ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 12/18/2013

ClinicalTrials.gov ID: NCT01042977

Study Identification

Unique Protocol ID:	D1690C00019
Brief Title:	Efficacy and Safety in Patients With Type 2 Diabetes Mellitus and Cardiovascular Disease
Official Title:	A 24-week, Multicentre, Randomised, Double-blind,Age-stratified, Placebo Controlled Phase III Study With an 80-week Extension Period to Evaluate the Efficacy and Safety of Dapagliflozin 10 mg Once Daily in Patients With T2DM and Cardiovascular Disease, Who Exhibit Inadequate Glycaemic Control on Usual Care
Secondary IDs:	

Study Status

Record Verification:	December 2013
Overall Status:	Completed
Study Start:	March 2010
Primary Completion:	May 2011 [Actual]
Study Completion:	December 2012 [Actual]

Sponsor/Collaborators

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

Oversight

FDA Regulated?:	Yes

Applicable Trial?:	Section 801 Clinical Trial? Yes Delayed Posting? No
IND/IDE Protocol?:	Yes
IND/IDE Information:	Grantor: CDER IND/IDE Number: 68,652 Serial Number: Has Expanded Access? No
Review Board:	Approval Status: Board Name: Board Affiliation: Phone: Email:
Data Monitoring?:	
Plan to Share Data?:	
Oversight Authorities:	United States: Food and Drug Administration

Study Description

Brief Summary:	This study is carried out to assess whether dapagliflozin improves glycemic control, decreases fasting plasma glucose levels, body weight and blood pressure when added to patient's existing medications and how it compares with their usual treatment without added dapagliflozin. Safety data will be collected and analysed to confirm that treatment with dapagliflozin is safe and well tolerated in patients who have diabetes and cardiovascular disease
Detailed Description:	

Conditions

Conditions:	Type 2 Diabetes Mellitus Cardiovascular Disease Inadequate Glycaemic Control
Keywords:	dapagliflozin diabetes cardiovascular disease

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment

Study Phase:	Phase 3
Intervention Model:	Parallel Assignment
Number of Arms:	2
Masking:	Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Allocation:	Randomized
Endpoint Classification:	Safety/Efficacy Study
Enrollment:	964 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: 1 dapagliflozin 10 mg tablet	Drug: Dapagliflozin 10 mg tablet, oral, once daily, 24- week treatment and 80-week extension period
Placebo Comparator: 2 matching placebo tablet	Drug: Placebo matching placebo tablet, oral, once daily, 24- week treatment and 80-week extension period

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age:	45 Years
Maximum Age:	
Gender:	Both
Accepts Healthy Volunteers?:	No
Criteria:	Inclusion Criteria:

- Type 2 diabetes mellitus.
- Cardiovascular disease
- Uninterrupted anti-diabetic treatment for at least 8 weeks before enrolment

Exclusion Criteria:

- Patients with type 1 diabetes or diabetes insipidus
- Patients with 3 or more oral anti-hyperglycaemic drugs with or without insulin and/or poorly controlled diabetes

- Any clinically significant illness, which would compromise the patient's safety and their participation in the study

Contacts/Locations

Study Officials: Dr. Lawrence A Leiter, MD
Study Principal Investigator
Division of Endocrinology & Metabolism, St Michael's Hospital

Locations: Argentina
Research Site
Buenos Aires, Caba, Argentina

Research Site
Cordoba, Cordoba, Argentina

Research Site
Rosario, Santa Fe, Argentina

Research Site
Salta, Salta, Argentina

Research Site
Santa Fe, Santa Fe, Argentina

Australia, South Australia
Research Site
Adelaide, South Australia, Australia

Research Site
Bedford Park, South Australia, Australia

Australia, New South Wales
Research Site
Blacktown, New South Wales, Australia

Australia, Victoria
Research Site
Box Hill, Victoria, Australia

Australia, New South Wales
Research Site
Broadmeadow, New South Wales, Australia

Australia, Queensland

Research Site
Carina Heights, Queensland, Australia

Australia, Victoria
Research Site
Heidelberg, Victoria, Australia

Australia
Research Site
Herston, Australia

Australia, New South Wales
Research Site
Hornsby, New South Wales, Australia

Australia, South Australia
Research Site
Keswick, South Australia, Australia

Australia, Queensland
Research Site
Kippa-ring, Queensland, Australia

Australia, New South Wales
Research Site
Wollongong, New South Wales, Australia

Austria
Research Site
Wien, Austria

Bulgaria
Research Site
Blagoevgrad, Bulgaria

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Pernik, Bulgaria

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Pleven, Bulgaria

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Russe, Bulgaria

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Sevlievo, Bulgaria

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Sofia, Bulgaria

Research Site
Stara Zagora, Bulgaria

Research Site
Varna, Bulgaria

Canada, Newfoundland and Labrador
Research Site
Bay Roberts, Newfoundland and Labrador, Canada

Canada, Alberta
Research Site
Calgary, Alberta, Canada

Research Site
Edmonton, Alberta, Canada

Canada, Ontario
Research Site
Etobicoke, Ontario, Canada

Canada, Nova Scotia
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Halifax, Nova Scotia, Canada

Canada, Quebec
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Mirabel, Quebec, Canada

Canada, New Brunswick
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Moncton, New Brunswick, Canada

Canada, Ontario
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Ottawa, Ontario, Canada

Canada, Quebec
Research Site
Quebec, Quebec, Canada

Canada, Ontario
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Scarborough, Ontario, Canada

Research Site
Thornhill, Ontario, Canada

Research Site
Toronto, Ontario, Canada

Chile
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Santiago, Region Metropolitana, Chile

Germany
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Damme, Germany

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Dortmund, Germany

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Homburg, Germany

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Munster, Germany

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Wangen, Germany

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Budapest, Hungary

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Gyor, Hungary

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Komarom, Hungary

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Mosonmagyarovar, Hungary

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TAT, Hungary

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Veszprem, Hungary

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Chrzanow, Poland

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Grodzisk Mazowiecki, Poland

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Zielona Gora, Poland

United States, Louisiana
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Anaheim, California, United States

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Asheboro, North Carolina, United States

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Austin, Texas, United States

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Avon, Indiana, United States

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Berlin, New Jersey, United States

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Clearwater, Florida, United States

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Corpus Christi, Texas, United States

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Dallas, Texas, United States

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Delray Beach, Florida, United States

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Erie, Pennsylvania, United States

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Fargo, North Dakota, United States

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Franklin, Indiana, United States

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Greenfield, Indiana, United States

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Holland, Pennsylvania, United States

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Huntington Beach, California, United States

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Irving, Texas, United States

United States, Michigan
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Kalamazoo, Michigan, United States

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Lancaster, Pennsylvania, United States

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Livonia, Michigan, United States

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Los Angeles, California, United States

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Manassas, Virginia, United States

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Media, Pennsylvania, United States

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Mission Hills, California, United States

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Muncie, Indiana, United States

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New Smyrna Beach, Florida, United States

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Paducah, Kentucky, United States

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Richardson, Texas, United States

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Rockville, Maryland, United States

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Sacramento, California, United States

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San Antonio, Texas, United States

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San Diego, California, United States

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Scottsdale, Arizona, United States

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Springfield, Illinois, United States

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Sugarland, Texas, United States

United States, Kansas
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Topeka, Kansas, United States

United States, California
Research Site
Torrance, California, United States

United States, Iowa
Research Site
Waterloo, Iowa, United States

United States, Florida
Research Site
Dania, Florida, United States

References

Citations:

Links:

Study Data/Documents:

Participant Flow

Recruitment Details	First participant enrolled 15 Mar 2010, last part. last visit for 24-week period: 30 May 2011. 1489 part. enrolled, 964 randomized in USA, Canada, Australia, Chile, Argentina and 5 European countries (value presented in 'Enrolment' field). One add. part. treated but not randomized. Part. with T2DM and CVD who showed inadequate glycemic control.
Pre-Assignment Details	During a placebo lead-in period, participants were counselled on dietary and life-style modifications. Anti-diabetic therapy should be kept constant 4 weeks prior to enrolment. Participants eligible for the study were stratified according to age (<65 years or ≥65 years), insulin use and time from most recent qualifying CV event (>1 or ≤1 year).

Reporting Groups

	Description
Dapagliflozin	Dapagliflozin 10 mg plus usual care
Placebo	Placebo plus usual care

Overall Study

	Dapagliflozin	Placebo
Started	482 [1]	483 [2]
Completed	441	428
Not Completed	41	55
Adverse Event	4	12
Death	2	1
Withdrawal by Subject	8	16
Lost to Follow-up	0	2
Poor/non-compliance	3	4
Subject no longer meets study criteria	15	13
Incorrect enrollment	6	4
Safety	0	2
Administrative reason by sponsor	0	1
Various	3	0

[1] Of 482 part. 480 were included in full analysis set. Thereof, 1 part. treated but not randomized.
[2] Of the 483 participants only 482 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
Dapagliflozin	Dapagliflozin 10 mg plus usual care
Placebo	Placebo plus usual care

Baseline Measures

	Dapagliflozin	Placebo	Total
Number of Participants	480	482	962
Age, Continuous [units: Years] Mean (Standard Deviation)	63.9 (7.60)	63.6 (7.02)	63.8 (7.31)
Gender, Male/Female [units: Participants]			
Female	159	159	318
Male	321	323	644
Race/Ethnicity, Customized [units: Participants]			
White	454	449	903
Black/African American	9	10	19
Asian	6	7	13
Other	11	16	27
HbA1c [units: Percent] Mean (Standard Deviation)	8.04 (0.759)	8.08 (0.795)	8.06 (0.777)

	Dapagliflozin	Placebo	Total
Body weight [units: kg] Mean (Standard Deviation)	94.53 (17.804)	93.23 (16.842)	93.88 (17.332)
Systolic Blood Pressure [units: mmHg] Mean (Standard Deviation)	134.9 (14.53)	134.6 (13.96)	134.7 (14.24)
Number of participants with BMI >= 27 kg/m2 at baseline [units: Participants]			
< 25 kg/m²	15	31	46
>= 25 kg/m²	465	451	916
>= 27 kg/m²	428	416	844
>= 30 kg/m²	339	325	664

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Adjusted Mean Change in HbA1c Levels
Measure Description	To compare the glycemic efficacy of dapagliflozin 10 mg versus placebo when added to usual care in type 2 diabetes patients with cardiovascular disease, measured as the mean change in HbA1c from baseline to week 24.
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
Dapagliflozin	Dapagliflozin 10 mg plus usual care
Placebo	Placebo plus usual care

Measured Values

	Dapagliflozin	Placebo
Number of Participants Analyzed	474	471

	Dapagliflozin	Placebo
Adjusted Mean Change in HbA1c Levels [units: Percent] Least Squares Mean (95% Confidence Interval)	-0.33 (-0.42 to -0.25)	0.07 (-0.02 to 0.15)

Statistical Analysis 1 for Adjusted Mean Change in HbA1c Levels

Statistical Analysis Overview	Comparison Groups	Dapagliflozin, Placebo
	Comments	H0: mean(treat) minus mean(placebo) = 0 versus the alternative 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=0.025 (2-sided). A hierarchical closed testing procedure was used to control Type I error across the primary & key secondary objectives
	Method	ANCOVA
	Comments	with treatment group and stratum as effects and baseline value as covariate for each endpoint

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.40
	Confidence Interval	(2-Sided) 95% -0.50 to -0.30
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.0489
	Estimation Comments	with stratum = age-by-insulin use-by-time from most recent qualifying CV event

2. Primary Outcome Measure:

Measure Title	Proportion of Responders Meeting All Criteria of a 3-item Endpoint of Clinical Benefit

Measure Description	To compare the clinical benefit of dapagliflozin 10 mg versus placebo when added to usual care in type 2 diabetes patients with cardiovascular disease at week 24, measured as the proportion of responders for a 3-item endpoint of clinical benefit, defined as an absolute drop of 0.5% or more from baseline HbA1c, and a relative drop of 3% or more from baseline for total body weight, and an absolute drop of 3 mmHg or more from baseline in seated systolic blood pressure.
Time Frame	Baseline to Week 24
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Dapagliflozin	Dapagliflozin 10 mg plus usual care
Placebo	Placebo plus usual care

Measured Values

	Dapagliflozin	Placebo
Number of Participants Analyzed	468	469
Proportion of Responders Meeting All Criteria of a 3-item Endpoint of Clinical Benefit [units: Percentage of participants] Number (95% Confidence Interval)	10.0 (7.3 to 12.8)	1.9 (0.7 to 3.2)

Statistical Analysis 1 for Proportion of Responders Meeting All Criteria of a 3-item Endpoint of Clinical Benefit

Statistical Analysis Overview	Comparison Groups	Dapagliflozin, Placebo
	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	<0.0001
	Comments	Significant at alpha=0.025 (2-sided). A hierarchical closed testing procedure was used to control Type I error across the primary & key secondary objectives

	Method	Cochran-Mantel-Haenszel
	Comments	with age-by-insulin use-by-time from most recent qualifying CV event as stratum

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	7.0
	Confidence Interval	(2-Sided) 95% 4.3 to 9.8
	Estimation Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Adjusted Mean Percent Change in Body Weight
Measure Description	To compare the mean percent change in body weight from baseline to week 24 between dapagliflozin 10 mg versus placebo.
Time Frame	Baseline to Week 24
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
Dapagliflozin	Dapagliflozin 10 mg plus usual care
Placebo	Placebo plus usual care

Measured Values

	Dapagliflozin	Placebo
Number of Participants Analyzed	480	481
Adjusted Mean Percent Change in Body Weight [units: Percentage of Body Weight] Least Squares Mean (95% Confidence Interval)	-2.53 (-2.87 to -2.18)	-0.61 (-0.96 to -0.26)

Statistical Analysis 1 for Adjusted Mean Percent Change in Body Weight

Statistical Analysis Overview	Comparison Groups	Dapagliflozin, Placebo
	Comments	H0: mean(treat) minus mean(placebo) = 0 versus the alternative 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
	Method	ANCOVA
	Comments	with treatment group and stratum as effects and baseline value as covariate
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-1.93
	Confidence Interval	(2-Sided) 95% -2.31 to -1.54
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.1957
	Estimation Comments	with stratum = age-by-insulin use-by-time from most recent qualifying CV event

4. Secondary Outcome Measure:

Measure Title	Proportion of Participants With a Reduction From Baseline of 5% or More in Body Weight in Participants With Baseline BMI ≥27 kg/m²
Measure Description	To compare the proportion of participants with BMI baseline ≥27 kg/m2 with a reduction from baseline of 5% or more in body weight with dapagliflozin 10 mg versus placebo from baseline to week 24. Least Squares Mean represents the percent of participants adjusted for baseline body weight and age stratum.
Time Frame	Baseline to Week 24
Safety Issue?	No

Analysis Population Description

Full Analysis Set, subjects with baseline BMI ≥27 kg/m2 and Week 24 (LOCF) values

Reporting Groups

	Description
Dapagliflozin	Dapagliflozin 10 mg plus usual care
Placebo	Placebo plus usual care

Measured Values

	Dapagliflozin	Placebo
Number of Participants Analyzed	428	415
Proportion of Participants With a Reduction From Baseline of 5% or More in Body Weight in Participants With Baseline BMI ≥27 kg/m² [units: Percentage of participants] Least Squares Mean (95% Confidence Interval)	18.4 (14.8 to 22.1)	4.8 (2.8 to 6.9)

Statistical Analysis 1 for Proportion of Participants With a Reduction From Baseline of 5% or More in Body Weight in Participants With Baseline BMI ≥27 kg/m²

Statistical Analysis Overview	Comparison Groups	Dapagliflozin, Placebo
	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	<0.0001
	Comments	Significant at alpha=0.05 (2-sided). Primary and key secondary endpoints are tested following a hierarchical closed testing procedure
	Method	Regression, Logistic
	Comments	Based on methodology of Zhang, Tsiatis & Davidian and Davidian, Tsiatis, Zhang & Lu, with adjustment for baseline total body weight and age stratum

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	13.6
	Confidence Interval	(2-Sided) 95% 9.4 to 17.8
	Parameter Dispersion	Type: Standard Error of the mean

		Value: 2.149
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Adjusted Mean Change in Systolic Blood Pressure at Week 8 (LOCF)
Measure Description	To compare the mean change in seated systolic blood pressure from baseline to week 8 between dapagliflozin 10 mg versus placebo.
Time Frame	Baseline to Week 8
Safety Issue?	No

Analysis Population Description

Full Analysis Set, subjects with non-missing baseline and Week 8 (LOCF) values

Reporting Groups

	Description
Dapagliflozin	Dapagliflozin 10 mg plus usual care
Placebo	Placebo plus usual care

Measured Values

	Dapagliflozin	Placebo
Number of Participants Analyzed	473	479
Adjusted Mean Change in Systolic Blood Pressure at Week 8 (LOCF) [units: mmHg] Least Squares Mean (95% Confidence Interval)	-1.85 (-3.25 to -0.45)	0.86 (-0.53 to 2.26)

Statistical Analysis 1 for Adjusted Mean Change in Systolic Blood Pressure at Week 8 (LOCF)

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

Statistical Test of Hypothesis	P-Value	0.0007
	Comments	Significant at alpha=0.05 (2-sided). Primary and key secondary endpoints are tested following a hierarchical closed testing procedure
	Method	ANCOVA
	Comments	with treatment group and stratum as effects and baseline value as covariate

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-2.71
	Confidence Interval	(2-Sided) 95% -4.28 to -1.15
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.7977
	Estimation Comments	with stratum = age-by-insulin use-by-time from most recent qualifying CV event

6. Secondary Outcome Measure:

Measure Title	Adjusted Mean Change in Seated Systolic Blood Pressure at Week 24 (LOCF)
Measure Description	To compare the mean change in seated systolic blood pressure from baseline to week 24 between dapagliflozin 10 mg versus placebo.
Time Frame	Baseline to Week 24
Safety Issue?	No

Analysis Population Description

Full Analysis set, subjects with non-missing baseline and Week 24 (LOCF) values

Reporting Groups

	Description
Dapagliflozin	Dapagliflozin 10 mg plus usual care
Placebo	Placebo plus usual care

Measured Values

	Dapagliflozin	Placebo
Number of Participants Analyzed	473	479
Adjusted Mean Change in Seated Systolic Blood Pressure at Week 24 (LOCF)	-2.70 (-4.10 to -1.30)	0.32 (-1.07 to 1.72)

	Dapagliflozin	Placebo
[units: mmHg] Least Squares Mean (95% Confidence Interval)		

Statistical Analysis 1 for Adjusted Mean Change in Seated Systolic Blood Pressure at Week 24 (LOCF)

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

Statistical Test of Hypothesis	P-Value	0.0002
	Comments	Significant at alpha=0.05 (2-sided). Primary and key secondary endpoints are tested following a hierarchical closed testing procedure
	Method	ANCOVA
	Comments	with treatment group and stratum as effects and baseline value as covariate

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-3.02
	Confidence Interval	(2-Sided) 95% -4.59 to -1.46
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.7983
	Estimation Comments	with stratum = age-by-insulin use-by-time from most recent qualifying CV event

7. Secondary Outcome Measure:

Measure Title	Adjusted Mean Change in Seated Systolic Blood Pressure (SBP) at Week 8 (LOCF) in Participants With Baseline SBP>=130 mmHg
Measure Description	To compare the mean change in seated systolic blood pressure (SBP) in participants with baseline seated SBP ≥130 mmHg achieved with dapagliflozin versus placebo from baseline to week 8.
Time Frame	Baseline to Week 8
Safety Issue?	No

Analysis Population Description

Full Analysis set, participants with baseline seated SBP ≥130 mmHg and Week 8 (LOCF) value

Reporting Groups

	Description
Dapagliflozin	Dapagliflozin 10 mg plus usual care
Placebo	Placebo plus usual care

Measured Values

	Dapagliflozin	Placebo
Number of Participants Analyzed	300	309
Adjusted Mean Change in Seated Systolic Blood Pressure (SBP) at Week 8 (LOCF) in Participants With Baseline SBP>=130 mmHg [units: mmHg] Least Squares Mean (95% Confidence Interval)	-5.33 (-7.02 to -3.64)	-1.89 (-3.58 to -0.20)

Statistical Analysis 1 for Adjusted Mean Change in Seated Systolic Blood Pressure (SBP) at Week 8 (LOCF) in Participants With Baseline SBP>=130 mmHg

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

Statistical Test of Hypothesis	P-Value	0.0004
	Comments	Significant at alpha=0.05 (2-sided). Primary and key secondary endpoints are tested following a hierarchical closed testing procedure
	Method	ANCOVA
	Comments	with treatment group and stratum as effects and baseline value as covariate

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-3.44
	Confidence Interval	(2-Sided) 95%

		-5.35 to -1.53
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.9746
	Estimation Comments	with stratum = age-by-insulin use-by-time from most recent qualifying CV event

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 plus 4/30 days or up to follow-up visit if earlier, or up to and including 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
Dapagliflozin	Dapagliflozin 10 mg plus usual care
Placebo	Placebo plus usual care

Serious Adverse Events

	Dapagliflozin	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Total	41/482 (8.51%)	46/483 (9.52%)
Cardiac disorders		
Acute coronary syndrome [A] †	2/482 (0.41%)	0/483 (0%)
Acute myocardial infarction [A] †	0/482 (0%)	1/483 (0.21%)
Angina pectoris [A] †	1/482 (0.21%)	1/483 (0.21%)
Angina unstable [A] †	3/482 (0.62%)	2/483 (0.41%)
Atrial fibrillation [A] †	2/482 (0.41%)	3/483 (0.62%)
Cardiac failure [A] †	1/482 (0.21%)	1/483 (0.21%)
Cardiac failure congestive [A] †	0/482 (0%)	1/483 (0.21%)

	Dapagliflozin	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Coronary artery disease [A] †	1/482 (0.21%)	1/483 (0.21%)
Myocardial infarction [A] †	3/482 (0.62%)	1/483 (0.21%)
Ventricular tachycardia [A] †	1/482 (0.21%)	0/483 (0%)
Ear and labyrinth disorders		
Acute vestibular syndrome [A] †	0/482 (0%)	1/482 (0.21%)
Gastrointestinal disorders		
Abdominal pain [A] †	1/482 (0.21%)	0/483 (0%)
Gastric haemorrhage [A] †	1/482 (0.21%)	0/483 (0%)
Gastric polyps [A] †	1/482 (0.21%)	0/483 (0%)
Gastritis [A] †	1/482 (0.21%)	0/483 (0%)
Haemorrhoids [A] †	1/482 (0.21%)	0/483 (0%)
Rectal haemorrhage [A] †	0/482 (0%)	1/483 (0.21%)
Small intestine obstruction [A] †	0/482 (0%)	1/483 (0.21%)
General disorders		
Chest pain [A] †	0/482 (0%)	3/483 (0.62%)
Immune system disorders		
Drug hypersensitivity [A] †	1/482 (0.21%)	0/482 (0%)
Infections and infestations		
Bronchitis [A] †	1/482 (0.21%)	0/483 (0%)
Gastroenterits [A] †	0/482 (0%)	1/483 (0.21%)
Herpes zoster [A] †	0/482 (0%)	1/483 (0.21%)
Lung abscess [A] †	0/482 (0%)	1/483 (0.21%)
Osteomyelitis [A] †	1/482 (0.21%)	0/483 (0%)

	Dapagliflozin	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Peritonsillar abscess [A] †	1/482 (0.21%)	0/483 (0%)
Pneumonia [A] †	0/482 (0%)	2/483 (0.41%)
Pyelonephritis [A] †	0/482 (0%)	1/483 (0.21%)
Respiratory tract infection [A] †	2/482 (0.41%)	1/483 (0.21%)
Upper respiratory tract infection [A] †	0/482 (0%)	1/483 (0.21%)
Injury, poisoning and procedural complications		
Cervical vertebral fracture [A] †	0/482 (0%)	1/482 (0.21%)
Clavicle fracture [A] †	0/482 (0%)	1/482 (0.21%)
Contusion [A] †	0/482 (0%)	1/482 (0.21%)
Excoriation [A] †	1/482 (0.21%)	0/482 (0%)
Femoral neck fracture [A] †	0/482 (0%)	1/482 (0.21%)
Road traffic accident [A] †	0/482 (0%)	1/482 (0.21%)
Vascular graft thrombosis [A] †	0/482 (0%)	1/482 (0.21%)
Investigations		
Blood parathyroid hormone decreased [A] †	1/482 (0.21%)	0/482 (0%)
Metabolism and nutrition disorders		
Hyperglycaemia [A] †	0/482 (0%)	1/482 (0.21%)
Hypoglycaemia [A] †	1/482 (0.21%)	0/482 (0%)
Musculoskeletal and connective tissue disorders		
Back pain [A] †	0/482 (0%)	2/483 (0.41%)
Intervertebral disc disorder [A] †	1/482 (0.21%)	0/483 (0%)
Intervertebral disc protrusion [A] †	1/482 (0.21%)	0/483 (0%)
Osteoarthritis [A] †	1/482 (0.21%)	0/483 (0%)

	Dapagliflozin	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Polyarthritis [A] †	1/482 (0.21%)	0/483 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Adrenal adenoma [A] †	1/482 (0.21%)	0/483 (0%)
Basal cell carcinoma [A] †	1/482 (0.21%)	0/483 (0%)
Benign salivary gland neoplasm [A] †	1/482 (0.21%)	0/483 (0%)
Bladder cancer [A] †	0/482 (0%)	1/483 (0.21%)
Meningioma [A] †	1/482 (0.21%)	0/483 (0%)
Prostate cancer [A] †	0/482 (0%)	1/483 (0.21%)
Renal neoplasm [A] †	1/482 (0.21%)	0/483 (0%)
Nervous system disorders		
Carotid artery stenosis [A] †	2/482 (0.41%)	0/483 (0%)
Cerebrovascular accident [A] †	0/482 (0%)	2/483 (0.41%)
Dizziness [A] †	1/482 (0.21%)	1/483 (0.21%)
Ischaemic stroke [A] †	1/482 (0.21%)	1/483 (0.21%)
Spinal cord compression [A] †	1/482 (0.21%)	0/483 (0%)
Syncope [A] †	1/482 (0.21%)	1/483 (0.21%)
Transient ischaemic attack [A] †	0/482 (0%)	1/483 (0.21%)
Psychiatric disorders		
Schizophrenia, paranoid type [A] †	0/482 (0%)	1/483 (0.21%)
Renal and urinary disorders		
Bladder diverticulum [A] †	1/482 (0.21%)	0/483 (0%)
Nephrolithiasis [A] †	0/482 (0%)	1/483 (0.21%)
Renal failure [A] †	1/482 (0.21%)	0/483 (0%)

	Dapagliflozin	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Renal failure acute [A] †	0/482 (0%)	1/482 (0.21%)
Urinary retention [A] †	1/482 (0.21%)	0/483 (0%)
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism [A] †	1/482 (0.21%)	1/482 (0.21%)
Skin and subcutaneous tissue disorders		
Angioedema [A] †	1/482 (0.21%)	0/482 (0%)
Skin ulcer [A] †	1/482 (0.21%)	0/482 (0%)
Surgical and medical procedures		
Angioplasty [A] †	1/482 (0.21%)	0/482 (0%)
Vascular disorders		
Circulatory collapse [A] †	0/482 (0%)	1/482 (0.21%)
Deep vein thrombosis [A] †	0/482 (0%)	1/482 (0.21%)
Diabetic vascular disorder [A] †	1/482 (0.21%)	0/482 (0%)
Extremity necrosis [A] †	0/482 (0%)	1/482 (0.21%)
Hypertensive crisis [A] †	0/482 (0%)	1/482 (0.21%)
Peripheral arterial occlusive disease [A] †	2/482 (0.41%)	2/482 (0.41%)
Peripheral ischaemia [A] †	0/482 (0%)	1/482 (0.21%)
Thrombosis [A] †	0/482 (0%)	1/482 (0.21%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 14.0

Other Adverse Events

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

	Dapagliflozin	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)
Total	147/482 (30.5%)	134/483 (27.74%)
Endocrine disorders		
Hypoglycemia [A] †	101/482 (20.95%)	84/483 (17.39%)
Infections and infestations		
Nasopharyngitis [A] †	26/482 (5.39%)	26/483 (5.38%)
Upper respiratory tract infection [A] †	15/482 (3.11%)	24/483 (4.97%)
Urinary tract infection [A] †	27/482 (5.6%)	18/483 (3.73%)

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA 14.0

Limitations and Caveats

For participants who did not complete 8 and/or 24 weeks, respectively, LOCF was used. For HbA1c: excluding data after glycemic rescue, Weight: including data after rescue, SBP: excluding data after anti-hypertensive rescue.

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.

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