ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 09/25/2013

ClinicalTrials.gov ID: NCT00673231

## Study Identification

| | |
|---|---|
| Unique Protocol ID: | D1690C00006 |
| Brief Title: | Efficacy and Safety of Dapagliflozin, Added to Therapy of Patients With Type 2 Diabetes With Inadequate Glycemic Control on Insulin |
| Official Title: | A 24-week International, Randomized, Parallel-group, Double-blind, Placebo-controlled Phase III Study With a 80-week Extension Period to Evaluate the Efficacy and Safety of Dapagliflozin Therapy When Added to the Therapy of Patients With Type 2 Diabetes With Inadequate Glycaemic Control on Insulin |
| Secondary IDs: | |

## Study Status

| | |
|---|---|
| Record Verification: | September 2013 |
| Overall Status: | Completed |
| Study Start: | April 2008 |
| Primary Completion: | May 2009 [Actual] |
| Study Completion: | January 2011 [Actual] |

## Sponsor/Collaborators

| | |
|---|---|
| Sponsor: | AstraZeneca |
| Responsible Party: | Sponsor |
| Collaborators: | Bristol-Myers Squibb |

## Oversight

| | |
|---|---|
| FDA Regulated?: | Yes |
| Applicable Trial?: | Section 801 Clinical Trial? Yes<br>Delayed Posting? No |
| IND/IDE Protocol?: | No |
| Review Board: | Approval Status: Approved<br>Approval Number: ЭК-33090<br>Board Name: Ethics Committee in the Federal Body Of a Quality Assurance in Health Care and Social Development Area<br>Board Affiliation: Ethics Committee in the Federal Body Of a Quality Assurance in Health Care and Social Development Area<br>Phone: 81-049-5628-2319<br>Email: |
| Data Monitoring?: | No |
| Plan to Share Data?: | |
| Oversight Authorities: | Austria: Agency for Health and Food Safety<br>Bulgaria: Ministry of Health<br>Canada: Health Canada<br>Finland: Finnish Medicines Agency<br>Germany: Federal Institute for Drugs and Medical Devices<br>Hungary: National Institute of Pharmacy<br>Netherlands: The Central Committee on Research Involving Human Subjects (CCMO)<br>Romania: National Medicines Agency<br>Russia: Ministry of Health of the Russian Federation<br>Slovakia: State Institute for Drug Control<br>Spain: Spanish Agency of Medicines<br>United Kingdom: Medicines and Healthcare Products Regulatory Agency<br>United States: Food and Drug Administration |

## Study Description

| | |
|---|---|
| Brief Summary: | This study is being carried out to see if Dapagliflozin in addition to insulin is effective and safe in treating patients with type 2 diabetes when compared to placebo (identical looking inactive treatment) in addition to insulin |
| Detailed Description: | |

## Conditions

| | |
|---|---|
| Conditions: | Type 2 Diabetes |
| Keywords: | Dapagliflozin |

efficacy
safety
add on to insulin
Oral AntiDiabetic
Type 2 diabetes

## Study Design

| | |
|---|---|
| Study Type: | Interventional |
| Primary Purpose: | Treatment |
| Study Phase: | Phase 3 |
| Intervention Model: | Parallel Assignment |
| Number of Arms: | 4 |
| Masking: | Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor) |
| Allocation: | Randomized |
| Endpoint Classification: | Safety/Efficacy Study |
| Enrollment: | 1240 [Actual] |

## Arms and Interventions

| Arms | Assigned Interventions |
|---|---|
| Experimental: 1<br>2.5mg | Drug: Dapagliflozin<br>tablet oral 2.5 mg total daily dose once daily 48 weeks (= 24 week randomised treatment period + 24 week study extension period I)<br>Drug: Dapagliflozin<br>tablet oral 2.5 total daily dose once daily 56 weeks (= 56 week study extension period II) |
| Experimental: 2<br>5mg | Drug: Dapagliflozin<br>Tablet oral 5 mg total daily dose once daily 48 weeks (= 24 week randomised treatment period + 24 week study extension period I) |
| Experimental: 3<br>10mg | Drug: Dapagliflozin<br>Tablet oral 10 mg total daily dose once daily 48 weeks (= 24 week randomised treatment period + 24 week study extension period I)<br>Drug: Dapagliflozin<br>tablet oral 10 mg total daily dose once daily 56 weeks (= 56 week study extension period II)patients that have been treated with 5 mg during the 24 week randomised treatment period and extension I period will during extension II period switched to 10 mg |
| Placebo Comparator: 4 | Drug: Placebo |

| Arms | Assigned Interventions |
|---|---|
| | Placebo |

## Outcome Measures

[See Results Section.]

## Eligibility

Minimum Age: 18 Years

Maximum Age: 80 Years

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Type 2 Diabetes
- Patients with HbA1c ≥7.5% and ≤10.5% and who are on a stable insulin regimen of at least 30 IU of injectable insulin per day either without any other oral antidiabetic drug or with a stable dose of oral antidiabetic drugs

Exclusion Criteria:

- Type 1 Diabetes
- Treatment with more than two additional oral antidiabetic drugs
- Moderate and severe renal (kidney) failure or dysfunction

## Contacts/Locations

Study Officials: John Wilding, MD
Study Principal Investigator
Clinical Sciences CentreUniversity Hospital AintreeLongmoor LaneLiverpool, UK

Locations: Austria
Research Site
Salzburg, Austria

Research Site
Wien, Austria

Bulgaria
Research Site
Pleven, Bulgaria

Research Site
Russe, Bulgaria

Research Site
Sofia, Bulgaria

Research Site
Varna, Bulgaria

Canada, Alberta
Research Site
Calgary, Alberta, Canada

Canada, British Columbia
Research Site
Kelowna, British Columbia, Canada

Research Site
Langley, British Columbia, Canada

Canada, Manitoba
Research Site
Winnipeg, Manitoba, Canada

Canada, New Brunswick
Research Site
Moncton, New Brunswick, Canada

Canada, Newfoundland and Labrador
Research Site
Mount Pearl, Newfoundland and Labrador, Canada

Research Site
St. John's, Newfoundland and Labrador, Canada

Canada, Nova Scotia
Research Site
Halifax, Nova Scotia, Canada

Canada, Ontario
Research Site
Etobicoke, Ontario, Canada

Research Site
Kingston, Ontario, Canada

Research Site
London, Ontario, Canada

Research Site
Oakville, Ontario, Canada

Research Site
Scarborough, Ontario, Canada

Research Site
Thornhill, Ontario, Canada

Canada, Quebec
Research Site
Chicoutimi, Quebec, Canada

Research Site
Longueuil, Quebec, Canada

Research Site
Mirabel, Quebec, Canada

Research Site
Sherbrooke, Quebec, Canada

Finland
Research Site
Lahti, Finland, Finland

Research Site
Helsinki, Finland

Research Site
Joensuu, Finland

Research Site
Jyvaskyla, Finland

Research Site
Kuopio, Finland

Research Site
Oulu, Finland

Research Site
Seinajoki, Finland

Research Site
Turku, Finland

Germany
Research Site
Bad Oeynhausen, Germany

Research Site
Dortmund, Germany

Research Site
Dresden, Germany

Research Site
Essen, Germany

Research Site
Frankfurt, Germany

Research Site
Magdeburg, Germany

Research Site
Münster, Germany

Research Site
Riesa, Germany

Research Site
Wolmirstedt, Germany

United Kingdom
Research Site
Reading, Berks, United Kingdom

Research Site
Aylesbury, Bucks, United Kingdom

Research Site
Ashford, United Kingdom

Research Site
Birmingham, United Kingdom

Research Site
Cardiff, United Kingdom

Research Site
Liverpool, United Kingdom

Research Site
Reading, United Kingdom

Research Site
Swansea, United Kingdom

Hungary
Research Site
Csongrad, Hungary

Research Site
Esztergom, Hungary

Research Site
Gyor, Hungary

Research Site
Kaposvar, Hungary

Research Site
Kecskemet, Hungary

Research Site
Komarom, Hungary

Research Site
Miskolc, Hungary

Research Site
Szekesfehervar, Hungary

Research Site
Veszprem, Hungary

Netherlands
Research Site
Amersfoort, Netherlands

Research Site
Den Helder, Netherlands

Research Site
Leiden, Netherlands

Research Site
Rotterdam, Netherlands

Romania
Research Site
Brasov, Brasov, Romania

Research Site
Tg Mures, Mures, Romania

Research Site
Bucuresti, Romania

Russian Federation
Research Site
Moscow, Russian Federation

Research Site
Nizhnii Novgorod, Russian Federation

Research Site
Saint- Petersburg, Russian Federation

Research Site
St Petersburg, Russian Federation

Research Site
St. Petersburg, Russian Federation

Research Site
St.petersburg, Russian Federation

Research Site
St.-petersburg, Russian Federation

Slovakia
Research Site
Kosice, Slovakia

Research Site
Bratislava, Slovakia

Research Site
Dolny Kubin, Slovakia

Research Site

Levice, Slovakia

Research Site
Lucenec, Slovakia

Research Site
Povazska Bystrica, Slovakia

Research Site
Presov, Slovakia

Spain
Research Site
Sevilla, Andalucia, Spain

Research Site
Sabadell (barcelona), Cataluna, Spain

Research Site
Madrid, Comunidad de Madrid, Spain

Research Site
Alicante, Comunidad Valenciana, Spain

United States, California
Research Site
Fresno, California, United States

Research Site
Greenbrae, California, United States

United States, Georgia
Research Site
Roswell, Georgia, United States

United States, Illinois
Research Site
Chicago, Illinois, United States

Research Site
Springfield, Illinois, United States

United States, Indiana
Research Site
Indianapolis, Indiana, United States

United States, Nebraska
Research Site
Omaha, Nebraska, United States

United States, Pennsylvania
Research Site
Philadelphia, Pennsylvania, United States

United States, Texas
Research Site
Corpus Christi, Texas, United States

Research Site
Dallas, Texas, United States

United States, Virginia
Research Site
Norfolk, Virginia, United States

Research Site
Richmond, Virginia, United States

United States, Washington
Research Site
Tacoma, Washington, United States

## References

Citations:

Links:

Study Data/Documents:

## Participant Flow

| | |
|---|---|
| Recruitment Details | First participant enrolled: 30 April 2008, Last participant completed 24 week period: 19 May 2009. 1240 enrolled at 126 centres in 13 countries. Men and women aged ≥18-≤80 years at time of consenting who have inadequate glycaemic control (HbA1c ≥7.5% and ≤10.5%) and are on a stable insulin regimen (≥30 IU of injectable insulin per day for 8 weeks). |
| Pre-Assignment Details | For two weeks prior to randomization, participants recorded their daily self monitored plasma glucose and insulin use. At randomization, qualified participants were stratified according to their use of other anti-diabetic (OAD) medication or not. No more than 60% of enrolled participants were to take insulin plus OADs. |

Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Dapagliflozin 2.5mg | Dapagliflozin tablet oral 2.5 mg total daily dose once daily 24 weeks |
| Dapagliflozin 5mg | Dapagliflozin tablet oral 5 mg total daily dose once daily 24 weeks |
| Dapagliflozin 10mg | Dapagliflozin tablet oral 10 mg total daily dose once daily 24 weeks |

Overall Study

| | Placebo | Dapagliflozin 2.5mg | Dapagliflozin 5mg | Dapagliflozin 10mg |
|---|---|---|---|---|
| Started | 197 [1] | 202 [2] | 212 [3] | 196 [4] |
| Completed | 168 | 180 | 186 | 178 |
| Not Completed | 29 | 22 | 26 | 18 |
| Withdrawal by Subject | 14 | 10 | 8 | 6 |
| Adverse Event | 6 | 5 | 9 | 6 |
| Lost to Follow-up | 1 | 2 | 1 | 2 |
| Death | 0 | 0 | 1 | 0 |
| Study criteria,compliance,safety, other | 8 | 5 | 7 | 4 |

[1] Of the 197 randomized participants only 193 were included in the full analysis set
[2] All 202 were included in the full analysis set
[3] Of the 212 randomized participants only 211 were included in the full analysis set
[4] Of the 196 randomized participants only 194 were included in the full analysis set

# Baseline Characteristics

Analysis Population Description

Full Analysis Set defined as all randomized participants (as randomized) who received at least one dose of double-blind study medication, who have a non-missing baseline value and at least one post-baseline efficacy value for at least one efficacy variable during double-blind treatment period.

Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Dapagliflozin 2.5mg | Dapagliflozin tablet oral 2.5 mg total daily dose once daily 24 weeks |
| Dapagliflozin 5mg | Dapagliflozin tablet oral 5 mg total daily dose once daily 24 weeks |
| Dapagliflozin 10mg | Dapagliflozin tablet oral 10 mg total daily dose once daily 24 weeks |

Baseline Measures

| | Placebo | Dapagliflozin 2.5mg | Dapagliflozin 5mg | Dapagliflozin 10mg | Total |
|---|---|---|---|---|---|
| Number of Participants | 193 | 202 | 211 | 194 | 800 |
| Age, Continuous<br>[units: Years]<br>Mean (Standard Deviation) | 58.8 (8.61) | 59.8 (7.64) | 59.3 (7.91) | 59.3 (8.75) | 59.3 (8.22) |
| Gender, Male/Female<br>[units: Participants] | | | | | |
| Female | 98 | 102 | 111 | 107 | 418 |
| Male | 95 | 100 | 100 | 87 | 382 |
| Race/Ethnicity, Customized<br>[units: Participants] | | | | | |
| White | 186 | 190 | 200 | 184 | 760 |
| Black/African American | 6 | 3 | 5 | 5 | 19 |
| Asian | 0 | 7 | 3 | 3 | 13 |
| Other | 1 | 2 | 3 | 2 | 8 |
| Body Mass Index<br>[units: kg/m2]<br>Mean (Standard Deviation) | 33.14 (5.862) | 32.95 (5.032) | 32.97 (5.261) | 33.41 (5.061) | 33.11 (5.303) |
| HbA1C<br>[units: Percent]<br>Mean (Standard Deviation) | 8.47 (0.768) | 8.46 (0.780) | 8.62 (0.892) | 8.57 (0.820) | 8.53 (0.819) |

| | Placebo | Dapagliflozin 2.5mg | Dapagliflozin 5mg | Dapagliflozin 10mg | Total |
|---|---|---|---|---|---|
| Fasting plasma glucose<br>[units: mg/dl]<br>Mean (Standard Deviation) | 170.62 (57.165) | 180.11 (59.9) | 185.38 (58.712) | 173.09 (54.916) | 177.58 (57.950) |

## Outcome Measures

1. Primary Outcome Measure:

| | |
|---|---|
| Measure Title | Adjusted Mean Change in HbA1c Levels |
| Measure Description | To assess the efficacy of 2.5 mg, 5 mg and 10 mg dapagliflozin compared to placebo as add-on therapy to insulin in improving glycaemic control in participants with type 2 diabetes who have inadequate glycaemic control on ≥ 30 IU injectable insulin daily for at least 8 weeks prior to enrolment, as determined by the change in HbA1c levels from baseline to Week 24, excluding data after insulin up-titration. |
| Time Frame | Baseline to Week 24 |
| Safety Issue? | No |

Analysis Population Description

Full Analysis Set, participants with non-missing baseline and Week 24 (LOCF) values

Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Dapagliflozin 2.5mg | Dapagliflozin tablet oral 2.5 mg total daily dose once daily 24 weeks |
| Dapagliflozin 5mg | Dapagliflozin tablet oral 5 mg total daily dose once daily 24 weeks |
| Dapagliflozin 10mg | Dapagliflozin tablet oral 10 mg total daily dose once daily 24 weeks |

Measured Values

| | Placebo | Dapagliflozin 2.5mg | Dapagliflozin 5mg | Dapagliflozin 10mg |
|---|---|---|---|---|
| Number of Participants Analyzed | 188 | 198 | 210 | 192 |
| Adjusted Mean Change in HbA1c Levels<br>[units: Percent]<br>Least Squares Mean (95% Confidence Interval) | -0.30 (-0.40 to -0.20) | -0.75 (-0.85 to -0.65) | -0.82 (-0.92 to -0.73) | -0.90 (-1.00 to -0.80) |

Statistical Analysis 1 for Adjusted Mean Change in HbA1c Levels

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Groups | Placebo, Dapagliflozin 2.5mg |
| | Comments | The null hypothesis is given as H0: mean(treat) minus mean(placebo) = 0 versus HA: mean(treat) minus mean(placebo) =/= 0 (with alpha = 0.019 applying Dunnett's adjustment, two-sided) |
| | Non-Inferiority or Equivalence Analysis? | No |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Statistical Test of Hypothesis | P-Value | <0.0001 |
| | Comments | significant at alpha=0.019 (2-sided) applying Dunnett's adjustment. A hierarchical closed testing procedure was used to control the Type I error rate across the primary and key secondary endpoints. |
| | Method | ANCOVA |
| | Comments | with treatment group (all treatment groups included) and stratum (other oral anti-diabetic med use) as effect and baseline value as covariate. |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Mean Difference (Final Values) |
| | Estimated Value | -0.45 |
| | Confidence Interval | (2-Sided) 95%<br>-0.59 to -0.31 |
| | Parameter Dispersion | Type: Standard Error of the mean<br>Value: 0.0726 |
| | Estimation Comments | [Not specified] |

Statistical Analysis 2 for Adjusted Mean Change in HbA1c Levels

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Groups | Placebo, Dapagliflozin 5mg |
| | Comments | The null hypothesis is given as H0: mean(treat) minus mean(placebo) = 0 versus HA: mean(treat) minus mean(placebo) =/= 0 (with alpha = 0.019 applying Dunnett's adjustment, two-sided) |
| | Non-Inferiority or Equivalence Analysis? | No |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Statistical Test of Hypothesis | P-Value | <0.0001 |
| | Comments | significant at alpha=0.019 (2-sided) applying Dunnett's adjustment. A hierarchical closed testing procedure was used to control the Type I error rate across the primary and key secondary endpoints. |
| | Method | ANCOVA |
| | Comments | with treatment group (all treatment groups included) and stratum (other oral anti-diabetic med use) as effect and baseline value as covariate. |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Mean Difference (Final Values) |
| | Estimated Value | -0.52 |
| | Confidence Interval | (2-Sided) 95%<br>-0.66 to -0.38 |
| | Parameter Dispersion | Type: Standard Error of the mean<br>Value: 0.0718 |
| | Estimation Comments | [Not specified] |

Statistical Analysis 3 for Adjusted Mean Change in HbA1c Levels

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Groups | Placebo, Dapagliflozin 10mg |
| | Comments | The null hypothesis is given as H0: mean(treat) minus mean(placebo) = 0 versus HA: mean(treat) minus mean(placebo) =/= 0 (with alpha = 0.019 applying Dunnett's adjustment, two-sided) |
| | Non-Inferiority or Equivalence Analysis? | No |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Statistical Test of Hypothesis | P-Value | <0.0001 |
| | Comments | significant at alpha=0.019 (2-sided) applying Dunnett's adjustment. A hierarchical closed testing procedure was used to control the Type I error rate across the primary and key secondary endpoints. |
| | Method | ANCOVA |
| | Comments | with treatment group (all treatment groups included) and stratum (other oral anti-diabetic med use) as effect and baseline value as covariate. |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Mean Difference (Final Values) |
| | Estimated Value | -0.60 |

| | | |
|---|---|---|
| | Confidence Interval | (2-Sided) 95%<br>-0.74 to -0.45 |
| | Parameter Dispersion | Type: Standard Error of the mean<br>Value: 0.0733 |
| | Estimation Comments | [Not specified] |

2. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Adjusted Mean Change in Body Weight |
| Measure Description | To examine whether treatment with dapagliflozin in combination with insulin is superior in reducing body weight or causing less weight gain as compared to placebo added to insulin treatment after 24 weeks of treatment (LOCF), excluding data after insulin up-titration. |
| Time Frame | Baseline to Week 24 |
| Safety Issue? | No |

Analysis Population Description

Full Analysis Set, participants with non-missing baseline and Week 24 (LOCF) values

Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Dapagliflozin 2.5mg | Dapagliflozin tablet oral 2.5 mg total daily dose once daily 24 weeks |
| Dapagliflozin 5mg | Dapagliflozin tablet oral 5 mg total daily dose once daily 24 weeks |
| Dapagliflozin 10mg | Dapagliflozin tablet oral 10 mg total daily dose once daily 24 weeks |

Measured Values

| | Placebo | Dapagliflozin 2.5mg | Dapagliflozin 5mg | Dapagliflozin 10mg |
|---|---|---|---|---|
| Number of Participants Analyzed | 188 | 198 | 210 | 192 |
| Adjusted Mean Change in Body Weight<br>[units: kg]<br>Least Squares Mean (95% Confidence Interval) | 0.02 (-0.34 to 0.38) | -0.98 (-1.33 to -0.63) | -0.98 (-1.32 to -0.64) | -1.67 (-2.02 to -1.31) |

Statistical Analysis 1 for Adjusted Mean Change in Body Weight

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Groups | Placebo, Dapagliflozin 2.5mg |
| | Comments | The null hypothesis is given as H0: mean(treat) minus mean(placebo) = 0 versus HA: mean(treat) minus mean(placebo) =/= 0 |
| | Non-Inferiority or Equivalence Analysis? | No |
| | Comments | [Not specified] |
| Statistical Test of Hypothesis | P-Value | 0.0001 |
| | Comments | significant at alpha=0.05 (2-sided). Primary and key secondary endpoints are tested following a hierarchical closed testing procedure within treatment group. |
| | Method | ANCOVA |
| | Comments | with treatment group (all treatment groups included) and stratum (other oral anti-diabetic med use) as effect and baseline value as covariate. |
| Method of Estimation | Estimation Parameter | Mean Difference (Final Values) |
| | Estimated Value | -1.00 |
| | Confidence Interval | (2-Sided) 95%<br>-1.50 to -0.49 |
| | Parameter Dispersion | Type: Standard Error of the mean<br>Value: 0.2560 |
| | Estimation Comments | [Not specified] |

Statistical Analysis 2 for Adjusted Mean Change in Body Weight

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Groups | Placebo, Dapagliflozin 5mg |
| | Comments | The null hypothesis is given as H0: mean(treat) minus mean(placebo) = 0 versus HA: mean(treat) minus mean(placebo) =/= 0 |
| | Non-Inferiority or Equivalence Analysis? | No |
| | Comments | [Not specified] |
| Statistical Test of Hypothesis | P-Value | <0.0001 |
| | Comments | significant at alpha=0.05 (2-sided). Primary and key secondary endpoints are tested following a hierarchical closed testing procedure within treatment group. |
| | Method | ANCOVA |

| | | |
|---|---|---|
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Mean Difference (Final Values) |
| | Estimated Value | -1.00 |
| | Confidence Interval | (2-Sided) 95%<br>-1.50 to -0.50 |
| | Parameter Dispersion | Type: Standard Error of the mean<br>Value: 0.2523 |
| | Estimation Comments | [Not specified] |

Statistical Analysis 3 for Adjusted Mean Change in Body Weight

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Groups | Placebo, Dapagliflozin 10mg |
| | Comments | The null hypothesis is given as H0: mean(treat) minus mean(placebo) = 0 versus HA: mean(treat) minus mean(placebo) =/= 0 |
| | Non-Inferiority or Equivalence Analysis? | No |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Statistical Test of Hypothesis | P-Value | <0.0001 |
| | Comments | significant at alpha=0.05 (2-sided). Primary and key secondary endpoints are tested following a hierarchical closed testing procedure within treatment group. |
| | Method | ANCOVA |
| | Comments | with treatment group (all treatment groups included) and stratum (other oral anti-diabetic med use) as effect and baseline value as covariate. |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Mean Difference (Final Values) |
| | Estimated Value | -1.68 |
| | Confidence Interval | (2-Sided) 95%<br>-2.19 to -1.18 |
| | Parameter Dispersion | Type: Standard Error of the mean<br>Value: 0.2578 |
| | Estimation Comments | [Not specified] |

3. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Adjusted Mean Change in Calculated Mean Daily Insulin Dose |
| Measure Description | To examine whether treatment with dapagliflozin in combination with insulin leads to a lower absolute calculated mean daily insulin dose as compared to placebo added to insulin treatment alone, from baseline to week 24, including data after insulin up-titration. |
| Time Frame | Baseline to Week 24 |
| Safety Issue? | No |

Analysis Population Description

Full Analysis Set, participants with non-missing baseline and Week 24 (LOCF) values

Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Dapagliflozin 2.5mg | Dapagliflozin tablet oral 2.5 mg total daily dose once daily 24 weeks |
| Dapagliflozin 5mg | Dapagliflozin tablet oral 5 mg total daily dose once daily 24 weeks |
| Dapagliflozin 10mg | Dapagliflozin tablet oral 10 mg total daily dose once daily 24 weeks |

Measured Values

| | Placebo | Dapagliflozin 2.5mg | Dapagliflozin 5mg | Dapagliflozin 10mg |
|---|---|---|---|---|
| Number of Participants Analyzed | 191 | 200 | 209 | 194 |
| Adjusted Mean Change in Calculated Mean Daily Insulin Dose<br>[units: IU/day]<br>Least Squares Mean (95% Confidence Interval) | 5.08 (3.23 to 6.93) | -1.80 (-3.60 to 0.01) | -0.61 (-2.38 to 1.15) | -1.16 (-2.99 to 0.68) |

Statistical Analysis 1 for Adjusted Mean Change in Calculated Mean Daily Insulin Dose

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Groups | Placebo, Dapagliflozin 2.5mg |
| | Comments | The null hypothesis is given as H0: mean(treat) minus mean(placebo) = 0 versus HA: mean(treat) minus mean(placebo) =/= 0 |
| | Non-Inferiority or Equivalence Analysis? | No |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Statistical Test of Hypothesis | P-Value | <0.0001 |
| | Comments | significant at alpha=0.05 (2-sided). Primary and key secondary endpoints are tested following a hierarchical closed testing procedure within treatment group. |
| | Method | ANCOVA |
| | Comments | with treatment group (all treatment groups included) and stratum (other oral anti-diabetic med use) as effect and baseline value as covariate. |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Mean Difference (Final Values) |
| | Estimated Value | -6.87 |
| | Confidence Interval | (2-Sided) 95%<br>-9.46 to -4.28 |
| | Parameter Dispersion | Type: Standard Error of the mean<br>Value: 1.3195 |
| | Estimation Comments | [Not specified] |

Statistical Analysis 2 for Adjusted Mean Change in Calculated Mean Daily Insulin Dose

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Groups | Placebo, Dapagliflozin 5mg |
| | Comments | The null hypothesis is given as H0: mean(treat) minus mean(placebo) = 0 versus HA: mean(treat) minus mean(placebo) =/= 0 |
| | Non-Inferiority or Equivalence Analysis? | No |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Statistical Test of Hypothesis | P-Value | <0.0001 |
| | Comments | significant at alpha=0.05 (2-sided). Primary and key secondary endpoints are tested following a hierarchical closed testing procedure within treatment group. |
| | Method | ANCOVA |
| | Comments | with treatment group (all treatment groups included) and stratum (other oral anti-diabetic med use) as effect and baseline value as covariate. |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Mean Difference (Final Values) |
| | Estimated Value | -5.69 |
| | Confidence Interval | (2-Sided) 95%<br>-8.25 to -3.13 |
| | Parameter Dispersion | Type: Standard Error of the mean |

| | | |
|---|---|---|
| | | Value: 1.3045 |
| | Estimation Comments | [Not specified] |

Statistical Analysis 3 for Adjusted Mean Change in Calculated Mean Daily Insulin Dose

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Groups | Placebo, Dapagliflozin 10mg |
| | Comments | The null hypothesis is given as H0: mean(treat) minus mean(placebo) = 0 versus HA: mean(treat) minus mean(placebo) =/= 0 |
| | Non-Inferiority or Equivalence Analysis? | No |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Statistical Test of Hypothesis | P-Value | <0.0001 |
| | Comments | significant at alpha=0.05 (2-sided). Primary and key secondary endpoints are tested following a hierarchical closed testing procedure within treatment group. |
| | Method | ANCOVA |
| | Comments | with treatment group (all treatment groups included) and stratum (other oral anti-diabetic med use) as effect and baseline value as covariate. |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Mean Difference (Final Values) |
| | Estimated Value | -6.23 |
| | Confidence Interval | (2-Sided) 95%<br>-8.84 to -3.63 |
| | Parameter Dispersion | Type: Standard Error of the mean<br>Value: 1.3286 |
| | Estimation Comments | [Not specified] |

4. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Proportion of Participants With Calculated Mean Daily Insulin Dose Reduction |
| Measure Description | To examine whether treatment with dapagliflozin in combination with insulin leads to higher percentage of participants with calculated mean daily insulin dose reduction from baseline to week 24 (i.e. reduction >= 10%) as compared to placebo added to insulin treatment. |
| Time Frame | Baseline to Week 24 |
| Safety Issue? | No |

Analysis Population Description

Full Analysis Set, participants with non-missing baseline and Week 24 (LOCF) values

Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Dapagliflozin 2.5mg | Dapagliflozin tablet oral 2.5 mg total daily dose once daily 24 weeks |
| Dapagliflozin 5mg | Dapagliflozin tablet oral 5 mg total daily dose once daily 24 weeks |
| Dapagliflozin 10mg | Dapagliflozin tablet oral 10 mg total daily dose once daily 24 weeks |

Measured Values

| | Placebo | Dapagliflozin 2.5mg | Dapagliflozin 5mg | Dapagliflozin 10mg |
|---|---|---|---|---|
| Number of Participants Analyzed | 191 | 200 | 209 | 194 |
| Proportion of Participants With Calculated Mean Daily Insulin Dose Reduction<br>[units: Percentage of participants]<br>Least Squares Mean (95% Confidence Interval) | 11.0 (6.5 to 15.4) | 18.1 (12.8 to 23.4) | 16.8 (11.7 to 21.8) | 19.7 (14.1 to 25.2) |

Statistical Analysis 1 for Proportion of Participants With Calculated Mean Daily Insulin Dose Reduction

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Groups | Placebo, Dapagliflozin 2.5mg |
| | Comments | H0: proportion(treat) minus proportion(placebo) = 0 versus the alternative HA: proportion(treat) minus proportion(placebo) =/= 0 |
| | Non-Inferiority or Equivalence Analysis? | No |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Statistical Test of Hypothesis | P-Value | 0.0427 |
| | Comments | significant at alpha=0.05 (2-sided). Primary and key secondary endpoints are tested following a hierarchical closed testing procedure within treatment group. |
| | Method | Regression, Logistic |
| | Comments | Methodology of Zhang, Tsiatis & Davidian and Davidian, Tsiatis, Zhang & Lu, adjustment for stratum (other oral anti-diab med use) and baseline value. |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Risk Difference (RD) |

| | | |
|---|---|---|
| | Estimated Value | 7.2 |
| | Confidence Interval | (2-Sided) 95%<br>0.2 to 14.1 |
| | Parameter Dispersion | Type: Standard Error of the mean<br>Value: 3.536 |
| | Estimation Comments | [Not specified] |

Statistical Analysis 2 for Proportion of Participants With Calculated Mean Daily Insulin Dose Reduction

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Groups | Placebo, Dapagliflozin 5mg |
| | Comments | H0: proportion(treat) minus proportion(placebo) = 0 versus the alternative HA: proportion(treat) minus proportion(placebo) =/= 0 |
| | Non-Inferiority or Equivalence Analysis? | No |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Statistical Test of Hypothesis | P-Value | 0.0903 |
| | Comments | not significant at alpha=0.05 (2-sided). Primary and key secondary endpoints are tested following a hierarchical closed testing procedure within treatment group. |
| | Method | Regression, Logistic |
| | Comments | Methodology of Zhang, Tsiatis & Davidian and Davidian, Tsiatis, Zhang & Lu, adjustment for stratum (other oral anti-diab med use) and baseline value. |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Risk Difference (RD) |
| | Estimated Value | 5.8 |
| | Confidence Interval | (2-Sided) 95%<br>-0.9 to 12.5 |
| | Parameter Dispersion | Type: Standard Error of the mean<br>Value: 3.434 |
| | Estimation Comments | [Not specified] |

Statistical Analysis 3 for Proportion of Participants With Calculated Mean Daily Insulin Dose Reduction

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Groups | Placebo, Dapagliflozin 10mg |
| | Comments | H0: proportion(treat) minus proportion(placebo) = 0 versus the alternative HA: proportion(treat) minus proportion(placebo) =/= 0 |

| | | |
|---|---|---|
| | Non-Inferiority or Equivalence Analysis? | No |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Statistical Test of Hypothesis | P-Value | 0.0166 |
| | Comments | significant at alpha=0.05 (2-sided). Primary and key secondary endpoints are tested following a hierarchical closed testing procedure within treatment group. |
| | Method | Regression, Logistic |
| | Comments | Methodology of Zhang, Tsiatis & Davidian and Davidian, Tsiatis, Zhang & Lu, adjustment for stratum (other oral anti-diab med use) and baseline value. |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Risk Difference (RD) |
| | Estimated Value | 8.7 |
| | Confidence Interval | (2-Sided) 95%<br>1.6 to 15.8 |
| | Parameter Dispersion | Type: Standard Error of the mean<br>Value: 3.634 |
| | Estimation Comments | [Not specified] |

5. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Adjusted Mean Change in Fasting Plasma Glucose (FPG) |
| Measure Description | To examine whether treatment with dapagliflozin in combination with insulin is superior in reducing Fasting Plasma Glucose (FPG) as compared to placebo added to insulin treatment after 24 weeks of treatment, excluding data after insulin up-titration. |
| Time Frame | Baseline to Week 24 |
| Safety Issue? | No |

Analysis Population Description

Full Analysis Set, participants with non-missing baseline and Week 24 (LOCF) values

Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Dapagliflozin 2.5mg | Dapagliflozin tablet oral 2.5 mg total daily dose once daily 24 weeks |

| | Description |
|---|---|
| Dapagliflozin 5mg | Dapagliflozin tablet oral 5 mg total daily dose once daily 24 weeks |
| Dapagliflozin 10mg | Dapagliflozin tablet oral 10 mg total daily dose once daily 24 weeks |

Measured Values

| | Placebo | Dapagliflozin 2.5mg | Dapagliflozin 5mg | Dapagliflozin 10mg |
|---|---|---|---|---|
| Number of Participants Analyzed | 177 | 190 | 204 | 183 |
| Adjusted Mean Change in Fasting Plasma Glucose (FPG)<br>[units: mg/dL]<br>Least Squares Mean (95% Confidence Interval) | 3.3 (-3.3 to 9.9) | -12.5 (-18.9 to -6.1) | -18.8 (-25.0 to -12.7) | -21.7 (-28.2 to -15.2) |

Statistical Analysis 1 for Adjusted Mean Change in Fasting Plasma Glucose (FPG)

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Groups | Placebo, Dapagliflozin 2.5mg |
| | Comments | The null hypothesis is given as H0: mean(treat) minus mean(placebo) = 0 versus HA: mean(treat) minus mean(placebo) =/= 0 |
| | Non-Inferiority or Equivalence Analysis? | No |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Statistical Test of Hypothesis | P-Value | 0.0008 |
| | Comments | significant at alpha=0.05 (2-sided). Primary and key secondary endpoints are tested following a hierarchical closed testing procedure within treatment group. |
| | Method | ANCOVA |
| | Comments | with treatment group (all treatment groups included) and stratum (other oral anti-diabetic med use) as effect and baseline value as covariate. |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Mean Difference (Final Values) |
| | Estimated Value | -15.8 |
| | Confidence Interval | (2-Sided) 95%<br>-25.0 to -6.6 |
| | Parameter Dispersion | Type: Standard Error of the mean<br>Value: 4.684 |
| | Estimation Comments | [Not specified] |

Statistical Analysis 2 for Adjusted Mean Change in Fasting Plasma Glucose (FPG)

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Groups | Placebo, Dapagliflozin 5mg |
| | Comments | The null hypothesis is given as H0: mean(treat) minus mean(placebo) = 0 versus HA: mean(treat) minus mean(placebo) =/= 0 |
| | Non-Inferiority or Equivalence Analysis? | No |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Statistical Test of Hypothesis | P-Value | |
| | Comments | Not significant. Hierarchical closed testing procedure within treatment group stopped at previous endpoint. |
| | Method | ANCOVA |
| | Comments | with treatment group (all treatment groups included) and stratum (other oral anti-diabetic med use) as effect and baseline value as covariate. |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Mean Difference (Final Values) |
| | Estimated Value | -22.1 |
| | Confidence Interval | (2-Sided) 95%<br>-31.2 to -13.1 |
| | Parameter Dispersion | Type: Standard Error of the mean<br>Value: 4.616 |
| | Estimation Comments | [Not specified] |

Statistical Analysis 3 for Adjusted Mean Change in Fasting Plasma Glucose (FPG)

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Groups | Placebo, Dapagliflozin 10mg |
| | Comments | The null hypothesis is given as H0: mean(treat) minus mean(placebo) = 0 versus HA: mean(treat) minus mean(placebo) =/= 0 |
| | Non-Inferiority or Equivalence Analysis? | No |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Statistical Test of Hypothesis | P-Value | <0.0001 |
| | Comments | significant at alpha=0.05 (2-sided). Primary and key secondary endpoints are tested following a hierarchical closed testing procedure within treatment group. |

| | | |
|---|---|---|
| | Method | ANCOVA |
| | Comments | with treatment group (all treatment groups included) and stratum (other oral anti-diabetic med use) as effect and baseline value as covariate. |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Mean Difference (Final Values) |
| | Estimated Value | -25.0 |
| | Confidence Interval | (2-Sided) 95%<br>-34.3 to -15.8 |
| | Parameter Dispersion | Type: Standard Error of the mean<br>Value: 4.718 |
| | Estimation Comments | [Not specified] |

6. Other Pre-specified Outcome Measure:

| | |
|---|---|
| Measure Title | Proportion of Participants With Lack of Glycemic Control |
| Measure Description | Participants with lack of glycemic control or insulin up-titration for failing to achieve pre-specified glycemic targets |
| Time Frame | Baseline to Week 24 |
| Safety Issue? | No |

Analysis Population Description
Full Analysis Set

Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Dapagliflozin 2.5mg | Dapagliflozin tablet oral 2.5 mg total daily dose once daily 24 weeks |
| Dapagliflozin 5mg | Dapagliflozin tablet oral 5 mg total daily dose once daily 24 weeks |
| Dapagliflozin 10mg | Dapagliflozin tablet oral 10 mg total daily dose once daily 24 weeks |

Measured Values

| | Placebo | Dapagliflozin 2.5mg | Dapagliflozin 5mg | Dapagliflozin 10mg |
|---|---|---|---|---|
| Number of Participants Analyzed | 193 | 202 | 211 | 194 |
| Proportion of Participants With Lack of Glycemic Control<br>[units: Participants] | 54 | 22 | 24 | 19 |

## Reported Adverse Events

| | |
|---|---|
| Time Frame | Non-serious/serious adverse events on or after the first day and on or prior to the last day of the 24-week double-blind treatment period plus 4/30 days or up to follow-up visit if earlier, or up to and incl the start date of extension period if earlier. |
| Additional Description | Participants were questioned at each study visit about the occurrence of any health problems and any examination conducted at a study visit was assessed in comparison to the status at study entry. |

Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Dapagliflozin 2.5mg | Dapagliflozin tablet oral 2.5 mg total daily dose once daily 24 weeks |
| Dapagliflozin 5mg | Dapagliflozin tablet oral 5 mg total daily dose once daily 24 weeks |
| Dapagliflozin 10mg | Dapagliflozin tablet oral 10 mg total daily dose once daily 24 weeks |

Serious Adverse Events

| | Placebo | Dapagliflozin 2.5mg | Dapagliflozin 5mg | Dapagliflozin 10mg |
|---|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Total | 14/197 (7.11%) | 15/202 (7.43%) | 10/212 (4.72%) | 14/196 (7.14%) |
| Cardiac disorders | | | | |
| Angina Pectoris [A] † | 0/197 (0%) | 1/202 (0.5%) | 1/212 (0.47%) | 0/196 (0%) |
| Atrial Fibrillation [A] † | 1/197 (0.51%) | 0/202 (0%) | 0/212 (0%) | 0/196 (0%) |
| Cardiogenic Shock [A] † | 0/197 (0%) | 0/202 (0%) | 1/212 (0.47%) | 0/196 (0%) |
| Sick Sinus Syndrome [A] † | 0/197 (0%) | 1/202 (0.5%) | 0/212 (0%) | 0/196 (0%) |
| Ear and labyrinth disorders | | | | |
| Vertigo Positional [A] † | 2/197 (1.02%) | 1/202 (0.5%) | 0/212 (0%) | 0/196 (0%) |
| Eye disorders | | | | |

| | Placebo | Dapagliflozin 2.5mg | Dapagliflozin 5mg | Dapagliflozin 10mg |
|---|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Glaucoma [A] † | 0/197 (0%) | 1/202 (0.5%) | 0/212 (0%) | 0/196 (0%) |
| Gastrointestinal disorders | | | | |
| Change Of Bowel Habit [A] † | 0/197 (0%) | 0/202 (0%) | 1/212 (0.47%) | 0/196 (0%) |
| Constipation [A] † | 0/197 (0%) | 0/202 (0%) | 0/212 (0%) | 1/196 (0.51%) |
| Small Intestinal Obstruction [A] † | 0/197 (0%) | 1/202 (0.5%) | 0/212 (0%) | 0/196 (0%) |
| General disorders | | | | |
| Non-Cardiac Chest Pain [A] † | 0/197 (0%) | 1/202 (0.5%) | 0/212 (0%) | 0/196 (0%) |
| Hepatobiliary disorders | | | | |
| Cholelithiasis [A] † | 0/197 (0%) | 1/202 (0.5%) | 0/212 (0%) | 0/196 (0%) |
| Infections and infestations | | | | |
| Abscess Limb [A] † | 0/197 (0%) | 0/202 (0%) | 0/212 (0%) | 1/196 (0.51%) |
| Ear Infection [A] † | 0/197 (0%) | 1/202 (0.5%) | 0/212 (0%) | 0/196 (0%) |
| Erysipelas [A] † | 0/197 (0%) | 0/202 (0%) | 1/212 (0.47%) | 0/196 (0%) |
| Laryngitis [A] † | 1/197 (0.51%) | 0/202 (0%) | 0/212 (0%) | 0/196 (0%) |
| Pneumonia [A] † | 0/197 (0%) | 0/202 (0%) | 0/212 (0%) | 2/196 (1.02%) |
| Injury, poisoning and procedural complications | | | | |
| Ankle Fracture [A] † | 1/197 (0.51%) | 0/202 (0%) | 0/212 (0%) | 1/196 (0.51%) |
| Dislocation Of Joint Prosthesis [A] † | 0/197 (0%) | 0/202 (0%) | 1/212 (0.47%) | 0/196 (0%) |
| Fall [A] † | 0/197 (0%) | 0/202 (0%) | 0/212 (0%) | 1/196 (0.51%) |
| Hip Fracture [A] † | 0/197 (0%) | 0/202 (0%) | 0/212 (0%) | 1/196 (0.51%) |
| Thrombosis In Device [A] † | 0/197 (0%) | 0/202 (0%) | 1/212 (0.47%) | 0/196 (0%) |
| Tibia Fracture [A] † | 0/197 (0%) | 0/202 (0%) | 1/212 (0.47%) | 0/196 (0%) |
| Metabolism and nutrition disorders | | | | |

| | Placebo | Dapagliflozin 2.5mg | Dapagliflozin 5mg | Dapagliflozin 10mg |
|---|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Hyperglycaemia [A] † | 0/197 (0%) | 1/202 (0.5%) | 0/212 (0%) | 0/196 (0%) |
| Hypoglycaemia [A] † | 0/197 (0%) | 0/202 (0%) | 2/212 (0.94%) | 0/196 (0%) |
| Musculoskeletal and connective tissue disorders | | | | |
| Arthralgia [A] † | 0/197 (0%) | 0/202 (0%) | 0/212 (0%) | 1/196 (0.51%) |
| Back Pain [A] † | 1/197 (0.51%) | 1/202 (0.5%) | 0/212 (0%) | 0/196 (0%) |
| Musculoskeletal Pain [A] † | 1/197 (0.51%) | 0/202 (0%) | 0/212 (0%) | 0/196 (0%) |
| Rotator Cuff Syndrome [A] † | 0/197 (0%) | 0/202 (0%) | 0/212 (0%) | 1/196 (0.51%) |
| Tenosynovitis [A] † | 0/197 (0%) | 0/202 (0%) | 0/212 (0%) | 1/196 (0.51%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | | |
| Bile Duct Cancer [A] † | 0/197 (0%) | 0/202 (0%) | 0/212 (0%) | 1/196 (0.51%) |
| Breast Cancer [A] † | 0/197 (0%) | 1/202 (0.5%) | 0/212 (0%) | 0/196 (0%) |
| Chronic Lymphocytic Leukaemia [A] † | 1/197 (0.51%) | 0/202 (0%) | 0/212 (0%) | 0/196 (0%) |
| Hepatic Neoplasm Malignant [A] † | 0/197 (0%) | 0/202 (0%) | 0/212 (0%) | 1/196 (0.51%) |
| Pancreatic Carcinoma [A] † | 0/197 (0%) | 0/202 (0%) | 0/212 (0%) | 1/196 (0.51%) |
| Pancreatic Neoplasm [A] † | 0/197 (0%) | 0/202 (0%) | 1/212 (0.47%) | 0/196 (0%) |
| Prostate Cancer Recurrent [A] † | 0/197 (0%) | 1/202 (0.5%) | 0/212 (0%) | 0/196 (0%) |
| Nervous system disorders | | | | |
| Burning Sensation [A] † | 0/197 (0%) | 0/202 (0%) | 0/212 (0%) | 1/196 (0.51%) |
| Carotid Artery Occlusion [A] † | 0/197 (0%) | 1/202 (0.5%) | 0/212 (0%) | 0/196 (0%) |
| Cerebrovascular Accident [A] † | 1/197 (0.51%) | 1/202 (0.5%) | 0/212 (0%) | 1/196 (0.51%) |
| Hypoglycaemic Coma [A] † | 1/197 (0.51%) | 0/202 (0%) | 0/212 (0%) | 0/196 (0%) |
| Neuropathy Peripheral [A] † | 0/197 (0%) | 1/202 (0.5%) | 0/212 (0%) | 0/196 (0%) |

| | Placebo | Dapagliflozin 2.5mg | Dapagliflozin 5mg | Dapagliflozin 10mg |
|---|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Transient Ischaemic Attack [A] † | 2/197 (1.02%) | 0/202 (0%) | 0/212 (0%) | 0/196 (0%) |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Asthma [A] † | 0/197 (0%) | 1/202 (0.5%) | 0/212 (0%) | 0/196 (0%) |
| Interstitial Lung Disease [A] † | 1/197 (0.51%) | 0/202 (0%) | 0/212 (0%) | 0/196 (0%) |
| Pulmonary Embolism [A] † | 1/197 (0.51%) | 0/202 (0%) | 0/212 (0%) | 0/196 (0%) |
| Surgical and medical procedures | | | | |
| Aortic Valve Replacement [A] † | 0/197 (0%) | 0/202 (0%) | 1/212 (0.47%) | 0/196 (0%) |
| Vascular disorders | | | | |
| Diabetic Microangiopathy [A] † | 0/197 (0%) | 0/202 (0%) | 1/212 (0.47%) | 0/196 (0%) |
| Hypertension [A] † | 0/197 (0%) | 0/202 (0%) | 0/212 (0%) | 1/196 (0.51%) |
| Thrombophlebitis Superficial [A] † | 0/197 (0%) | 0/202 (0%) | 0/212 (0%) | 1/196 (0.51%) |

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 12.0

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

| | Placebo | Dapagliflozin 2.5mg | Dapagliflozin 5mg | Dapagliflozin 10mg |
|---|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Total | 115/197 (58.38%) | 135/202 (66.83%) | 128/212 (60.38%) | 107/196 (54.59%) |
| Endocrine disorders | | | | |
| Hypoglycemia [A] † | 83/197 (42.13%) | 111/202 (54.95%) | 101/212 (47.64%) | 88/196 (44.9%) |
| Infections and infestations | | | | |
| Nasopharyngitis [A] † | 22/197 (11.17%) | 28/202 (13.86%) | 29/212 (13.68%) | 17/196 (8.67%) |
| Upper Respiratory Tract Infection [A] † | 10/197 (5.08%) | 5/202 (2.48%) | 6/212 (2.83%) | 6/196 (3.06%) |
| Urinary Tract Infection [A] † | 6/197 (3.05%) | 10/202 (4.95%) | 12/212 (5.66%) | 11/196 (5.61%) |

| | Placebo | Dapagliflozin 2.5mg | Dapagliflozin 5mg | Dapagliflozin 10mg |
|---|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Musculoskeletal and connective tissue disorders | | | | |
| Back Pain [A] † | 10/197 (5.08%) | 8/202 (3.96%) | 4/212 (1.89%) | 9/196 (4.59%) |
| Nervous system disorders | | | | |
| Headache [A] † | 14/197 (7.11%) | 8/202 (3.96%) | 9/212 (4.25%) | 2/196 (1.02%) |
| Vascular disorders | | | | |
| Hypertension [A] † | 16/197 (8.12%) | 11/202 (5.45%) | 13/212 (6.13%) | 7/196 (3.57%) |

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 12.0

## Limitations and Caveats

For participants who did not complete 24 weeks LOCF (last observation carried forward) was used. Only values prior to insulin up-titration were used for outcome measures except for mean daily insulin dose which was evaluated regardless of.

## More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

If an Investigator requests permission to publish data from this study any such publication is to be agreed with AstraZeneca (AZ) in advance. The investigator agrees to provide AZ as soon as possible with drafts of proposed publications. Unless otherwise agreed, AZ shall have a period of 60 days from receipt of the proposed final manuscript to review it and may within such time require that submission for publication of the manuscript be delayed in order for AZ to file patent applications.

Results Point of Contact:

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