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 357 (0.28%) | 0 / 156 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Dyspepsia                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Gastric ulcer                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haematemesis                                    |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Large intestine polyp                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Melaena                                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Pancreatitis acute                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Hepatic mass                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Jaundice cholestatic                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |
| Erythema multiforme                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |

|                                                 |                 |                 |                  |
|-------------------------------------------------|-----------------|-----------------|------------------|
| Acute kidney injury                             |                 |                 |                  |
| subjects affected / exposed                     | 3 / 357 (0.84%) | 7 / 156 (4.49%) | 10 / 154 (6.49%) |
| occurrences causally related to treatment / all | 0 / 3           | 1 / 9           | 0 / 13           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Renal impairment                                |                 |                 |                  |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 3 / 156 (1.92%) | 0 / 154 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 3           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| End stage renal disease                         |                 |                 |                  |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 1 / 154 (0.65%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Urinary retention                               |                 |                 |                  |
| subjects affected / exposed                     | 2 / 357 (0.56%) | 0 / 156 (0.00%) | 0 / 154 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Chronic kidney disease                          |                 |                 |                  |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0            |
| Diabetic nephropathy                            |                 |                 |                  |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Dysuria                                         |                 |                 |                  |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Haematuria                                      |                 |                 |                  |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Nephrolithiasis                                 |                 |                 |                  |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Nephropathy                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Renal failure                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Renal mass                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subcapsular renal haematoma                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urethral stenosis                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 357 (0.28%) | 0 / 156 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Cervical spinal stenosis                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Intervertebral disc protrusion                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Infections and infestations                     |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 3 / 156 (1.92%) | 5 / 154 (3.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Covid-19                                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 2 / 156 (1.28%) | 5 / 154 (3.25%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| Covid-19 pneumonia                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 3 / 156 (1.92%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Osteomyelitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 357 (0.28%) | 1 / 156 (0.64%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gangrene                                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arthritis bacterial                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Bacteraemia                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bronchitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 357 (0.28%) | 0 / 156 (0.00%) | 0 / 154 (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           |
| Bursitis infective                              |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Cellulitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Cystitis                                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Escherichia bacteraemia                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Herpes zoster                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Influenza                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 357 (0.28%) | 0 / 156 (0.00%) | 0 / 154 (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           |
| Large intestine infection                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Otitis externa                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 357 (0.28%) | 0 / 156 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyelonephritis                                  |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Pyelonephritis acute                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Scrotal abscess                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Septic shock                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 357 (0.28%) | 0 / 156 (0.00%) | 0 / 154 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Soft tissue infection                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Staphylococcal infection                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Urosepsis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Wound infection                                 |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Hypervolaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 3 / 156 (1.92%) | 3 / 154 (1.95%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoglycaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 357 (0.28%) | 1 / 156 (0.64%) | 3 / 154 (1.95%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperkalaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 357 (0.28%) | 1 / 156 (0.64%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dehydration                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetes mellitus inadequate control            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 1 / 156 (0.64%) | 0 / 154 (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           |
| Hyperglycaemia                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyponatraemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 357 (0.28%) | 0 / 156 (0.00%) | 0 / 154 (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           |
| Hypovolaemia                                    |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Iron deficiency                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 357 (0.00%) | 0 / 156 (0.00%) | 1 / 154 (0.65%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

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

| <b>Non-serious adverse events</b>                     | Run-in SEL 18 mg  | Randomised Placebo | Randomised SEL 18 mg |
|-------------------------------------------------------|-------------------|--------------------|----------------------|
| Total subjects affected by non-serious adverse events |                   |                    |                      |
| subjects affected / exposed                           | 37 / 357 (10.36%) | 49 / 156 (31.41%)  | 55 / 154 (35.71%)    |
| Vascular disorders                                    |                   |                    |                      |
| Hypertension                                          |                   |                    |                      |
| subjects affected / exposed                           | 10 / 357 (2.80%)  | 7 / 156 (4.49%)    | 11 / 154 (7.14%)     |
| occurrences (all)                                     | 10                | 7                  | 11                   |
| Blood and lymphatic system disorders                  |                   |                    |                      |
| Anaemia                                               |                   |                    |                      |
| subjects affected / exposed                           | 1 / 357 (0.28%)   | 8 / 156 (5.13%)    | 5 / 154 (3.25%)      |
| occurrences (all)                                     | 1                 | 9                  | 5                    |
| General disorders and administration site conditions  |                   |                    |                      |
| Oedema peripheral                                     |                   |                    |                      |
| subjects affected / exposed                           | 5 / 357 (1.40%)   | 8 / 156 (5.13%)    | 11 / 154 (7.14%)     |
| occurrences (all)                                     | 5                 | 8                  | 11                   |
| Gastrointestinal disorders                            |                   |                    |                      |
| Constipation                                          |                   |                    |                      |
| subjects affected / exposed                           | 7 / 357 (1.96%)   | 3 / 156 (1.92%)    | 11 / 154 (7.14%)     |
| occurrences (all)                                     | 7                 | 3                  | 11                   |
| Renal and urinary disorders                           |                   |                    |                      |
| Acute kidney injury                                   |                   |                    |                      |
| subjects affected / exposed                           | 1 / 357 (0.28%)   | 4 / 156 (2.56%)    | 10 / 154 (6.49%)     |
| occurrences (all)                                     | 1                 | 5                  | 10                   |
| Infections and infestations                           |                   |                    |                      |
| Urinary tract infection                               |                   |                    |                      |

|                                                  |                      |                       |                      |
|--------------------------------------------------|----------------------|-----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 6 / 357 (1.68%)<br>6 | 9 / 156 (5.77%)<br>10 | 5 / 154 (3.25%)<br>5 |
| Metabolism and nutrition disorders               |                      |                       |                      |
| Hyperkalaemia                                    |                      |                       |                      |
| subjects affected / exposed                      | 8 / 357 (2.24%)      | 11 / 156 (7.05%)      | 12 / 154 (7.79%)     |
| occurrences (all)                                | 8                    | 12                    | 15                   |
| Hypoglycaemia                                    |                      |                       |                      |
| subjects affected / exposed                      | 4 / 357 (1.12%)      | 9 / 156 (5.77%)       | 6 / 154 (3.90%)      |
| occurrences (all)                                | 4                    | 13                    | 10                   |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|---------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 10 June 2019  | <ul style="list-style-type: none"><li>• To address comments received from regulatory agencies.</li><li>• To provide further clarifications on guidelines for participants who permanently discontinued study drug and remained on study.</li><li>• To correct minor errors and inconsistencies throughout the protocol.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 13 April 2020 | <p>The Phase 3 study was designed based on the hypothesis that the acute decline in eGFR is solely an artefact of SEL's interaction with kidney transporters. Based upon the measured GFR results from the GS-US-223-0110 Phase 1b iohexol study with SEL, this hypothesis was challenged. Importantly, the new data did not alter our understanding of the safety of selonsertib, and the acute changes in kidney function were reversible as expected. Accordingly, Gilead decided to convert the Phase 3 study to a Phase 2b study in order to confirm the results of the prior post-hoc Phase 2 analysis using a Run-in design that prospectively accounted for the acute decline in eGFR associated with SEL. Additionally, efficacy was assessed in multiple ways to evaluate for consistency of effect on kidney outcomes.</p> |

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported