



## Clinical trial results:

### A Phase 2b, Randomised, Double-Blind, Active-Controlled, Multi-Centre Study to Evaluate the Efficacy, Safety and Tolerability of Oral AZD9977 and Dapagliflozin Treatment in Patients with Heart Failure and Chronic Kidney Disease

#### Summary

|                          |                                     |
|--------------------------|-------------------------------------|
| EudraCT number           | 2020-003126-23                      |
| Trial protocol           | BE LT HU DK SE CZ SK BG PL DE IT ES |
| Global end of trial date | 22 September 2023                   |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1              |
| This version publication date  | 06 October 2024 |
| First version publication date | 06 October 2024 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | D6402C00001 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04595370 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | AstraZeneca  |
| Sponsor organisation address | Södertälje, Södertälje, Sweden, 151 85   |
| Public contact               | Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com |
| Scientific contact           | Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.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                       | 20 October 2023   |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 22 September 2023 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the effect of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone on urinary albumin to creatinine ratio (UACR).

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH)-Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 26 January 2021 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |   |
|--------------------------------------|---|
| Country: Number of subjects enrolled | Bulgaria: 38                              |
| Country: Number of subjects enrolled | Canada: 3                                 |
| Country: Number of subjects enrolled | Germany: 1                                |
| Country: Number of subjects enrolled | Czechia: 7                                |
| Country: Number of subjects enrolled | Hungary: 4                                |
| Country: Number of subjects enrolled | Japan: 14                                 |
| Country: Number of subjects enrolled | Poland: 13                                |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 1 |
| Country: Number of subjects enrolled | Russian Federation: 10                    |
| Country: Number of subjects enrolled | Slovakia: 15                              |
| Country: Number of subjects enrolled | Spain: 8                                  |
| Country: Number of subjects enrolled | Sweden: 5                                 |
| Country: Number of subjects enrolled | Taiwan: 1                                 |
| Country: Number of subjects enrolled | Ukraine: 3                                |
| Country: Number of subjects enrolled | United States: 21                         |
| Worldwide total number of subjects   | 144                                       |
| EEA total number of subjects         | 91  |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 21  |
| From 65 to 84 years                       | 114 |
| 85 years and over                         | 9   |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted between 26-January-2021 (first subject first visit) to 22-September-2023 (last subject last visit). Study had 6 arms, however, AZD9977 monotherapy and placebo arms closed early due to change in Heart Failure (HF) treatment guidelines.

### Pre-assignment

Screening details:

Subjects were enrolled after signing the Informed Consent Form (ICF). The study had an optional pre-screening visit. Study enrolled 153 subjects across 6 arms. Due to ERF limitations, subject disposition and baseline data were presented for only 144 subjects. Nine subjects were excluded from analysis due to site misconduct and GCP non-compliance.

### Period 1

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

### Arms

|                              |                                     |
|------------------------------|-------------------------------------|
| Are arms mutually exclusive? | Yes                                 |
| <b>Arm title</b>             | AZD9977 15 mg + Dapagliflozin 10 mg |

Arm description:

Subjects received AZD9977 15 mg and dapagliflozin 10 mg orally once daily for 12 weeks.

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Dapagliflozin |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Tablet        |
| Routes of administration               | Oral use      |

Dosage and administration details:

Subjects received dapagliflozin 10 mg once daily for 12 weeks.

|  |          |
|--|----------|
| Investigational medicinal product name | AZD9977  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Capsule  |
| Routes of administration               | Oral use |

Dosage and administration details:

Subjects received AZD9977 once daily for 12 weeks.

|                  |                                     |
|------------------|-------------------------------------|
| <b>Arm title</b> | AZD9977 50 mg + Dapagliflozin 10 mg |
|------------------|-------------------------------------|

Arm description:

Subjects received AZD9977 50 mg and dapagliflozin 10 mg orally once daily for 12 weeks.

|  |               |
|--|---------------|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Dapagliflozin |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Tablet        |
| Routes of administration               | Oral use      |

Dosage and administration details:

Subjects received dapagliflozin 10 mg once daily for 12 weeks.

|  |                                      |
|--|--------------------------------------|
| Investigational medicinal product name   | AZD9977                              |
| Investigational medicinal product code   |                                      |
| Other name   |                                      |
| Pharmaceutical forms   | Capsule                              |
| Routes of administration   | Oral use                             |
| Dosage and administration details:   |                                      |
| Subjects received AZD9977 once daily for 12 weeks.                                       |                                      |
| <b>Arm title</b>   | AZD9977 150 mg + Dapagliflozin 10 mg |
| Arm description:   |                                      |
| Subjects received AZD9977 150 mg and dapagliflozin 10 mg orally once daily for 12 weeks. |                                      |
| Arm type   | Experimental                         |
| Investigational medicinal product name   | Dapagliflozin                        |
| Investigational medicinal product code   |                                      |
| Other name   |                                      |
| Pharmaceutical forms   | Tablet                               |
| Routes of administration   | Oral use                             |
| Dosage and administration details:   |                                      |
| Subjects received dapagliflozin 10 mg once daily for 12 weeks.                           |                                      |
| Investigational medicinal product name   | AZD9977                              |
| Investigational medicinal product code   |                                      |
| Other name   |                                      |
| Pharmaceutical forms   | Capsule                              |
| Routes of administration   | Oral use                             |
| Dosage and administration details:   |                                      |
| Subjects received AZD9977 once daily for 12 weeks.                                       |                                      |
| <b>Arm title</b>   | AZD9977 150 mg                       |
| Arm description:   |                                      |
| Subjects received AZD9977 150 mg orally once daily for 12 weeks.                         |                                      |
| Arm type   | Experimental                         |
| Investigational medicinal product name   | Placebo                              |
| Investigational medicinal product code   |                                      |
| Other name   |                                      |
| Pharmaceutical forms   | Capsule                              |
| Routes of administration   | Oral use                             |
| Dosage and administration details:   |                                      |
| Subjects received matching placebo to Dapagliflozin once daily for 12 weeks.             |                                      |
| Investigational medicinal product name   | AZD9977                              |
| Investigational medicinal product code   |                                      |
| Other name   |                                      |
| Pharmaceutical forms   | Capsule                              |
| Routes of administration   | Oral use                             |
| Dosage and administration details:   |                                      |
| Subjects received AZD9977 once daily for 12 weeks.                                       |                                      |
| <b>Arm title</b>   | Dapagliflozin 10 mg                  |
| Arm description:   |                                      |
| Subjects received dapagliflozin 10 mg orally once daily for 12 weeks.                    |                                      |
| Arm type   | Experimental                         |

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

Dosage and administration details:

Subjects received matching placebo to AZD9977 once daily for 12 weeks.

|  |               |
|--|---------------|
| Investigational medicinal product name | Dapagliflozin |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Tablet        |
| Routes of administration               | Oral use      |

Dosage and administration details:

Subjects received dapagliflozin 10 mg once daily for 12 weeks.

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

Arm description:

Placebo subjects received placebo matching to AZD9977 and dapagliflozin orally once daily for 12 weeks.

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

Dosage and administration details:

Subjects received matching placebo to dapagliflozin once daily for 12 weeks.

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

Dosage and administration details:

Subjects received matching placebo to AZD9977 once daily for 12 weeks.

| <b>Number of subjects in period 1</b>       | AZD9977 15 mg +<br>Dapagliflozin 10 mg | AZD9977 50 mg +<br>Dapagliflozin 10 mg | AZD9977 150 mg +<br>Dapagliflozin 10 mg |
|---|--|--|---|
| Started                                     | 34                                     | 31                                     | 35                                      |
| Completed                                   | 32                                     | 23                                     | 26                                      |
| Not completed                               | 2                                      | 8                                      | 9                                       |
| Withdrawal of Consent                       | 1                                      | 1                                      | 1                                       |
| Adverse event, non-fatal                    | -                                      | 4                                      | 3                                       |
| Death                                       | -                                      | 1                                      | -                                       |
| Subjects not treated, Withdrawal by subject | -                                      | -                                      | 1                                       |
| Subjects not treated, Protocol Deviation    | 1                                      | -                                      | -                                       |
| Withdrawal by Subject                       | -                                      | -                                      | 1                                       |

|   |   |   |   |
|---|---|---|---|
| Protocol-Specified Withdrawal Criterion Met | - | - | 1 |
| Lost to follow-up                           | - | - | - |
| Discontinued treatment due to other reasons | - | 2 | 2 |

| <b>Number of subjects in period 1</b>       | AZD9977 150 mg | Dapagliflozin 10 mg | Placebo |
|---|----------------|---------------------|---------|
| Started                                     | 6              | 33                  | 5       |
| Completed                                   | 5              | 27                  | 4       |
| Not completed                               | 1              | 6                   | 1       |
| Withdrawal of Consent                       | -              | -                   | -       |
| Adverse event, non-fatal                    | 1              | 1                   | 1       |
| Death                                       | -              | 1                   | -       |
| Subjects not treated, Withdrawal by subject | -              | -                   | -       |
| Subjects not treated, Protocol Deviation    | -              | -                   | -       |
| Withdrawal by Subject                       | -              | 2                   | -       |
| Protocol-Specified Withdrawal Criterion Met | -              | -                   | -       |
| Lost to follow-up                           | -              | 1                   | -       |
| Discontinued treatment due to other reasons | -              | 1                   | -       |

## Baseline characteristics

### Reporting groups

|   |                                      |
|---|--------------------------------------|
| Reporting group title   | AZD9977 15 mg + Dapagliflozin 10 mg  |
| Reporting group description:  |                                      |
| Subjects received AZD9977 15 mg and dapagliflozin 10 mg orally once daily for 12 weeks.                 |                                      |
| Reporting group title   | AZD9977 50 mg + Dapagliflozin 10 mg  |
| Reporting group description:  |                                      |
| Subjects received AZD9977 50 mg and dapagliflozin 10 mg orally once daily for 12 weeks.                 |                                      |
| Reporting group title   | AZD9977 150 mg + Dapagliflozin 10 mg |
| Reporting group description:  |                                      |
| Subjects received AZD9977 150 mg and dapagliflozin 10 mg orally once daily for 12 weeks.                |                                      |
| Reporting group title   | AZD9977 150 mg                       |
| Reporting group description:  |                                      |
| Subjects received AZD9977 150 mg orally once daily for 12 weeks.  |                                      |
| Reporting group title   | Dapagliflozin 10 mg                  |
| Reporting group description:  |                                      |
| Subjects received dapagliflozin 10 mg orally once daily for 12 weeks.                                   |                                      |
| Reporting group title   | Placebo                              |
| Reporting group description:  |                                      |
| Placebo subjects received placebo matching to AZD9977 and dapagliflozin orally once daily for 12 weeks. |                                      |

| Reporting group values                                | AZD9977 15 mg +<br>Dapagliflozin 10 mg | AZD9977 50 mg +<br>Dapagliflozin 10 mg | AZD9977 150 mg +<br>Dapagliflozin 10 mg |
|---|--|--|---|
| Number of subjects                                    | 34                                     | 31                                     | 35                                      |
| Age categorical                                       |  |  |   |
| Units: Subjects                                       |  |  |   |
| In utero  | 0                                      | 0                                      | 0                                       |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                                      | 0                                      | 0                                       |
| Newborns (0-27 days)                                  | 0                                      | 0                                      | 0                                       |
| Infants and toddlers (28 days-23<br>months)           | 0                                      | 0                                      | 0                                       |
| Children (2-11 years)                                 | 0                                      | 0                                      | 0                                       |
| Adolescents (12-17 years)                             | 0                                      | 0                                      | 0                                       |
| Adults (18-64 years)                                  | 6                                      | 6                                      | 4                                       |
| From 65-84 years                                      | 27                                     | 23                                     | 30                                      |
| 85 years and over                                     | 1                                      | 2                                      | 1                                       |
| Age Continuous  |  |  |   |
| Units: Years  |  |  |   |
| arithmetic mean                                       | 70.9                                   | 72.4                                   | 73.7                                    |
| standard deviation                                    | ± 7.1                                  | ± 8.4                                  | ± 8.1                                   |
| Sex: Female, Male                                     |  |  |   |
| Units: Subjects                                       |  |  |   |
| Female  | 11                                     | 5                                      | 8                                       |
| Male  | 23                                     | 26                                     | 27                                      |
| Race  |  |  |   |
| Units: Subjects                                       |  |  |   |
| Asian   | 4                                      | 3                                      | 7                                       |



|                           |    |    |    |
|---------------------------|----|----|----|
| Black or African American | 0  | 1  | 1  |
| White                     | 30 | 27 | 27 |

| Reporting group values                             | AZD9977 150 mg | Dapagliflozin 10 mg | Placebo |
|--|----------------|---------------------|---------|
| Number of subjects                                 | 6              | 33                  | 5       |
| Age categorical<br>Units: Subjects                 |                |                     |         |
| In utero   | 0              | 0                   | 0       |
| Preterm newborn infants (gestational age < 37 wks) | 0              | 0                   | 0       |
| Newborns (0-27 days)                               | 0              | 0                   | 0       |
| Infants and toddlers (28 days-23 months)           | 0              | 0                   | 0       |
| Children (2-11 years)                              | 0              | 0                   | 0       |
| Adolescents (12-17 years)                          | 0              | 0                   | 0       |
| Adults (18-64 years)                               | 0              | 5                   | 0       |
| From 65-84 years                                   | 5              | 25                  | 4       |
| 85 years and over                                  | 1              | 3                   | 1       |
| Age Continuous<br>Units: Years                     |                |                     |         |
| arithmetic mean                                    | 77.0           | 72.2                | 77.2    |
| standard deviation                                 | ± 8.7          | ± 9.4               | ± 5.8   |
| Sex: Female, Male<br>Units: Subjects               |                |                     |         |
| Female   | 1              | 10                  | 1       |
| Male   | 5              | 23                  | 4       |
| Race<br>Units: Subjects                            |                |                     |         |
| Asian  | 0              | 3                   | 0       |
| Black or African American                          | 0              | 2                   | 1       |
| White  | 6              | 28                  | 4       |

| Reporting group values                             | Total |  |  |
|--|-------|--|--|
| Number of subjects                                 | 144   |  |  |
| Age categorical<br>Units: Subjects                 |       |  |  |
| In utero   | 0     |  |  |
| Preterm newborn infants (gestational age < 37 wks) | 0     |  |  |
| Newborns (0-27 days)                               | 0     |  |  |
| Infants and toddlers (28 days-23 months)           | 0     |  |  |
| Children (2-11 years)                              | 0     |  |  |
| Adolescents (12-17 years)                          | 0     |  |  |
| Adults (18-64 years)                               | 21    |  |  |
| From 65-84 years                                   | 114   |  |  |
| 85 years and over                                  | 9     |  |  |
| Age Continuous<br>Units: Years                     |       |  |  |
| arithmetic mean                                    |       |  |  |
| standard deviation                                 | -     |  |  |

|                           |     |  |  |
|---------------------------|-----|--|--|
| Sex: Female, Male         |     |  |  |
| Units: Subjects           |     |  |  |
| Female                    | 36  |  |  |
| Male                      | 108 |  |  |
| Race                      |     |  |  |
| Units: Subjects           |     |  |  |
| Asian                     | 17  |  |  |
| Black or African American | 5   |  |  |
| White                     | 122 |  |  |

## End points

### End points reporting groups

|   |                                      |
|---|--------------------------------------|
| Reporting group title   | AZD9977 15 mg + Dapagliflozin 10 mg  |
| Reporting group description:<br>Subjects received AZD9977 15 mg and dapagliflozin 10 mg orally once daily for 12 weeks.                 |                                      |
| Reporting group title   | AZD9977 50 mg + Dapagliflozin 10 mg  |
| Reporting group description:<br>Subjects received AZD9977 50 mg and dapagliflozin 10 mg orally once daily for 12 weeks.                 |                                      |
| Reporting group title   | AZD9977 150 mg + Dapagliflozin 10 mg |
| Reporting group description:<br>Subjects received AZD9977 150 mg and dapagliflozin 10 mg orally once daily for 12 weeks.                |                                      |
| Reporting group title   | AZD9977 150 mg                       |
| Reporting group description:<br>Subjects received AZD9977 150 mg orally once daily for 12 weeks.  |                                      |
| Reporting group title   | Dapagliflozin 10 mg                  |
| Reporting group description:<br>Subjects received dapagliflozin 10 mg orally once daily for 12 weeks.                                   |                                      |
| Reporting group title   | Placebo                              |
| Reporting group description:<br>Placebo subjects received placebo matching to AZD9977 and dapagliflozin orally once daily for 12 weeks. |                                      |

### Primary: Percent Change from Baseline in Urinary Albumin to Creatinine Ratio (UACR) at Week 12

|  |   |
|--|---|
| End point title  | Percent Change from Baseline in Urinary Albumin to Creatinine Ratio (UACR) at Week 12 |
| End point description:<br>Change from baseline in UACR at the end of 12 weeks of study treatment was calculated as the average of the UACR values at Week 12 and was analyzed by a mixed-effects model for repeated measures (MMRM). Due to early removal of arms (AZD9977 150 mg monotherapy and Placebo), the study objectives were revised and the MMRM analysis included the 4 remaining arms (AZD9977 15/50/150 mg + Dapagliflozin, and Dapagliflozin 10 mg). Since 2 arms were removed from the study resulting in fewer subjects only descriptive statistics are shown for those two arms without formal comparison. Here, -999.999 and 999.999 indicates that lower limit and upper limit of 95% CI was not calculated and only a descriptive statistic of mean percent change from baseline was shown while the estimates for the remaining 4 arms were from the mixed model for repeated measure. FAS included all subjects who were randomized and either received or did not receive any study intervention. |   |
| End point type   | Primary   |
| End point timeframe:<br>Baseline (Day 1) and Week 12   |   |

| End point values                    | AZD9977 15 mg + Dapagliflozin 10 mg | AZD9977 50 mg + Dapagliflozin 10 mg | AZD9977 150 mg + Dapagliflozin 10 mg | AZD9977 150 mg               |
|-------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|------------------------------|
| Subject group type                  | Reporting group                     | Reporting group                     | Reporting group                      | Reporting group              |
| Number of subjects analysed         | 32                                  | 23                                  | 25                                   | 5                            |
| Units: Percent change from baseline |                                     |                                     |                                      |                              |
| number (confidence interval 95%)    | -56.391 (-71.528 to -33.207)        | -42.085 (-64.174 to -6.376)         | -58.047 (-73.560 to -33.430)         | -45.01 (-999.999 to 999.999) |

| End point values                    | Dapagliflozin 10 mg        | Placebo                      |  |  |
|-------------------------------------|----------------------------|------------------------------|--|--|
| Subject group type                  | Reporting group            | Reporting group              |  |  |
| Number of subjects analysed         | 28                         | 3                            |  |  |
| Units: Percent change from baseline |                            |                              |  |  |
| number (confidence interval 95%)    | -34.318 (-58.204 to 3.220) | 230.32 (-999.999 to 999.999) |  |  |

### Statistical analyses

| Statistical analysis title              | AZD9977 + Dapagliflozin v/s Dapagliflozin  |
|---|--|
| Comparison groups                       | AZD9977 50 mg + Dapagliflozin 10 mg v AZD9977 15 mg + Dapagliflozin 10 mg v AZD9977 150 mg + Dapagliflozin 10 mg v Dapagliflozin 10 mg |
| Number of subjects included in analysis | 108  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           |  |
| P-value                                 | = 0.3645   |
| Method                                  | F-Test   |
| Parameter estimate                      | F test statistic   |
| Point estimate                          | 1.07   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -999.999   |
| upper limit                             | 999.999  |

### Secondary: Percent Change from Baseline in Urinary Albumin to Creatinine Ratio (UACR) at 12 weeks to Assess Dose-Response Relationship

|                 |   |
|-----------------|---|
| End point title | Percent Change from Baseline in Urinary Albumin to Creatinine Ratio (UACR) at 12 weeks to Assess Dose-Response Relationship |
|-----------------|---|

#### End point description:

Change from baseline in UACR at the end of 12 weeks of study treatment was calculated as the average of the UACR values at Week 12 and was analyzed by a mixed-effects model for repeated measures (MMRM). Due to early removal of arms (AZD9977 150 mg monotherapy and placebo), the study objectives were revised and the MMRM analysis included the 4 remaining arms (AZD9977 15/50/150 mg

+ Dapagliflozin, and Dapagliflozin 10 mg). Since 2 arms were removed from the study resulting in fewer subjects, only descriptive statistics was shown for those two arms without formal comparison. Here, -999.999 and 999.999 indicates that lower limit and upper limit of 95% CI was not calculated and only a descriptive statistic of mean percent change from baseline was shown while the estimates for the remaining 4 arms were from the mixed model for repeated measure. FAS included all subjects who were randomized and either received or did not receive any study intervention.

|                              |           |
|------------------------------|-----------|
| End point type               | Secondary |
| End point timeframe:         |           |
| Baseline (Day 1) and Week 12 |           |

| End point values                    | AZD9977 15 mg + Dapagliflozin 10 mg | AZD9977 50 mg + Dapagliflozin 10 mg | AZD9977 150 mg + Dapagliflozin 10 mg | AZD9977 150 mg               |
|-------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|------------------------------|
| Subject group type                  | Reporting group                     | Reporting group                     | Reporting group                      | Reporting group              |
| Number of subjects analysed         | 32                                  | 23                                  | 25                                   | 5                            |
| Units: Percent change from baseline |                                     |                                     |                                      |                              |
| number (confidence interval 95%)    | -56.391 (-71.528 to -33.207)        | -42.085 (-64.174 to -6.376)         | -58.047 (-73.560 to -33.430)         | -45.01 (-999.999 to 999.999) |

| End point values                    | Dapagliflozin 10 mg        | Placebo                      |  |  |
|-------------------------------------|----------------------------|------------------------------|--|--|
| Subject group type                  | Reporting group            | Reporting group              |  |  |
| Number of subjects analysed         | 28                         | 3                            |  |  |
| Units: Percent change from baseline |                            |                              |  |  |
| number (confidence interval 95%)    | -34.318 (-58.204 to 3.220) | 230.32 (-999.999 to 999.999) |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | AZD9977 15mg + Dapagliflozin v/s Dapagliflozin            |
| Comparison groups                       | AZD9977 15 mg + Dapagliflozin 10 mg v Dapagliflozin 10 mg |
| Number of subjects included in analysis | 60  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| P-value                                 | = 0.1588  |
| Method                                  | Mixed models analysis                                     |
| Parameter estimate                      | Percent difference between treatment                      |
| Point estimate                          | -33.606   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -62.53  |
| upper limit                             | 17.644  |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | AZD9977 150mg + Dapagliflozin v/s Dapagliflozin            |
| Comparison groups                       | AZD9977 150 mg + Dapagliflozin 10 mg v Dapagliflozin 10 mg |
| Number of subjects included in analysis | 53   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           |  |
| P-value                                 | = 0.1398   |
| Method                                  | Mixed models analysis                                      |
| Parameter estimate                      | Percent difference between treatment                       |
| Point estimate                          | -36.127  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -64.85   |
| upper limit                             | 16.066   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | AZD9977 50mg + Dapagliflozin v/s Dapagliflozin            |
| Comparison groups                       | AZD9977 50 mg + Dapagliflozin 10 mg v Dapagliflozin 10 mg |
| Number of subjects included in analysis | 51  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| P-value                                 | = 0.6846  |
| Method                                  | Mixed models analysis                                     |
| Parameter estimate                      | Percent difference between treatment                      |
| Point estimate                          | -11.826   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -52.195   |
| upper limit                             | 62.634  |

## Secondary: Number of Subjects with Adverse Events (AEs)

|  |  |
|--|--|
| End point title  | Number of Subjects with Adverse Events (AEs) |
| End point description:   |  |
| The safety and tolerability of AZD9977 combined with dapagliflozin 10 mg, AZD9977 monotherapy, dapagliflozin 10 mg monotherapy and placebo was assessed. |  |
| Safety analysis set included all subjects who were randomized and received any study intervention.   |  |
| End point type   | Secondary                                    |
| End point timeframe:   |  |
| From baseline (Day 1) until Day 113  |  |

| End point values                        | AZD9977 15 mg + Dapagliflozin 10 mg | AZD9977 50 mg + Dapagliflozin 10 mg | AZD9977 150 mg + Dapagliflozin 10 mg | AZD9977 150 mg  |
|---|-------------------------------------|-------------------------------------|--------------------------------------|-----------------|
| Subject group type                      | Reporting group                     | Reporting group                     | Reporting group                      | Reporting group |
| Number of subjects analysed             | 33                                  | 31                                  | 34                                   | 6               |
| Units: Subjects                         |                                     |                                     |                                      |                 |
| Any AE                                  | 9                                   | 12                                  | 18                                   | 5               |
| Any SAE                                 | 1                                   | 3                                   | 2                                    | 0               |
| Any SAE with outcome death              | 0                                   | 2                                   | 0                                    | 0               |
| Any AE leading to discontinuation of IP | 0                                   | 4                                   | 3                                    | 1               |
| Any AE leading to withdrawal from study | 0                                   | 5                                   | 2                                    | 0               |
| Any AE leading to dose interruption     | 1                                   | 1                                   | 1                                    | 0               |

| End point values                        | Dapagliflozin 10 mg | Placebo         |  |  |
|---|---------------------|-----------------|--|--|
| Subject group type                      | Reporting group     | Reporting group |  |  |
| Number of subjects analysed             | 33                  | 5               |  |  |
| Units: Subjects                         |                     |                 |  |  |
| Any AE                                  | 14                  | 3               |  |  |
| Any SAE                                 | 4                   | 2               |  |  |
| Any SAE with outcome death              | 1                   | 0               |  |  |
| Any AE leading to discontinuation of IP | 1                   | 1               |  |  |
| Any AE leading to withdrawal from study | 1                   | 0               |  |  |
| Any AE leading to dose interruption     | 3                   | 1               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Serum Potassium (K+)

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Serum Potassium (K+) |
|-----------------|--|

End point description:

Effect of AZD9977 combined with dapagliflozin 10 mg, AZD9977 monotherapy, dapagliflozin 10 mg monotherapy and placebo on serum K+ was assessed.

Here, -999.999 and 999.999 indicates that lower limit and upper limit of 95% CI was not calculated and only a descriptive statistic of mean change from baseline was shown while the estimates for the remaining 4 arms were from the mixed model for repeated measure.

Safety analysis set included all subjects who were randomized and received any study intervention.

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

End point timeframe:

At 12 weeks

| End point values                             | AZD9977 15 mg + Dapagliflozin 10 mg | AZD9977 50 mg + Dapagliflozin 10 mg | AZD9977 150 mg + Dapagliflozin 10 mg | AZD9977 150 mg             |
|--|-------------------------------------|-------------------------------------|--------------------------------------|----------------------------|
| Subject group type                           | Reporting group                     | Reporting group                     | Reporting group                      | Reporting group            |
| Number of subjects analysed                  | 27                                  | 21                                  | 25                                   | 4                          |
| Units: millimoles per liter (mmol/L)         |                                     |                                     |                                      |                            |
| least squares mean (confidence interval 95%) | 0.056 (-0.106 to 0.219)             | 0.003 (-0.184 to 0.190)             | 0.109 (-0.061 to 0.279)              | 0.55 (-999.999 to 999.999) |

| End point values                             | Dapagliflozin 10 mg     | Placebo                    |  |  |
|--|-------------------------|----------------------------|--|--|
| Subject group type                           | Reporting group         | Reporting group            |  |  |
| Number of subjects analysed                  | 25                      | 3                          |  |  |
| Units: millimoles per liter (mmol/L)         |                         |                            |  |  |
| least squares mean (confidence interval 95%) | 0.040 (-0.129 to 0.209) | 0.03 (-999.999 to 999.999) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute Value of Serum Potassium Over Time

|   |   |
|---|---|
| End point title   | Absolute Value of Serum Potassium Over Time |
| End point description:  |   |
| Effect of AZD9977 combined with dapagliflozin 10 mg, AZD9977 monotherapy, dapagliflozin 10 mg monotherapy and placebo on serum K <sup>+</sup> was assessed.   |   |
| Safety analysis set included all subjects who were randomized and received any study intervention. Here, "n" specifies the number of subjects who were evaluated for this outcome measure at the specified timepoint. |   |
| End point type  | Secondary                                   |
| End point timeframe:  |   |
| Baseline (Day 1) and Week 12  |   |

| End point values                     | AZD9977 15 mg + Dapagliflozin 10 mg | AZD9977 50 mg + Dapagliflozin 10 mg | AZD9977 150 mg + Dapagliflozin 10 mg | AZD9977 150 mg  |
|--------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|-----------------|
| Subject group type                   | Reporting group                     | Reporting group                     | Reporting group                      | Reporting group |
| Number of subjects analysed          | 30                                  | 25                                  | 29                                   | 5               |
| Units: mmol/L                        |                                     |                                     |                                      |                 |
| arithmetic mean (standard deviation) |                                     |                                     |                                      |                 |
| Baseline (n=30, 25, 29, 5, 33, 5)    | 4.60 (± 0.38)                       | 4.44 (± 0.61)                       | 4.46 (± 0.44)                        | 4.50 (± 0.38)   |
| Week 12 (n=27, 21, 25, 4, 25, 3)     | 4.62 (± 0.50)                       | 4.53 (± 0.43)                       | 4.63 (± 0.43)                        | 5.00 (± 0.61)   |



| End point values                     | Dapagliflozin 10 mg | Placebo         |  |  |
|--------------------------------------|---------------------|-----------------|--|--|
| Subject group type                   | Reporting group     | Reporting group |  |  |
| Number of subjects analysed          | 33                  | 5               |  |  |
| Units: mmol/L                        |                     |                 |  |  |
| arithmetic mean (standard deviation) |                     |                 |  |  |
| Baseline (n=30, 25, 29, 5, 33, 5)    | 4.60 (± 0.66)       | 4.50 (± 0.28)   |  |  |
| Week 12 (n=27, 21, 25, 4, 25, 3)     | 4.64 (± 0.40)       | 4.33 (± 0.32)   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Estimated Glomerular Filtration Rate (eGFR)

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in Estimated Glomerular Filtration Rate (eGFR) |
|-----------------|---|

End point description:

Effect of AZD9977 combined with dapagliflozin 10 mg, AZD9977 monotherapy, dapagliflozin 10 mg monotherapy and placebo on eGFR was assessed.

Here, -999.999 and 999.999 indicates that lower limit and upper limit of 95% CI was not calculated and only a descriptive statistic of mean change from baseline was shown while the estimates for the remaining 4 arms were from the mixed model for repeated measure.

Safety analysis set included all subjects who were randomized and received any study intervention.

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

End point timeframe:

At 12 weeks

| End point values                             | AZD9977 15 mg + Dapagliflozin 10 mg | AZD9977 50 mg + Dapagliflozin 10 mg | AZD9977 150 mg + Dapagliflozin 10 mg | AZD9977 150 mg               |
|--|-------------------------------------|-------------------------------------|--------------------------------------|------------------------------|
| Subject group type                           | Reporting group                     | Reporting group                     | Reporting group                      | Reporting group              |
| Number of subjects analysed                  | 26                                  | 21                                  | 24                                   | 4                            |
| Units: mL/min/1.73 m <sup>2</sup>            |                                     |                                     |                                      |                              |
| least squares mean (confidence interval 95%) | -1.432 (-4.305 to 1.441)            | -1.160 (-4.351 to 2.030)            | -5.307 (-8.295 to -2.320)            | -0.923 (-999.999 to 999.999) |

| End point values                  | Dapagliflozin 10 mg | Placebo         |  |  |
|-----------------------------------|---------------------|-----------------|--|--|
| Subject group type                | Reporting group     | Reporting group |  |  |
| Number of subjects analysed       | 23                  | 3               |  |  |
| Units: mL/min/1.73 m <sup>2</sup> |                     |                 |  |  |

|  |                           |                             |  |  |
|--|---------------------------|-----------------------------|--|--|
| least squares mean (confidence interval 95%) | -3.498 (-6.528 to -0.469) | 6.880 (-999.999 to 999.999) |  |  |
|--|---------------------------|-----------------------------|--|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute Value of eGFR Over Time

|                 |                                  |
|-----------------|----------------------------------|
| End point title | Absolute Value of eGFR Over Time |
|-----------------|----------------------------------|

End point description:

Effect of all doses of AZD9977 combined with dapagliflozin 10 mg, AZD9977 monotherapy, dapagliflozin 10 mg monotherapy and placebo on eGFR was assessed.

Safety analysis set included all subjects who were randomized and received any study intervention. Here, "n" specifies the number of subjects who were evaluated for this outcome measure at the specified timepoint.

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

End point timeframe:

Baseline (Day 1) and Week 12

| End point values                     | AZD9977 15 mg + Dapagliflozin 10 mg | AZD9977 50 mg + Dapagliflozin 10 mg | AZD9977 150 mg + Dapagliflozin 10 mg | AZD9977 150 mg    |
|--------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|-------------------|
| Subject group type                   | Reporting group                     | Reporting group                     | Reporting group                      | Reporting group   |
| Number of subjects analysed          | 32                                  | 31                                  | 33                                   | 5                 |
| Units: mL/min/1.73 m <sup>2</sup>    |                                     |                                     |                                      |                   |
| arithmetic mean (standard deviation) |                                     |                                     |                                      |                   |
| Baseline (n=32, 31, 33, 5, 32, 5)    | 41.341 (± 12.902)                   | 38.586 (± 10.155)                   | 43.663 (± 16.168)                    | 36.874 (± 12.626) |
| Week 12 (n=26, 21, 24, 4, 23, 3)     | 41.219 (± 15.112)                   | 39.429 (± 8.998)                    | 39.063 (± 13.819)                    | 34.075 (± 21.071) |

| End point values                     | Dapagliflozin 10 mg | Placebo           |  |  |
|--------------------------------------|---------------------|-------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group   |  |  |
| Number of subjects analysed          | 32                  | 5                 |  |  |
| Units: mL/min/1.73 m <sup>2</sup>    |                     |                   |  |  |
| arithmetic mean (standard deviation) |                     |                   |  |  |
| Baseline (n=32, 31, 33, 5, 32, 5)    | 41.895 (± 12.791)   | 40.288 (± 15.176) |  |  |
| Week 12 (n=26, 21, 24, 4, 23, 3)     | 37.973 (± 11.571)   | 48.920 (± 21.111) |  |  |

## Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From baseline (Day 1) until Day 113

Adverse event reporting additional description:

Safety set included all subjects who were randomized and received any study intervention. All AEs that were reported with an onset date and time, or worsening, on or after date and time of first dose of IP up to and including 5 days after last dose of IP were included in the safety analysis.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 26.0 |
|--------------------|------|

### Reporting groups

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | AZD9977 15 mg + Dapagliflozin 10 mg |
|-----------------------|-------------------------------------|

Reporting group description:

Subjects received AZD9977 15 mg and dapagliflozin 10 mg orally once daily for 12 weeks.

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | AZD9977 50 mg + Dapagliflozin 10 mg |
|-----------------------|-------------------------------------|

Reporting group description:

Subjects received AZD9977 50 mg and dapagliflozin 10 mg orally once daily for 12 weeks.

|                       |                |
|-----------------------|----------------|
| Reporting group title | AZD9977 150 mg |
|-----------------------|----------------|

Reporting group description:

Subjects received AZD9977 150 mg orally once daily for 12 weeks.

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | AZD9977 150 mg + Dapagliflozin 10 mg |
|-----------------------|--------------------------------------|

Reporting group description:

Subjects received AZD9977 150 mg and dapagliflozin 10 mg orally once daily for 12 weeks.

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

Reporting group description:

Placebo subjects received placebo matching to AZD9977 and dapagliflozin orally once daily for 12 weeks.

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Dapagliflozin 10 mg |
|-----------------------|---------------------|

Reporting group description:

Subjects received dapagliflozin 10 mg orally once daily for 12 weeks.

| Serious adverse events                            | AZD9977 15 mg + Dapagliflozin 10 mg | AZD9977 50 mg + Dapagliflozin 10 mg | AZD9977 150 mg |
|---|-------------------------------------|-------------------------------------|----------------|
| Total subjects affected by serious adverse events |                                     |                                     |                |
| subjects affected / exposed                       | 1 / 33 (3.03%)                      | 3 / 31 (9.68%)                      | 0 / 6 (0.00%)  |
| number of deaths (all causes)                     | 0                                   | 2                                   | 0              |
| number of deaths resulting from adverse events    | 0                                   | 2                                   | 0              |
| Investigations                                    |                                     |                                     |                |
| Hepatic enzyme increased                          |                                     |                                     |                |
| subjects affected / exposed                       | 1 / 33 (3.03%)                      | 0 / 31 (0.00%)                      | 0 / 6 (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          |

|  |                |                |               |
|--|----------------|----------------|---------------|
| Cardiac disorders                                    |                |                |               |
| Cardiac failure congestive                           |                |                |               |
| subjects affected / exposed                          | 0 / 33 (0.00%) | 0 / 31 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0         |
| Cardiac failure                                      |                |                |               |
| subjects affected / exposed                          | 0 / 33 (0.00%) | 1 / 31 (3.23%) | 0 / 6 (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         |
| Left ventricular failure                             |                |                |               |
| subjects affected / exposed                          | 0 / 33 (0.00%) | 1 / 31 (3.23%) | 0 / 6 (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                             |                |                |               |
| Transient ischaemic attack                           |                |                |               |
| subjects affected / exposed                          | 0 / 33 (0.00%) | 0 / 31 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0         |
| General disorders and administration site conditions |                |                |               |
| Sudden cardiac death                                 |                |                |               |
| subjects affected / exposed                          | 0 / 33 (0.00%) | 0 / 31 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0         |
| Peripheral swelling                                  |                |                |               |
| subjects affected / exposed                          | 0 / 33 (0.00%) | 0 / 31 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0         |
| Gastrointestinal disorders                           |                |                |               |
| Lower gastrointestinal haemorrhage                   |                |                |               |
| subjects affected / exposed                          | 0 / 33 (0.00%) | 0 / 31 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0         |
| Musculoskeletal and connective tissue disorders      |                |                |               |
| Osteoarthritis                                       |                |                |               |

|   |                |                |               |
|---|----------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 33 (0.00%) | 1 / 31 (3.23%) | 0 / 6 (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                     |                |                |               |
| COVID-19  |                |                |               |
| subjects affected / exposed                     | 0 / 33 (0.00%) | 1 / 31 (3.23%) | 0 / 6 (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         |

| <b>Serious adverse events</b>                     | AZD9977 150 mg +<br>Dapagliflozin 10 mg | Placebo        | Dapagliflozin 10 mg |
|---|---|----------------|---------------------|
| Total subjects affected by serious adverse events |   |                |                     |
| subjects affected / exposed                       | 2 / 34 (5.88%)                          | 2 / 5 (40.00%) | 4 / 33 (12.12%)     |
| number of deaths (all causes)                     | 0                                       | 0              | 1                   |
| number of deaths resulting from adverse events    | 0                                       | 0              | 1                   |
| Investigations                                    |   |                |                     |
| Hepatic enzyme increased                          |   |                |                     |
| subjects affected / exposed                       | 0 / 34 (0.00%)                          | 0 / 5 (0.00%)  | 0 / 33 (0.00%)      |
| occurrences causally related to treatment / all   | 0 / 0                                   | 0 / 0          | 0 / 0               |
| deaths causally related to treatment / all        | 0 / 0                                   | 0 / 0          | 0 / 0               |
| Cardiac disorders                                 |   |                |                     |
| Cardiac failure congestive                        |   |                |                     |
| subjects affected / exposed                       | 0 / 34 (0.00%)                          | 0 / 5 (0.00%)  | 1 / 33 (3.03%)      |
| 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 failure                                   |   |                |                     |
| subjects affected / exposed                       | 1 / 34 (2.94%)                          | 1 / 5 (20.00%) | 0 / 33 (0.00%)      |
| occurrences causally related to treatment / all   | 0 / 1                                   | 0 / 1          | 0 / 0               |
| deaths causally related to treatment / all        | 0 / 0                                   | 0 / 0          | 0 / 0               |
| Left ventricular failure                          |   |                |                     |
| subjects affected / exposed                       | 0 / 34 (0.00%)                          | 0 / 5 (0.00%)  | 0 / 33 (0.00%)      |
| occurrences causally related to treatment / all   | 0 / 0                                   | 0 / 0          | 0 / 0               |
| deaths causally related to treatment / all        | 0 / 0                                   | 0 / 0          | 0 / 0               |
| Nervous system disorders                          |   |                |                     |
| Transient ischaemic attack                        |   |                |                     |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                          | 1 / 34 (2.94%) | 0 / 5 (0.00%)  | 0 / 33 (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          |
| General disorders and administration site conditions |                |                |                |
| Sudden cardiac death                                 |                |                |                |
| subjects affected / exposed                          | 0 / 34 (0.00%) | 0 / 5 (0.00%)  | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 1          |
| Peripheral swelling                                  |                |                |                |
| subjects affected / exposed                          | 0 / 34 (0.00%) | 0 / 5 (0.00%)  | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                           |                |                |                |
| Lower gastrointestinal haemorrhage                   |                |                |                |
| subjects affected / exposed                          | 0 / 34 (0.00%) | 0 / 5 (0.00%)  | 1 / 33 (3.03%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders      |                |                |                |
| Osteoarthritis                                       |                |                |                |
| subjects affected / exposed                          | 0 / 34 (0.00%) | 0 / 5 (0.00%)  | 0 / 33 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                          |                |                |                |
| COVID-19   |                |                |                |
| subjects affected / exposed                          | 0 / 34 (0.00%) | 1 / 5 (20.00%) | 0 / 33 (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          |

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

| Non-serious adverse events                            | AZD9977 15 mg + Dapagliflozin 10 mg | AZD9977 50 mg + Dapagliflozin 10 mg | AZD9977 150 mg |
|---|-------------------------------------|-------------------------------------|----------------|
| Total subjects affected by non-serious adverse events |                                     |                                     |                |
| subjects affected / exposed                           | 1 / 33 (3.03%)                      | 4 / 31 (12.90%)                     | 5 / 6 (83.33%) |

|  |                |                |                |
|--|----------------|----------------|----------------|
| Injury, poisoning and procedural complications |                |                |                |
| Fall   |                |                |                |
| subjects affected / exposed                    | 0 / 33 (0.00%) | 0 / 31 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                              | 0              | 0              | 0              |
| Vascular disorders                             |                |                |                |
| Hypertensive crisis                            |                |                |                |
| subjects affected / exposed                    | 0 / 33 (0.00%) | 0 / 31 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                              | 0              | 0              | 0              |
| Hypotension                                    |                |                |                |
| subjects affected / exposed                    | 0 / 33 (0.00%) | 0 / 31 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)                              | 0              | 0              | 1              |
| Syncope  |                |                |                |
| subjects affected / exposed                    | 0 / 33 (0.00%) | 0 / 31 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                              | 0              | 0              | 0              |
| Nervous system disorders                       |                |                |                |
| Headache                                       |                |                |                |
| subjects affected / exposed                    | 0 / 33 (0.00%) | 0 / 31 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)                              | 0              | 0              | 1              |
| Gastrointestinal disorders                     |                |                |                |
| Nausea   |                |                |                |
| subjects affected / exposed                    | 0 / 33 (0.00%) | 0 / 31 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                              | 0              | 0              | 0              |
| Diarrhoea                                      |                |                |                |
| subjects affected / exposed                    | 0 / 33 (0.00%) | 0 / 31 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                              | 0              | 0              | 0              |
| Colitis  |                |                |                |
| subjects affected / exposed                    | 0 / 33 (0.00%) | 0 / 31 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                              | 0              | 0              | 0              |
| Gingival recession                             |                |                |                |
| subjects affected / exposed                    | 0 / 33 (0.00%) | 0 / 31 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)                              | 0              | 0              | 1              |
| Renal and urinary disorders                    |                |                |                |
| Chronic kidney disease                         |                |                |                |
| subjects affected / exposed                    | 1 / 33 (3.03%) | 1 / 31 (3.23%) | 1 / 6 (16.67%) |
| occurrences (all)                              | 1              | 1              | 1              |
| Endocrine disorders                            |                |                |                |



|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Hyperthyroidism<br>subjects affected / exposed<br>occurrences (all)  | 0 / 33 (0.00%)<br>0 | 0 / 31 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Diabetes mellitus<br>subjects affected / exposed<br>occurrences (all)  | 0 / 33 (0.00%)<br>0 | 0 / 31 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders<br>Spinal osteoarthritis<br>subjects affected / exposed<br>occurrences (all) | 0 / 33 (0.00%)<br>0 | 0 / 31 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Spinal pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 33 (0.00%)<br>0 | 0 / 31 (0.00%)<br>0 | 1 / 6 (16.67%)<br>1 |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 33 (0.00%)<br>0 | 0 / 31 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)  | 0 / 33 (0.00%)<br>0 | 1 / 31 (3.23%)<br>1 | 0 / 6 (0.00%)<br>0  |
| Urinary tract infection bacterial<br>subjects affected / exposed<br>occurrences (all)  | 0 / 33 (0.00%)<br>0 | 2 / 31 (6.45%)<br>2 | 0 / 6 (0.00%)<br>0  |
| Metabolism and nutrition disorders<br>Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 33 (0.00%)<br>0 | 1 / 31 (3.23%)<br>1 | 1 / 6 (16.67%)<br>1 |

| <b>Non-serious adverse events</b>  | AZD9977 150 mg +<br>Dapagliflozin 10 mg | Placebo            | Dapagliflozin 10 mg |
|--|---|--------------------|---------------------|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed                       | 13 / 34 (38.24%)                        | 2 / 5 (40.00%)     | 7 / 33 (21.21%)     |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all) | 1 / 34 (2.94%)<br>1                     | 0 / 5 (0.00%)<br>0 | 2 / 33 (6.06%)<br>2 |
| Vascular disorders   |   |                    |                     |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| Hypertensive crisis<br>subjects affected / exposed<br>occurrences (all)                                   | 2 / 34 (5.88%)<br>2 | 0 / 5 (0.00%)<br>0  | 0 / 33 (0.00%)<br>0 |
| Hypotension<br>subjects affected / exposed<br>occurrences (all)   | 0 / 34 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  | 0 / 33 (0.00%)<br>0 |
| Syncope<br>subjects affected / exposed<br>occurrences (all)   | 1 / 34 (2.94%)<br>1 | 1 / 5 (20.00%)<br>1 | 0 / 33 (0.00%)<br>0 |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 34 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  | 0 / 33 (0.00%)<br>0 |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)                  | 2 / 34 (5.88%)<br>2 | 0 / 5 (0.00%)<br>0  | 0 / 33 (0.00%)<br>0 |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)   | 2 / 34 (5.88%)<br>2 | 1 / 5 (20.00%)<br>1 | 0 / 33 (0.00%)<br>0 |
| Colitis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 34 (0.00%)<br>0 | 1 / 5 (20.00%)<br>1 | 0 / 33 (0.00%)<br>0 |
| Gingival recession<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 34 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  | 0 / 33 (0.00%)<br>0 |
| Renal and urinary disorders<br>Chronic kidney disease<br>subjects affected / exposed<br>occurrences (all) | 2 / 34 (5.88%)<br>2 | 0 / 5 (0.00%)<br>0  | 1 / 33 (3.03%)<br>1 |
| Endocrine disorders<br>Hyperthyroidism<br>subjects affected / exposed<br>occurrences (all)                | 0 / 34 (0.00%)<br>0 | 1 / 5 (20.00%)<br>1 | 0 / 33 (0.00%)<br>0 |
| Diabetes mellitus<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 34 (0.00%)<br>0 | 1 / 5 (20.00%)<br>1 | 0 / 33 (0.00%)<br>0 |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Musculoskeletal and connective tissue disorders |                |                |                |
| Spinal osteoarthritis                           |                |                |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 1 / 5 (20.00%) | 0 / 33 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Spinal pain                                     |                |                |                |
| subjects affected / exposed                     | 0 / 34 (0.00%) | 0 / 5 (0.00%)  | 0 / 33 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Infections and infestations                     |                |                |                |
| Nasopharyngitis                                 |                |                |                |
| subjects affected / exposed                     | 3 / 34 (8.82%) | 0 / 5 (0.00%)  | 1 / 33 (3.03%) |
| occurrences (all)                               | 3              | 0              | 1              |
| Urinary tract infection                         |                |                |                |
| subjects affected / exposed                     | 1 / 34 (2.94%) | 0 / 5 (0.00%)  | 3 / 33 (9.09%) |
| occurrences (all)                               | 1              | 0              | 3              |
| Urinary tract infection bacterial               |                |                |                |
| subjects affected / exposed                     | 1 / 34 (2.94%) | 0 / 5 (0.00%)  | 0 / 33 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Metabolism and nutrition disorders              |                |                |                |
| Hyperkalaemia                                   |                |                |                |
| subjects affected / exposed                     | 2 / 34 (5.88%) | 0 / 5 (0.00%)  | 3 / 33 (9.09%) |
| occurrences (all)                               | 2              | 0              | 3              |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 06 October 2020  | Protocol version 1.0 was updated to include modifications to the number of sites and countries and updates to laboratory parameters for clarity.  |
| 26 January 2021  | Protocol version 2.0 was updated to clarify randomisation of subgroups; to clarify the analysis model; to clarify that the lower limit of eGFR is 20 mL/min in this study; addition of text "to use of bioimpedance devices that was contraindicated for patients with pacemakers or other electronic implanted devices"; to clarify that hypertension treatment can be adjusted if needed at the screening visit; to describe addition of new device to the protocol for site-based ECG monitoring; to include findings from recent clinical trials with dapagliflozin that suggest it had an additive treatment effect when given concomitantly with mineralocorticoid receptor antagonists (MRAs) (DAPA-HF trial) and to further describe the dapagliflozin risk and benefit in patients with chronic kidney disease (DAPA-CKD trial); to clarify eligibility criteria; to clarify medication restrictions, when patients should return to their usual treatments, time frames for procedures performed at another facility than the study site, availability of results and handling of health-related issues, overdose definition whilst maintaining the study blinding; addition of new section Clinical Study Medical Device/ Device Constituent Report Form included as an appendix; and to further describe statistical considerations of the study. |
| 15 July 2021     | Protocol version 4.0 was updated to implement patient-centric measures and improve recruitment.   |
| 20 December 2021 | Protocol version 5.0 was updated to adjust the design to heart failure treatment guidelines (ESC Guidelines 2021), by dropping the placebo and AZD9977 monotherapy arms to ensure all patients receive SGLT2i (dapagliflozin) during the study, as well as to reduce the burden of study assessments on study patients.   |
| 02 February 2022 | Protocol Version 6.0 was updated to correct the typo in Table 1, clarification of study procedures, provide the correct literature reference and to align with revised study design.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date             | Interruption   | Restart date  |
|------------------|--|---------------|
| 26 November 2021 | Recruitment was paused while implementing the amended Protocol (Protocol amendment number 5) | 01 March 2022 |

Notes:

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Enrolment stopped early because of slow recruitment. Therefore, pre-specified sample size of 500 and planned statistical power were not achieved. Nine subjects were excluded from analysis due to site misconduct and GCP non-compliance.

Notes: