ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 09/24/2013

ClinicalTrials.gov ID: NCT01031680

Study Identification

Unique Protocol ID:	D1690C00018
Brief Title:	Efficacy and Safety in Patients With Type 2 Diabetes Mellitus, Cardiovascular Disease and Hypertension
Official Title:	A 24-week, Multicentre, Randomised, Double-blind, Age-stratified, Placebo Controlled, Phase III Study With a 80-week Extension Period to Evaluate the Efficacy and Safety of Dapagliflozin 10 mg Once Daily in Pts With T2DM, CV Disease and Hypertension Who Exhibit Inadequate Glycaemic Control on Usual Care
Secondary IDs:	

Study Status

Record Verification:	September 2013
Overall Status:	Completed
Study Start:	February 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: Not Yet Assigned 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 lowers blood glucose, body weight and blood pressure, when added to patients 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, cardiovascular disease and hypertension.
Detailed Description:	

Conditions

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

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:	922 [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

- Hypertension

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. William Cefalu
Study Principal Investigator
Pennington Biomedical Research Center

Locations: Argentina
Research Site
Buenos Aires, Argentina

Research Site
Caba, Caba, Argentina

Research Site
Cordoba, Cordoba, Argentina

Research Site
La Plata, Buenos Aires, Argentina

Research Site
Mendoza, Mendoza, Argentina

Research Site
Santa Fe, Santa Fe, Argentina

Canada, Alberta
Research Site
Calgary, Alberta, Canada

Canada, Newfoundland and Labrador
Research Site
Carbonear, Newfoundland and Labrador, Canada

Canada, Ontario
Research Site
Courtice, Ontario, Canada

Research Site
Hamilton, Ontario, Canada

Canada, Quebec
Research Site
Lachine, Quebec, Canada

Research Site
Laval, Quebec, Canada

Canada, Ontario
Research Site
Mississauga, Ontario, Canada

Canada, Quebec
Research Site
Montreal, Quebec, Canada

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

Canada, British Columbia
Research Site
New Westminster, British Columbia, Canada

Canada, Ontario
Research Site
Ottawa, Ontario, Canada

Canada, Quebec
Research Site
Saint-marc-des-carrieres, Quebec, Canada

Research Site
Sherbrooke, Quebec, Canada

Canada, Ontario
Research Site
Smiths Falls, Ontario, Canada

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

Canada, Ontario

Research Site
Toronto, Ontario, Canada

Canada, Manitoba
Research Site
Winnipeg, Manitoba, Canada

Germany
Research Site
Bad Nauheim, Germany

Research Site
Berlin, Germany

Research Site
Erdmannhausen, Germany

Research Site
Frankfurt, Germany

Research Site
Hamburg, Germany

Research Site
Heilbronn, Germany

Research Site
Hildesheim, Germany

Research Site
Mainz, Germany

Research Site
Munster, Germany

Research Site
Potsdam, BR, Germany

Research Site
Speyer, Germany

Research Site
Wahlstedt, Germany

Romania
Research Site

Braila, Romania

Research Site
Brasov, Brasov, Romania

Research Site
Bucharest, Romania

Research Site
Constanta, Romania

Research Site
Iasi, Romania

Research Site
Sibiu, Romania

Research Site
Suceava, Suceava, Romania

Slovakia
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Banska Bystrica, Slovakia

Research Site
Bratislava, Slovakia

Research Site
Dolny Kubin, Slovakia

Research Site
Komarno, Slovakia

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Kosice, Slovakia

Research Site
Kysucke Nove Mesto, Slovakia

Research Site
Liptovsky Hradok, Slovakia

Research Site
Lucenec, Slovakia

Research Site

Nitra, Slovakia

Research Site
Povazska Bystrica, Slovakia

Research Site
Prievidza, Slovakia

Research Site
Rimavska Sobota, Slovakia

Research Site
Ruzomberok, Slovakia

Research Site
Zilina, Slovakia

Spain
Research Site
A Coruna, Galicia, Spain

Research Site
Barcelona, Cataluna, Spain

Research Site
Cordoba, Andalucia, Spain

Research Site
Granada, Andalucia, Spain

Research Site
Lerida, Cataluna, Spain

Research Site
Majadahonda, Comunidad de Madrid, Spain

Research Site
Olot (girona), Cataluna, Spain

Research Site
Oviedo, Asturias, Spain

Research Site
Palma de Mallorca, Islas Baleares, Spain

Research Site

San Juan (alicante), Comunidad Valenciana, Spain

Research Site
Santiago de Compostela, Galicia, Spain

Research Site
Sevilla, Andalucia, Spain

Research Site
Valencia, Comunidad Valenciana, Spain

Taiwan
Research Site
Changhua, Taiwan

Research Site
Kaohsiung, Taiwan

Research Site
Taichung, Taiwan

Research Site
Tainan County, Taiwan, Taiwan

Research Site
Taipei, Taiwan

Research Site
Tao-yuan, Taiwan

United States, Maryland
Research Site
Baltimore, Maryland, United States

United States, Louisiana
Research Site
Baton Rouge, Louisiana, United States

United States, New Jersey
Research Site
Brick, New Jersey, United States

United States, New York
Research Site
Bronx, New York, United States

United States, Texas
Research Site
Carrollton, Texas, United States

United States, South Carolina
Research Site
Charleston, South Carolina, United States

United States, Illinois
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Chicago, Illinois, United States

United States, Ohio
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Cincinnati, Ohio, United States

United States, Florida
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Clearwater, Florida, United States

United States, Colorado
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Colorado Springs, Colorado, United States

United States, Georgia
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Columbus, Georgia, United States

United States, Texas
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Dallas, Texas, United States

United States, Virginia
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Danville, Virginia, United States

United States, Ohio
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Dayton, Ohio, United States

United States, Georgia
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Decatur, Georgia, United States

United States, Florida
Research Site

Deerfield Beach, Florida, United States

United States, Texas
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Fort Worth, Texas, United States

United States, California
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Garden Grove, California, United States

United States, Alabama
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Gulf Shores, Alabama, United States

United States, Florida
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Hialeah, Florida, United States

Research Site
Hollywood, Florida, United States

United States, Hawaii
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Honolulu, Hawaii, United States

United States, Texas
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Houston, Texas, United States

United States, California
Research Site
Huntington Park, California, United States

United States, Florida
Research Site
Jacksonville, Florida, United States

United States, Missouri
Research Site
Kansas City, Missouri, United States

United States, Tennessee
Research Site
Kingsport, Tennessee, United States

United States, Louisiana

Research Site
Lake Charles, Louisiana, United States

United States, California
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Lancaster, California, United States

United States, Nevada
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Las Vegas, Nevada, United States

United States, Florida
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Miami, Florida, United States

United States, New York
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New Hyde Park, New York, United States

United States, Texas
Research Site
North Richland Hills, Texas, United States

United States, Utah
Research Site
Ogden, Utah, United States

United States, Oklahoma
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Oklahoma City, Oklahoma, United States

United States, New Jersey
Research Site
Oradell, New Jersey, United States

United States, Pennsylvania
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Philadelphia, Pennsylvania, United States

United States, Arizona
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Phoenix, Arizona, United States

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Phoenixville, Pennsylvania, United States

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Pittsburgh, Pennsylvania, United States

United States, Texas
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Plano, Texas, United States

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Port Charlotte, Florida, United States

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Port Orange, Florida, United States

United States, Pennsylvania
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Reading, Pennsylvania, United States

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Salinas, California, United States

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San Antonio, Texas, United States

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San Ramon, California, United States

United States, Washington
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Spokane, Washington, United States

United States, Missouri
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St Louis, Missouri, United States

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Stone Mountain, Georgia, United States

United States, Washington

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Tacoma, Washington, United States

United States, Florida
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Tampa, Florida, United States

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Tomball, Texas, United States

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Tustin, California, United States

United States, Connecticut
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Waterbury, Connecticut, United States

United States, Louisiana
Research Site
West Monroe, Louisiana, United States

United States, Kansas
Research Site
Wichita, Kansas, United States

United States, Florida
Research Site
Winter Park, Florida, United States

Vietnam
Research Site
Hanoi, Vietnam, Vietnam

Research Site
Ho Chi Minh, Vietnam

United States, California
Research Site
Burbank, California, United States

Argentina
Research Site
Ciudad de Buenos Aires, Argentina

Research Site
Buenos Aires, Caba, Argentina

Germany
Research Site
Potsdam, Germany

Romania
Research Site
Bucuresti, Romania

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Recruitment Details	First participant enrolled: 10 Feb 2010, last participant for last visit for the 24-week period: 26 May 2011. This study was conducted in 4 European countries, 2 countries in Asia/the Pacific Region, The United States, Canada, and Argentina. In total 1429 participants were enrolled and 922 participants were randomized.
Pre-Assignment Details	During a placebo lead-in period, participants were counselled on dietary and life-style modifications.

Reporting Groups

	Description
Experimental	Dapagliflozin, 10 mg tablet, oral, once daily
Placebo Comparator	Placebo, Matching placebo tablet, oral, once daily

Overall Study

	Experimental	Placebo Comparator
Started	460 [1]	462 [2]
Completed	403	404

	Experimental	Placebo Comparator
Not Completed	57	58
Adverse Event	8	3
Lost to Follow-up	2	10
Withdrawal by Subject	12	16
Death	2	1
Subject No Longer Meets Study Criteria	26	17
Poor/Non-compliance	5	6
Safety	1	0
Incorrect Enrolment	1	2
Administrative Reason by Sponsor	0	1
Various	0	2

[1] Of the 460 randomized participants only 455 were included in the full analysis set.
[2] Of the 462 randomized participants only 459 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
Experimental	Dapagliflozin, 10 mg tablet, oral, once daily
Placebo Comparator	Placebo, Matching placebo tablet, oral, once daily

Baseline Measures

	Experimental	Placebo Comparator	Total
Number of Participants	455	459	914
Age, Continuous [units: Years] Mean (Standard Deviation)	62.8 (6.97)	63.0 (7.66)	62.9 (7.32)

	Experimental	Placebo Comparator	Total
Age, Customized [units: Participants]			
<55	58	74	132
>=55 and <65	205	189	394
>=65 and <75	164	165	329
>=75	28	31	59
Gender, Male/Female [units: Participants]			
Female	146	144	290
Male	309	315	624
Haemoglobin A1c (HbA1c) [units: Percent] Mean (Standard Deviation)	8.18 (0.841)	8.08 (0.802)	8.13 (0.823)
Seated Systolic Blood Pressure [units: mm Hg] Mean (Standard Deviation)	133.5 (13.48)	133.0 (13.81)	133.2 (13.64)
Total Body Weight [units: kg] Mean (Standard Deviation)	92.63 (20.504)	93.59 (19.467)	93.11 (19.985)
Body Mass Index (BMI) [units: Participants]			
< 25 kg/m²	29	30	59
>= 25 kg/m²	426	429	855
>= 27 kg/m²	388	397	785
>= 30 kg/m²	291	304	595

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 and hypertension, 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
Experimental	Dapagliflozin, 10 mg tablet, oral, once daily
Placebo Comparator	Placebo, Matching placebo tablet, oral, once daily

Measured Values

	Experimental	Placebo Comparator
Number of Participants Analyzed	448	451
Adjusted Mean Change in HbA1c Levels [units: Percent] Least Squares Mean (95% Confidence Interval)	-0.38 (-0.46 to -0.30)	0.08 (0.01 to 0.16)

Statistical Analysis 1 for Adjusted Mean Change in HbA1c Levels

Statistical Analysis Overview	Comparison Groups	Experimental, Placebo Comparator
	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	-0.46
	Confidence Interval	(2-Sided) 95% -0.56 to -0.37
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.0473
	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 and hypertension 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, participants with non-missing baseline and Week 24 (LOCF) values

Reporting Groups

	Description
Experimental	Dapagliflozin, 10 mg tablet, oral, once daily
Placebo Comparator	Placebo, Matching placebo tablet, oral, once daily

Measured Values

	Experimental	Placebo Comparator
Number of Participants Analyzed	444	451
Proportion of Responders Meeting All Criteria of a 3-item Endpoint of Clinical Benefit [units: Percentage of participants] Number (95% Confidence Interval)	11.7 (8.7 to 14.7)	0.9 (0.0 to 1.8)

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

Statistical Analysis Overview	Comparison Groups	Experimental, Placebo Comparator
	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	9.9
	Confidence Interval	(2-Sided) 95% 7.0 to 12.9
	Estimation Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Adjusted Mean Change in Seated Systolic Blood Pressure (SBP)
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, participants with non-missing baseline and Week 8 (LOCF) values

Reporting Groups

	Description
Experimental	Dapagliflozin, 10 mg tablet, oral, once daily
Placebo Comparator	Placebo, Matching placebo tablet, oral, once daily

Measured Values

	Experimental	Placebo Comparator
Number of Participants Analyzed	451	459
Adjusted Mean Change in Seated Systolic Blood Pressure (SBP) [units: mmHg] Least Squares Mean (95% Confidence Interval)	-2.96 (-4.29 to -1.64)	-0.99 (-2.29 to 0.32)

Statistical Analysis 1 for Adjusted Mean Change in Seated Systolic Blood Pressure (SBP)

Statistical Analysis Overview	Comparison Groups	Experimental, Placebo Comparator
	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	0.0126
	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	-1.97
	Confidence Interval	(2-Sided) 95% -3.52 to -0.42
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.7898
	Estimation Comments	with stratum = age-by-insulin use-by-time from most recent qualifying CV event

4. 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, participants with non-missing baseline and Week 24 (LOCF) values

Reporting Groups

	Description
Experimental	Dapagliflozin, 10 mg tablet, oral, once daily
Placebo Comparator	Placebo, Matching placebo tablet, oral, once daily

Measured Values

	Experimental	Placebo Comparator
Number of Participants Analyzed	455	459
Adjusted Mean Percent Change in Body Weight [units: Percentage of Body Weight] Least Squares Mean (95% Confidence Interval)	-2.56 (-2.88 to -2.24)	-0.30 (-0.62 to 0.03)

Statistical Analysis 1 for Adjusted Mean Percent Change in Body Weight

Statistical Analysis Overview	Comparison Groups	Experimental, Placebo Comparator
	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	-2.27
	Confidence Interval	(2-Sided) 95% -2.64 to -1.89
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.1910
	Estimation Comments	with stratum = age-by-insulin use-by-time from most recent qualifying CV event

5. Secondary Outcome Measure:

Measure Title	Adjusted Mean Change in Seated Systolic Blood Pressure (SBP) 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, participants with non-missing baseline and Week 24 (LOCF) values

Reporting Groups

	Description
Experimental	Dapagliflozin, 10 mg tablet, oral, once daily
Placebo Comparator	Placebo, Matching placebo tablet, oral, once daily

Measured Values

	Experimental	Placebo Comparator
Number of Participants Analyzed	451	459
Adjusted Mean Change in Seated Systolic Blood Pressure (SBP) at Week 24 (LOCF) [units: mmHg] Least Squares Mean (95% Confidence Interval)	-2.99 (-4.36 to -1.61)	-1.03 (-2.39 to 0.32)

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

Statistical Analysis Overview	Comparison Groups	Experimental, Placebo Comparator
	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	0.0174
	Comments	Significant at alpha=0.05 (2-sided). 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	-1.95
	Confidence Interval	(2-Sided) 95% -3.56 to -0.34
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.8203
	Estimation Comments	with stratum = age-by-insulin use-by-time from most recent qualifying CV event

6. 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; participants with baseline BMI ≥27 kg/m² and Week 24 (LOCF) body weight value

Reporting Groups

	Description
Experimental	Dapagliflozin, 10 mg tablet, oral, once daily
Placebo Comparator	Placebo, Matching placebo tablet, oral, once daily

Measured Values

	Experimental	Placebo Comparator
Number of Participants Analyzed	388	397
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)	16.5 (12.8 to 20.2)	4.0 (2.1 to 5.9)

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	Experimental, Placebo Comparator
	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 value and stratum (gender)

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	12.5
	Confidence Interval	(2-Sided) 95% 8.3 to 16.6
	Parameter Dispersion	Type: Standard Error of the mean

		Value: 2.126
	Estimation Comments	[Not specified]

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
Experimental	Dapagliflozin, 10 mg tablet, oral, once daily
Placebo Comparator	Placebo, Matching placebo tablet, oral, once daily

Serious Adverse Events

	Experimental	Placebo Comparator
	Affected/At Risk (%)	Affected/At Risk (%)
Total	27/460 (5.87%)	26/462 (5.63%)
Cardiac disorders		
Acute Coronary Syndrome [A] †	1/460 (0.22%)	0/462 (0%)
Acute Myocardial Infarction [A] †	1/460 (0.22%)	1/462 (0.22%)
Angina Pectoris [A] †	1/460 (0.22%)	0/462 (0%)
Angina Unstable [A] †	1/460 (0.22%)	3/462 (0.65%)
Atrial Flutter [A] †	0/460 (0%)	1/462 (0.22%)
Cardiac Failure Congestive [A] †	0/460 (0%)	1/462 (0.22%)
Cardiogenic Shock [A] †	1/460 (0.22%)	0/462 (0%)
Coronary Artery Disease [A] †	1/460 (0.22%)	1/462 (0.22%)

	Experimental	Placebo Comparator
	Affected/At Risk (%)	Affected/At Risk (%)
Gastrointestinal disorders		
Diarrhoea [A] †	1/460 (0.22%)	0/462 (0%)
Gastric Ulcer [A] †	1/460 (0.22%)	0/462 (0%)
Gastritis [A] †	0/460 (0%)	1/462 (0.22%)
Nausea [A] †	0/460 (0%)	1/462 (0.22%)
Peptic Ulcer [A] †	1/460 (0.22%)	0/462 (0%)
Peritonitis [A] †	1/460 (0.22%)	0/462 (0%)
General disorders		
Chest Pain [A] †	1/460 (0.22%)	2/462 (0.43%)
Sudden Death [A] †	1/460 (0.22%)	0/462 (0%)
Unassigned [A] †	0/460 (0%)	1/462 (0.22%)
Hepatobiliary disorders		
Cholelithiasis [A] †	1/460 (0.22%)	0/462 (0%)
Infections and infestations		
Abscess Limb [A] †	0/460 (0%)	1/462 (0.22%)
Anal Abscess [A] †	1/460 (0.22%)	0/462 (0%)
Diarrhoea Infectious [A] †	1/460 (0.22%)	0/462 (0%)
Diverticulitis [A] †	1/460 (0.22%)	0/462 (0%)
Gangrene [A] †	1/460 (0.22%)	1/462 (0.22%)
Gastroenteritis [A] †	2/460 (0.43%)	1/462 (0.22%)
Localised Infection [A] †	1/460 (0.22%)	0/462 (0%)
Lung Infection [A] †	0/460 (0%)	1/462 (0.22%)
Nasopharyngitis [A] †	1/460 (0.22%)	0/462 (0%)

	Experimental	Placebo Comparator
	Affected/At Risk (%)	Affected/At Risk (%)
Otitis Media [A] †	1/460 (0.22%)	0/462 (0%)
Pneumonia [A] †	1/460 (0.22%)	1/462 (0.22%)
Septic Shock [A] †	1/460 (0.22%)	0/462 (0%)
Urinary Tract Infection [A] †	1/460 (0.22%)	0/462 (0%)
Injury, poisoning and procedural complications		
Alcohol Poisoning [A] †	0/460 (0%)	1/462 (0.22%)
Ankle Fracture [A] †	0/460 (0%)	1/462 (0.22%)
Epicondylitis [A] †	1/460 (0.22%)	0/462 (0%)
Patella Fracture [A] †	0/460 (0%)	1/462 (0.22%)
Metabolism and nutrition disorders		
Diabetic Foot [A] †	1/460 (0.22%)	0/462 (0%)
Hyperkalaemia [A] †	1/460 (0.22%)	0/462 (0%)
Hypoglycaemia [A] †	1/460 (0.22%)	0/462 (0%)
Musculoskeletal and connective tissue disorders		
Osteitis [A] †	1/460 (0.22%)	0/462 (0%)
Osteoarthritis [A] †	0/460 (0%)	1/462 (0.22%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Basal Cell Carcinoma [A] †	1/460 (0.22%)	1/462 (0.22%)
Bladder Transitional Cell Carcinoma [A] †	2/460 (0.43%)	0/462 (0%)
Nervous system disorders		
Cerebrovascular Accident [A] †	1/460 (0.22%)	1/462 (0.22%)
Ischaemic Stroke [A] †	1/460 (0.22%)	1/462 (0.22%)
Psychiatric disorders		

	Experimental	Placebo Comparator
	Affected/At Risk (%)	Affected/At Risk (%)
Depression [A] †	1/460 (0.22%)	0/462 (0%)
Renal and urinary disorders		
Renal Failure Acute [A] †	1/460 (0.22%)	0/462 (0%)
Respiratory, thoracic and mediastinal disorders		
Respiratory Failure [A] †	1/460 (0.22%)	0/462 (0%)
Vascular disorders		
Arteriosclerosis Obliterans [A] †	0/460 (0%)	1/462 (0.22%)
Hypertension [A] †	0/460 (0%)	1/462 (0.22%)
Hypertensive Crisis [A] †	1/460 (0.22%)	0/462 (0%)
Vascular Occlusion [A] †	0/460 (0%)	1/462 (0.22%)

† 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%

	Experimental	Placebo Comparator
	Affected/At Risk (%)	Affected/At Risk (%)
Total	89/460 (19.35%)	84/462 (18.18%)
Endocrine disorders		
Hypoglycemia [A] †	89/460 (19.35%)	84/462 (18.18%)

† 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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