ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 06/09/2014

ClinicalTrials.gov ID: NCT00984867

Study Identification

Unique Protocol ID:	D1690C00010
Brief Title:	Dapagliflozin DPPIV Inhibitor add-on Study
Official Title:	A 24-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, International Phase III Study With 24 Week Extension to Evaluate the Safety and Efficacy of Dapagliflozin 10 mg/Day in Patients With Type 2 Diabetes Who Have Inadequate Glycemic Control on a DPP-4 Inhibitor Sitagliptin+/-Metformin
Secondary IDs:	

Study Status

Record Verification:	June 2014
Overall Status:	Completed
Study Start:	October 2009
Primary Completion:	March 2011 [Actual]
Study Completion:	September 2011 [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 aims to investigate how dapagliflozin can control blood sugar in patients with type 2 diabetes when added to existing treatments (sitagliptin alone or in combination with metformin). The effect of dapagliflozin on weight and blood pressure will also be studied.
Detailed Description:	

Conditions

Conditions:	Type 2 Diabetes
Keywords:	Dapagliflozin DPP IV inhibitor add on study Inadequate control

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:	833 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Active Comparator: 1 Dapagliflozin 10 mg tablet	Drug: Dapagliflozin 10 mg tablet, oral, once daily, 48 weeks
Placebo Comparator: 2 Matching placebo tablet	Drug: Placebo Matching placebo tablet

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age:	18 Years
Maximum Age:	
Gender:	Both
Accepts Healthy Volunteers?:	No
Criteria:	Inclusion Criteria:

- Patients with type 2 diabetes
- Patients who are not receiving treatment , or those who currently receive metformin, sitagliptin or vildagliptin or the combination of these
- Patients will be screened by a blood test and only those who need additional therapy can be enrolled

Exclusion Criteria:

- Patients with type 1 diabetes
- Patients with very poorly controlled diabetes
- Any clinically significant illness, which in the judgement of the investigator would compromise the patient’s safety or successful participation in the clinical study

Contacts/Locations

Study Officials: Serge Jabbour, MD
Study Principal Investigator
Thomas Jefferson University, Philadelphia

Locations: Argentina
Research Site
Berazategui, Buenos Aires, Argentina

Research Site
Buenos Aires, Caba, Argentina

Research Site
Caba, Caba, Argentina

Research Site
Cordoba, Cordoba, Argentina

Research Site
La Plata, Buenos Aires, Argentina

Research Site
Lanus, Buenos Aires, Argentina

Research Site
Mar Del Plata, Buenos Aires, Argentina

Research Site
Moron, Buenos Aires, Argentina

Research Site
Salta, Salta, Argentina

Research Site
Santa Fe, Santa Fe, Argentina

Germany
Research Site
Bad Nauheim, Germany

Research Site
Berlin, Germany

Research Site

Dresden, Germany

Research Site
Hamburg, Germany

Research Site
Meissen, Germany

Research Site
Munster, Germany

Research Site
Pirna, Germany

Research Site
Wangen, Germany

United Kingdom
Research Site
Addlestone, Surrey, United Kingdom

Research Site
Bath, United Kingdom

Research Site
Belfast, United Kingdom

Research Site
Blackpool, United Kingdom

Research Site
Bolton, Lancs, United Kingdom

Research Site
Burbage, Leicester, United Kingdom

Research Site
Coventry, United Kingdom

Research Site
Ecclesfield, Sheffield, United Kingdom

Research Site
Harrow, United Kingdom

Research Site

Sunbury on Thames, Middlesex, United Kingdom

Research Site
Wansford, Peterborough, United Kingdom

Mexico
Research Site
Guadalajara, Jalisco, Mexico

Research Site
Mexico, DF, Mexico

Poland
Research Site
Ciechocinek, Poland

Research Site
Czechowice-dziedzice, Poland

Research Site
Gdansk, Poland

Research Site
Gniewkowo, Poland

Research Site
Krakow, Poland

Research Site
Krotoszyn, Poland

Research Site
Leczyca, Poland

Research Site
Mragowo, Poland

Research Site
Poznan, Poland

Research Site
Sopot, Poland

Research Site
Torun, Poland

Research Site
Zabrze, Poland

United States, California
Research Site
Anaheim, California, United States

United States, Florida
Research Site
Boca Raton, Florida, United States

United States, Tennessee
Research Site
Bristol, Tennessee, United States

United States, Virginia
Research Site
Burke, Virginia, United States

United States, California
Research Site
Chula Vista, California, United States

United States, Ohio
Research Site
Cincinnati, Ohio, United States

Research Site
Columbus, Ohio, United States

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

Research Site
Dallas, Texas, United States

United States, Ohio
Research Site
Dayton, Ohio, United States

United States, Florida
Research Site
Deland, Florida, United States

United States, Minnesota

Research Site
Edina, Minnesota, United States

United States, California
Research Site
Greenbrae, California, United States

United States, Alabama
Research Site
Huntsville, Alabama, United States

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

United States, California
Research Site
Laguna Hills, California, United States

United States, Louisiana
Research Site
Lake Charles, Louisiana, United States

United States, Washington
Research Site
Lakewood, Washington, United States

United States, Pennsylvania
Research Site
Lancaster, Pennsylvania, United States

United States, Nevada
Research Site
Las Vegas, Nevada, United States

United States, Florida
Research Site
Longwood, Florida, United States

United States, California
Research Site
Los Angeles, California, United States

United States, Virginia
Research Site
Manassas, Virginia, United States

United States, Oregon
Research Site
Medord, Oregon, United States

United States, Florida
Research Site
Miami, Florida, United States

United States, South Carolina
Research Site
Mount Pleasant, South Carolina, United States

Research Site
Myrtle Beach, South Carolina, United States

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

United States, Oklahoma
Research Site
Oklahoma City, Oklahoma, United States

United States, Alabama
Research Site
Ozark, Alabama, United States

United States, Nevada
Research Site
Pahrump, Nevada, United States

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

United States, Florida
Research Site
Port Orange, Florida, United States

United States, Virginia
Research Site
Richmond, Virginia, United States

United States, California
Research Site
Riverside, California, United States

United States, Utah
Research Site
Salt Lake City, Utah, United States

United States, Texas
Research Site
San Antonio, Texas, United States

United States, South Carolina
Research Site
Simpsonville, South Carolina, United States

United States, Missouri
Research Site
St Louis, Missouri, United States

United States, New York
Research Site
Staten Island, New York, United States

United States, Georgia
Research Site
Stone Mountain, Georgia, United States

United States, California
Research Site
West Hills, California, United States

United States, Florida
Research Site
West Palm Beach, Florida, United States

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

United States, North Carolina
Research Site
Wilmington, North Carolina, United States

References

Citations: [Study Results] Jabbour SA, Hardy E, Sugg J, Parikh S; Study 10 Group. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Diabetes Care. 2014;37(3):740-50. doi: 10.2337/dc13-0467. Epub 2013 Oct 21. PubMed 24144654

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Description D1690C00010_Clinical_Study_Report_Synopsis

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Study Data/Documents:

Study Results

Participant Flow

Recruitment Details	First participant enrolled: 10 Oct 2009. Last participant last visit for 24-week period: 10 Mar 2011. 833 participants were enrolled, 452 randomized and 451 treated in 3 European countries, USA, Argentina and Mexico. Participants with T2DM who showed inadequate glycemic control (7.0% ≤ HbA1c ≤ 10.0% at randomization) on sitagliptin +/- metformin.
Pre-Assignment Details	During a placebo lead-in period, participants were counselled on dietary and life-style modifications. Participants eligible for the study were stratified according to use of metformin.

Reporting Groups

	Description
Placebo	Placebo plus sitagliptin alone or in combination with metformin
Dapagliflozin	Dapagliflozin 10 mg plus sitagliptin alone or in combination with metformin

Overall Study

	Placebo	Dapagliflozin
Started	226 [1]	225 [2]
Completed	203	208
Not Completed	23	17
Adverse Event	3	7

	Placebo	Dapagliflozin
Death	1	0
Withdrawal by Subject	13	4
Lost to Follow-up	3	4
Poor/non-compliance	0	1
Subject no longer meets study criteria	1	1
site closing	1	0
lack of efficacy and subject compliance	1	0

[1] Of the 226 randomized and treated participants only 224 were included in the full analysis set.
[2] Of the 225 randomized and treated participants only 223 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 plus sitagliptin alone or in combination with metformin
Dapagliflozin	Dapagliflozin 10 mg plus sitagliptin alone or in combination with metformin

Baseline Measures

	Placebo	Dapagliflozin	Total
Number of Participants	224	223	447
Age, Continuous [units: Years] Mean (Standard Deviation)	55.0 (10.20)	54.8 (10.42)	54.9 (10.30)
Gender, Male/Female [units: participants]			
Female	106	96	202
Male	118	127	245

	Placebo	Dapagliflozin	Total
HbA1c [units: HbA1c [%]] Mean (Standard Deviation)	7.97 (0.778)	7.90 (0.806)	7.93 (0.792)
Body weight [units: kg] Mean (Standard Deviation)	89.23 (20.887)	91.02 (21.637)	90.12 (21.259)
FPG [units: mg/dL] Mean (Standard Deviation)	162.97 (34.452)	162.19 (36.825)	162.58 (35.618)
Seated SBP in subjects with baseline seated SBP ≥130 mmHg [units: mmHg] Mean (Standard Deviation)	139.30 (8.507)	140.46 (8.018)	139.85 (8.279)

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Adjusted Mean Change in HbA1c Levels
Measure Description	To compare the change from baseline in HbA1c after 24 weeks treatment (LOCF) between dapagliflozin and placebo in patients with type 2 diabetes who are inadequately controlled on sitagliptin alone or on sitagliptin plus metformin.
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 plus sitagliptin alone or in combination with metformin
Dapagliflozin	Dapagliflozin 10 mg plus sitagliptin alone or in combination with metformin

Measured Values

	Placebo	Dapagliflozin
Number of Participants Analyzed	223	223
Adjusted Mean Change in HbA1c Levels [units: Percent]	0.04 (-0.06 to 0.14)	-0.45 (-0.55 to -0.35)

	Placebo	Dapagliflozin
Least Squares Mean (95% Confidence Interval)		

Statistical Analysis 1 for Adjusted Mean Change in HbA1c Levels

Statistical Analysis Overview	Comparison Groups	Placebo, Dapagliflozin
	Comments	H0: mean(treat) minus mean(placebo) = 0 versus the alternative HA: mean(treat) minus mean(placebo) =/= 0. The study consisted of two strata: sitagliptin monotherapy group and sitagliptin plus metformin group
	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). A hierarchical closed testing procedure was used to control Type I error across the primary & key secondary objectives, based on data from both strata combined
	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	-0.48
	Confidence Interval	(2-Sided) 95% -0.62 to -0.34
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.0720
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Adjusted Mean Change in Body Weight
Measure Description	To compare the change in total body weight achieved with dapagliflozin versus placebo 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
Placebo	Placebo plus sitagliptin alone or in combination with metformin. Full analysis set.
Dapagliflozin	Dapagliflozin 10 mg plus sitagliptin alone or in combination with metformin. Full analysis set.

Measured Values

	Placebo	Dapagliflozin
Number of Participants Analyzed	224	223
Adjusted Mean Change in Body Weight [units: kg] Least Squares Mean (95% Confidence Interval)	-0.26 (-0.60 to 0.09)	-2.14 (-2.48 to -1.80)

Statistical Analysis 1 for Adjusted Mean Change in Body Weight

Statistical Analysis Overview	Comparison Groups	Placebo, Dapagliflozin
	Comments	H0: mean(treat) minus mean(placebo) = 0 versus the alternative HA: mean(treat) minus mean(placebo) =/= 0. The study consisted of two strata: sitagliptin monotherapy group and sitagliptin plus metformin group
	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	-1.89
	Confidence Interval	(2-Sided) 95% -2.37 to -1.40
	Parameter Dispersion	Type: Standard Error of the mean

		Value: 0.2466
	Estimation Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Adjusted Mean Change in HbA1c in Participants With Baseline HbA1c ≥8%
Measure Description	To compare the change in HbA1c in participants with baseline HbA1c ≥8% achieved with dapagliflozin versus placebo from baseline to week 24.
Time Frame	Baseline to Week 24
Safety Issue?	No

Analysis Population Description

Full analysis set, participants with baseline HbA1c >=8% and Week 24 (LOCF) value

Reporting Groups

	Description
Placebo	Placebo plus sitagliptin alone or in combination with metformin. Full analysis set.
Dapagliflozin	Dapagliflozin 10 mg plus sitagliptin alone or in combination with metformin. Full analysis set.

Measured Values

	Placebo	Dapagliflozin
Number of Participants Analyzed	99	94
Adjusted Mean Change in HbA1c in Participants With Baseline HbA1c ≥8% [units: Percent] Least Squares Mean (95% Confidence Interval)	0.03 (-0.12 to 0.18)	-0.80 (-0.96 to -0.65)

Statistical Analysis 1 for Adjusted Mean Change in HbA1c in Participants With Baseline HbA1c ≥8%

Statistical Analysis Overview	Comparison Groups	Placebo, Dapagliflozin
	Comments	H0: mean(treat) minus mean(placebo) = 0 versus the alternative HA: mean(treat) minus mean(placebo) =/= 0. The study consisted of two strata: sitagliptin monotherapy group and sitagliptin plus metformin group
	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	-0.83
	Confidence Interval	(2-Sided) 95% -1.05 to -0.62
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.1106
	Estimation Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Adjusted Mean Change in Fasting Plasma Glucose (FPG)
Measure Description	To compare the change in FPG achieved with dapagliflozin versus placebo 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
Placebo	Placebo plus sitagliptin alone or in combination with metformin. Full analysis set.
Dapagliflozin	Dapagliflozin 10 mg plus sitagliptin alone or in combination with metformin. Full analysis set.

Measured Values

	Placebo	Dapagliflozin
Number of Participants Analyzed	222	222
Adjusted Mean Change in Fasting Plasma Glucose (FPG) [units: mg/dL]	3.81 (-0.80 to 8.42)	-24.11 (-28.73 to -19.50)

	Placebo	Dapagliflozin
Least Squares Mean (95% Confidence Interval)		

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

Statistical Analysis Overview	Comparison Groups	Placebo, Dapagliflozin
	Comments	H0: mean(treat) minus mean(placebo) = 0 versus the alternative HA: mean(treat) minus mean(placebo) =/= 0. The study consisted of two strata: sitagliptin monotherapy group and sitagliptin plus metformin group
	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	-27.92
	Confidence Interval	(2-Sided) 95% -34.45 to -21.40
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.3200
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Adjusted Mean Change in Seated Systolic Blood Pressure (SBP) in Participants With Baseline SBP>=130 mmHg
Measure Description	To compare the change in seated systolic blood pressure (SBP) in participants with baseline seated SBP >=130 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 SBP>=130mmHg and Week 8 (LOCF) value

Reporting Groups

	Description
Placebo	Placebo plus sitagliptin alone or in combination with metformin. Full analysis set.
Dapagliflozin	Dapagliflozin 10 mg plus sitagliptin alone or in combination with metformin. Full analysis set.

Measured Values

	Placebo	Dapagliflozin
Number of Participants Analyzed	111	101
Adjusted Mean Change in Seated Systolic Blood Pressure (SBP) in Participants With Baseline SBP>=130 mmHg [units: mmHg] Least Squares Mean (95% Confidence Interval)	-5.12 (-7.14 to -3.11)	-5.98 (-8.08 to -3.89)

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

Statistical Analysis Overview	Comparison Groups	Placebo, Dapagliflozin
	Comments	H0: mean(treat) minus mean(placebo) = 0 versus the alternative HA: mean(treat) minus mean(placebo) =/= 0. The study consisted of two strata: sitagliptin monotherapy group and sitagliptin plus metformin group
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5583
	Comments	Not 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	-0.86
	Confidence Interval	(2-Sided) 95%

		-3.75 to 2.03
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.4659
	Estimation Comments	[Not specified]

6. Secondary Outcome Measure:

Measure Title	Adjusted Mean Change in 2-hour Post Liquid Meal Glucose Rise
Measure Description	To compare the change in 2-hour post liquid meal glucose rise achieved with dapagliflozin versus placebo 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
Placebo	Placebo plus sitagliptin alone or in combination with metformin. Full analysis set.
Dapagliflozin	Dapagliflozin 10 mg plus sitagliptin alone or in combination with metformin. Full analysis set.

Measured Values

	Placebo	Dapagliflozin
Number of Participants Analyzed	197	205
Adjusted Mean Change in 2-hour Post Liquid Meal Glucose Rise [units: mg/dL] Least Squares Mean (95% Confidence Interval)	-6.84 (-11.77 to -1.90)	-21.65 (-26.49 to -16.81)

Statistical Analysis 1 for Adjusted Mean Change in 2-hour Post Liquid Meal Glucose Rise

Statistical Analysis Overview	Comparison Groups	Placebo, Dapagliflozin
	Comments	H0: mean(treat) minus mean(placebo) = 0 versus the alternative HA: mean(treat) minus mean(placebo) =/= 0. The study consisted of two strata: sitagliptin monotherapy group and sitagliptin plus metformin group

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	
	Comments	Not significant. Hierarchical testing procedure stopped at previous endpoint
	Method	ANCOVA
	Comments	with treatment group and stratum as effect and baseline value as covariate
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-14.82
	Confidence Interval	(2-Sided) 95% -21.73 to -7.90
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.5160
	Estimation Comments	[Not specified]

7. Secondary Outcome Measure:

Measure Title	Proportion of Participants Achieving a Therapeutic Glycemic Response Defined as a Reduction in HbA1c of ≥0.7% Compared to Baseline
Measure Description	To compare the proportion of participants achieving a therapeutic glycaemic response, defined as a reduction in HbA1c of ≥0.7% compared to baseline, with dapagliflozin versus placebo at week 24. Least Squares Mean represents the percent of participants adjusted for HbA1c baseline value.
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 plus sitagliptin alone or in combination with metformin. Full analysis set.
Dapagliflozin	Dapagliflozin 10 mg plus sitagliptin alone or in combination with metformin. Full analysis set.

Measured Values

	Placebo	Dapagliflozin
Number of Participants Analyzed	223	223
Proportion of Participants Achieving a Therapeutic Glycemic Response Defined as a Reduction in HbA1c of ≥0.7% Compared to Baseline [units: Percentage of participants] Least Squares Mean (95% Confidence Interval)	16.6 (11.7 to 21.4)	35.3 (29.3 to 41.2)

Statistical Analysis 1 for Proportion of Participants Achieving a Therapeutic Glycemic Response Defined as a Reduction in HbA1c of ≥0.7% Compared to Baseline

Statistical Analysis Overview	Comparison Groups	Placebo, Dapagliflozin
	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	
	Comments	Not significant. Hierarchical testing procedure stopped at previous endpoint
	Method	Regression, Logistic
	Comments	Based on methodology of Zhang, Tsiatis & Davidian and Davidian, Tsiatis, Zhang & Lu, with adjustment for baseline value and stratum

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	18.7
	Confidence Interval	(2-Sided) 95% 11.1 to 26.4
	Parameter Dispersion	Type: Standard Error of the mean Value: 41.2
	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
Placebo	Placebo plus sitagliptin alone or in combination with metformin. Safety analysis set.
Dapagliflozin	Dapagliflozin 10 mg plus sitagliptin alone or in combination with metformin. Safety analysis set.

Serious Adverse Events

	Placebo	Dapagliflozin
	Affected/At Risk (%)	Affected/At Risk (%)
Total	9/226 (3.98%)	10/225 (4.44%)
Cardiac disorders		
Angina pectoris [A] †	0/226 (0%)	1/225 (0.44%)
Angina unstable [A] †	0/226 (0%)	1/225 (0.44%)
Gastrointestinal disorders		
Abdominal pain upper [A] †	0/226 (0%)	1/225 (0.44%)
Colonic polyp [A] †	1/226 (0.44%)	0/225 (0%)
Gastrooesophageal reflux disease [A] †	0/226 (0%)	1/225 (0.44%)
Umbilical hernia [A] †	0/226 (0%)	1/225 (0.44%)
General disorders		
Device dislocation [A] †	0/226 (0%)	1/225 (0.44%)
Medical device pain [A] †	0/226 (0%)	1/225 (0.44%)
Non-cardiac chest pain [A] †	0/226 (0%)	1/225 (0.44%)

	Placebo	Dapagliflozin
	Affected/At Risk (%)	Affected/At Risk (%)
Hepatobiliary disorders		
Cholecystitis [A] †	0/226 (0%)	1/225 (0.44%)
Cholecystitis acute [A] †	0/226 (0%)	1/225 (0.44%)
Infections and infestations		
Pneumonia [A] †	0/226 (0%)	1/225 (0.44%)
Viral infection [A] †	1/226 (0.44%)	0/225 (0%)
Injury, poisoning and procedural complications		
Upper limb fracture [A] †	1/226 (0.44%)	0/225 (0%)
Musculoskeletal and connective tissue disorders		
Rotator cuff syndrome [A] †	0/226 (0%)	1/225 (0.44%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Basal cell carcinoma [A] †	2/226 (0.88%)	0/225 (0%)
Breast cancer [A] †	1/226 (0.44%)	0/225 (0%)
Metastatic squamous cell carcinoma [A] †	1/226 (0.44%)	0/225 (0%)
Skin and subcutaneous tissue disorders		
Eczema nummular [A] †	1/226 (0.44%)	0/225 (0%)
Vascular disorders		
Arteriosclerosis [A] †	0/226 (0%)	1/225 (0.44%)
Ischaemia [A] †	1/226 (0.44%)	0/225 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 13.1

Other Adverse Events

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

	Placebo	Dapagliflozin
	Affected/At Risk (%)	Affected/At Risk (%)
Total	14/226 (6.19%)	9/225 (4%)
Infections and infestations		
Nasopharyngitis [A] †	14/226 (6.19%)	9/225 (4%)

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA 13.1

Limitations and Caveats

For participants who did not complete 8 and/or 24 weeks, respectively, LOCF was used. All endpoints were evaluated by excluding data after rescue with the exception of systolic blood pressure which was evaluated regardless of rescue medication.

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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