ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 10/16/2014

ClinicalTrials.gov ID: NCT01217892

Study Identification

Unique Protocol ID:	D1691C00003
Brief Title:	Evaluation of Dapagliflozin Taken Twice-daily
Official Title:	A 16-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Safety and Efficacy of Dapagliflozin 2.5 mg BID, 5 mg BID and 10 mg QD Versus Placebo in Patients With Type 2 Diabetes Who Are Inadequately Controlled on Metformin-IR Monotherapy
Secondary IDs:	

Study Status

Record Verification:	October 2014
Overall Status:	Completed
Study Start:	November 2010
Primary Completion:	August 2011 [Actual]
Study Completion:	August 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?:	No
Review Board:	Approval Status: Approved Approval Number: 8/26/10 Board Name: Ethics Committee of the Self-Governing Region of Kosice Board Affiliation: KOSICE Phone: +421 55 72 68 295 Email: Peter.Dringus@vucke.sk
Data Monitoring?:	No
Plan to Share Data?:	
Oversight Authorities:	Germany: Federal Institute for Drugs and Medical Devices Hungary: National Institute of Pharmacy Romania: National Medicines Agency Slovakia: State Institute for Drug Control South Africa: Medicines Control Council Switzerland: Swissmedic Ukraine: Ministry of Health

Study Description

Brief Summary:	This study is being carried out to see if dapagliflozin - administered in a daily dose of 2.5 mg given twice a day or 5 mg twice a day or 10mg once daily - in addition to metformin, is beneficial in diabetes treatment, and if so, how it compares to treatment with metformin alone.
Detailed Description:	

Conditions

Conditions:	Type 2 Diabetes
Keywords:	Type 2 diabetes metformin treated inadequate control metformin treatment alone

Study Design

Study Type:	Interventional

Primary Purpose:	Treatment
Study Phase:	Phase 3
Intervention Model:	Parallel Assignment
Number of Arms:	4
Masking:	Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Allocation:	Randomized
Endpoint Classification:	Safety Study
Enrollment:	400 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: 1 Dapagliflozin 2.5 mg twice-daily plus open-label metformin	Drug: dapagliflozin 2.5 mg tablet, taken orally, twice daily Drug: metformin >/= 1500 mg total daily dose, tablets taken orally, twice daily
Experimental: 2 Dapagliflozin 5.0 mg twice-daily plus open-label metformin	Drug: dapagliflozin 5 mg tablet taken orally, twice daily Drug: metformin >/= 1500 mg total daily dose, tablets taken orally, twice daily
Experimental: 3 Dapagliflozin 10 mg once-daily plus open-label metformin	Drug: dapagliflozin 10 mg tablet taken orally, once daily Drug: metformin >/= 1500 mg total daily dose, tablets taken orally, twice daily
Placebo Comparator: 4 Placebo plus open-label metformin	Drug: metformin >/= 1500 mg total daily dose, tablets taken orally, twice daily Drug: placebo placebo

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age:	18 Years
Maximum Age:	77 Years

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Provision of informed consent prior to any study specific procedures
- Diagnosis of T2DM
- Current antihyperglycaemic treatment with metformin immediate release formulation monotherapy >/= 1500 mg/day at a stable dose for at least 10 weeks prior to enrolment. Other treatment with OADs within the 10 weeks prior to enrolment is not permitted.
- HbA1c ≥ 6.7% and ≤10.5%, based on central laboratory values from Screening Visit, and Enrolment Visit 1.

Exclusion Criteria:

- Diagnosis of Type 1 diabetes mellitus, known diagnosis of Maturity Onset Diabetes of the Young (MODY) or secondary causes of diabetes mellitus
- History of diabetic ketoacidosis
- Symptoms of poorly controlled diabetes including, but not limited to, marked polyuria, polydipsia, and/or greater than 10% weight loss during the 3 months prior to enrolment
- FPG >270 mg/dL (>15.0 mmol/L)
- BMI >45 kg/m2

Contacts/Locations

Study Officials: Shamik Parikh
Study Director
AstraZeneca

Locations: Germany
Research Site
Asslar, Germany

Research Site
Berlin, Germany

Research Site
Biberach A.d. Riss, Germany

Research Site
Bosenheim, Germany

Research Site
Dippoldiswalde, Germany

Research Site

Falkensee, Germany

Research Site
Meissen, Germany

Research Site
Munchen, Germany

Research Site
Neuwied, Germany

Research Site
Pirna, Germany

Research Site
Wahlstedt, Germany

Hungary
Research Site
Balatonfured, Hungary

Research Site
Budapest, Hungary

Research Site
Csongrad, Hungary

Research Site
Debrecen, Hungary

Research Site
Gyongyos, Hungary

Research Site
Kecskemet, Hungary

Research Site
Mako, Hungary

Research Site
Nyiregyhaza, Hungary

Research Site
TAT, Hungary

Research Site

Zalaegerszeg, Hungary

Romania
Research Site
Brasov, Brasov, Romania

Research Site
Bucuresti, Romania

Research Site
Iasi, Romania

Research Site
Sibiu, Romania

Research Site
Suceava, Romania

Slovakia
Research Site
Banska Bystrica, Slovakia

Research Site
Bratislava, Slovakia

Research Site
Dolny Kubin, Slovakia

Research Site
Kosice, Slovakia

Research Site
Lucenec, Slovakia

Research Site
Namestovo, Slovakia

Research Site
Piestany, Slovakia

Research Site
Prievidza, Slovakia

Research Site
Rimavska Sobota, Slovakia

Research Site
Ruzomberok, Slovakia

Research Site
Zilina, Slovakia

South Africa
Research Site
Verulam, Kwa Zulu Natal, South Africa

Research Site
Cape Town, South Africa, South Africa

Research Site
Durban, South Africa, South Africa

Research Site
Johannesburg, South Africa, South Africa

Research Site
Umkomaas, South Africa, South Africa

Research Site
Durban, South Africa

Switzerland
Research Site
Chur, Graubunden, Switzerland

Research Site
Basel, Switzerland

Research Site
Bern, Switzerland

Research Site
Geneva 14, Switzerland

Research Site
Kreuzlingen, Switzerland

Research Site
Lugano, Switzerland

Research Site
Rorschach, Switzerland

Ukraine
Research Site
Vynnitsa, Ukraine, Ukraine

Research Site
Zaporozhye, Ukraine, Ukraine

Research Site
Dnipropetrov'sk, Ukraine

Research Site
Kiev, Ukraine

Research Site
Vinnytsia, Ukraine

References

Citations: Schumm-Draeger PM, Burgess L, Korányi L, Hruba V, Hamer-Maansson JE, de Bruin TW. Twice-daily dapagliflozin co-administered with metformin in type 2 diabetes: a 16-week randomized, placebo-controlled clinical trial. Diabetes Obes Metab. 2015 Jan;17(1):42-51. doi: 10.1111/dom.12387. Epub 2014 Oct 16. PubMed 25200570

Links: URL: http://filehosting.pharmacm.com/DownloadService.ashx?client=CTR_MED_6111&studyid=296&fil...
Description CSR-D1691C00003.pdf

URL: http://filehosting.pharmacm.com/DownloadService.ashx?client=CTR_MED_7111&studyid=296&fil...
Description D1691C00003_Clinical_Study_Protocol_Redacted

Study Data/Documents:

Study Results

Participant Flow

Recruitment Details	First participant enrolled: 5 November 2010. Last participant last visit for the 16-week period: 25 August 2011. 520 participants were enrolled, and 400 were randomized in 53 study centers in Europe and South Africa. Subjects with T2DM who showed inadequate glycemic control on metformin therapy alone.
Pre-Assignment Details	During a placebo lead-in period, participants were counselled on dietary and life-style modifications. Subjects eligible for the study were stratified according to their baseline HbA1c.

Reporting Groups

	Description
Dapagliflozin 2.5mg BID Plus Metformin	Dapagliflozin 2.5mg, oral, twice daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Dapagliflozin 5mg BID Plus Metformin	Dapagliflozin 5mg, oral, twice daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Dapagliflozin 10mg OD Plus Metformin	Dapagliflozin 10mg, oral, once daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Placebo Plus Metformin	Placebo plus Metformin, oral, twice daily, >=1500mg total daily dose

Overall Study

	Dapagliflozin 2.5mg BID Plus Metformin	Dapagliflozin 5mg BID Plus Metformin	Dapagliflozin 10mg OD Plus Metformin	Placebo Plus Metformin
Started	100	100	99	101
Completed	93	94	90	93
Not Completed	7	6	9	8
Adverse Event	1	1	1	0
Withdrawal by Subject	0	2	1	0
Lab value	1	0	1	0
Subject no longer meets study criteria	5	2	4	8
Incorrect enrollment	0	1	1	0
Poor/Non-Compliance	0	0	1	0

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 2.5mg BID Plus Metformin	Dapagliflozin 2.5mg, oral, twice daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Dapagliflozin 5mg BID Plus Metformin	Dapagliflozin 5mg, oral, twice daily plus Metformin, oral, twice daily, >=1500mg total daily dose

	Description
Dapagliflozin 10mg OD Plus Metformin	Dapagliflozin 10mg, oral, once daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Placebo Plus Metformin	Placebo plus Metformin, oral, twice daily, >=1500mg total daily dose

Baseline Measures

	Dapagliflozin 2.5mg BID Plus Metformin	Dapagliflozin 5mg BID Plus Metformin	Dapagliflozin 10mg OD Plus Metformin	Placebo Plus Metformin	Total
Number of Participants	100	99	99	101	399
Age, Continuous [units: Years] Mean (Standard Deviation)	58.3 (9.01)	55.3 (9.34)	58.5 (9.78)	58.5 (9.40)	57.7 (9.45)
Gender, Male/Female [units: Participants]					
Female	63	53	50	54	220
Male	37	46	49	47	179
HbA1c [units: Percent [%]] Mean (Standard Deviation)	7.77 (0.747)	7.78 (0.762)	7.71 (0.709)	7.94 (0.848)	7.80 (0.770)
Fasting Plasma Glucose (FPG) [units: mg/dL] Mean (Standard Deviation)	153.3 (33.27)	155.3 (31.92)	155.3 (36.26)	157.8 (35.93)	155.4 (34.30)
Body weight [units: kg] Mean (Standard Deviation)	92.49 (18.632)	93.62 (16.641)	90.58 (15.929)	88.82 (15.327)	91.37 (16.716)

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Adjusted Mean Change in HbA1c Levels
Measure Description	To compare the change from baseline in HbA1c achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.
Time Frame	Baseline to Week 16
Safety Issue?	No

Analysis Population Description

Full Analysis Set, participants with non-missing baseline and Week 16 (LOCF) values

Reporting Groups

	Description
Dapagliflozin 2.5mg BID Plus Metformin	Dapagliflozin 2.5mg, oral, twice daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Dapagliflozin 5mg BID Plus Metformin	Dapagliflozin 5mg, oral, twice daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Dapagliflozin 10mg OD Plus Metformin	Dapagliflozin 10mg, oral, once daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Placebo Plus Metformin	Placebo plus Metformin, oral, twice daily, >=1500mg total daily dose

Measured Values

	Dapagliflozin 2.5mg BID Plus Metformin	Dapagliflozin 5mg BID Plus Metformin	Dapagliflozin 10mg OD Plus Metformin	Placebo Plus Metformin
Number of Participants Analyzed	99	97	98	100
Adjusted Mean Change in HbA1c Levels [units: Percent] Least Squares Mean (Standard Error)	-0.52 (0.0594)	-0.65 (0.0600)	-0.59 (0.0598)	-0.30 (0.0593)

Statistical Analysis 1 for Adjusted Mean Change in HbA1c Levels

Statistical Analysis Overview	Comparison Groups	Dapagliflozin 2.5mg BID Plus Metformin, Placebo Plus Metformin
	Comments	The null hypothesis is given as H0: mean(treat) minus mean(placebo) = 0 versus HA: mean(treat) minus mean(placebo) =/= 0 (with alpha = 0.05 using Hochberg's method to control the overall Type I error across hypotheses in the two Dapagliflozin BID groups, two-sided)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0106
	Comments	significant at alpha=0.05 (2-sided) applying Hochberg's method across the two Dapagliflozin BID groups.
	Method	ANCOVA

	Comments	with treatment group as effect (all treatment groups included) and baseline value as covariate.

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.22
	Confidence Interval	(2-Sided) 95% -0.38 to -0.05
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.0840
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Adjusted Mean Change in HbA1c Levels

Statistical Analysis Overview	Comparison Groups	Dapagliflozin 5mg BID Plus Metformin, Placebo Plus Metformin
	Comments	The null hypothesis is given as H0: mean(treat) minus mean(placebo) = 0 versus HA: mean(treat) minus mean(placebo) =/= 0 (with alpha = 0.05 using Hochberg's method to control the overall Type I error across hypotheses in the two Dapagliflozin BID groups, two-sided)
	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) applying Hochberg's method across the two Dapagliflozin BID groups.
	Method	ANCOVA
	Comments	with treatment group as effect (all treatment groups included) and baseline value as covariate.

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.35
	Confidence Interval	(2-Sided) 95% -0.52 to -0.18
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.0843
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Adjusted Percent Change in Body Weight
Measure Description	To compare the percent change from baseline in body weight achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID, and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.
Time Frame	Baseline to Week 16
Safety Issue?	No

Analysis Population Description

Full Analysis Set, participants with non-missing baseline and Week 16 (LOCF) values

Reporting Groups

	Description
Dapagliflozin 2.5mg BID Plus Metformin	Dapagliflozin 2.5mg, oral, twice daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Dapagliflozin 5mg BID Plus Metformin	Dapagliflozin 5mg, oral, twice daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Dapagliflozin 10mg OD Plus Metformin	Dapagliflozin 10mg, oral, once daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Placebo Plus Metformin	Placebo plus Metformin, oral, twice daily, >=1500mg total daily dose

Measured Values

	Dapagliflozin 2.5mg BID Plus Metformin	Dapagliflozin 5mg BID Plus Metformin	Dapagliflozin 10mg OD Plus Metformin	Placebo Plus Metformin
Number of Participants Analyzed	100	99	99	101
Adjusted Percent Change in Body Weight [units: Percent] Least Squares Mean (Standard Error)	-2.84 (0.3099)	-3.20 (0.3125)	-2.76 (0.3086)	-1.04 (0.3105)

Statistical Analysis 1 for Adjusted Percent Change in Body Weight

Statistical Analysis Overview	Comparison Groups	Dapagliflozin 2.5mg BID Plus Metformin, Placebo Plus Metformin
	Comments	The null hypothesis is given as H0: mean(treat) minus mean(placebo) = 0 versus HA: mean(treat) minus mean(placebo) =/= 0 (with alpha = 0.05, two-sided)
	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). Key secondary endpoints are tested following a hierarchical closed testing procedure within treatment group for treatment groups tested significantly different from placebo for the primary endpoint.
	Method	ANCOVA
	Comments	with treatment group (all treatment groups included) and stratum (HbA1c <7.0% vs >=7.0% at randomization) as effect and baseline value as covariate.

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-1.82
	Confidence Interval	(2-Sided) 95% -2.53 to -1.10
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.3630
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Adjusted Percent Change in Body Weight

Statistical Analysis Overview	Comparison Groups	Dapagliflozin 5mg BID Plus Metformin, Placebo Plus Metformin
	Comments	The null hypothesis is given as H0: mean(treat) minus mean(placebo) = 0 versus HA: mean(treat) minus mean(placebo) =/= 0 (with alpha = 0.05, two-sided)
	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). Key secondary endpoints are tested following a hierarchical closed testing procedure within treatment group for treatment groups tested significantly different from placebo for the primary endpoint.
	Method	ANCOVA
	Comments	with treatment group (all treatment groups included) and stratum (HbA1c <7.0% vs >=7.0% at randomization) as effect and baseline value as covariate.

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-2.18

	Confidence Interval	(2-Sided) 95% -2.89 to -1.46
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.3636
	Estimation Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Adjusted Mean Change in Fasting Plasma Glucose (FPG) From Baseline to Week 1
Measure Description	To compare the change from baseline in fasting plasma glucose (FPG) achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 1 week of double-blind treatment.
Time Frame	Baseline to Week 1
Safety Issue?	No

Analysis Population Description

Full Analysis Set, participants with non-missing baseline and Week 1 values

Reporting Groups

	Description
Dapagliflozin 2.5mg BID Plus Metformin	Dapagliflozin 2.5mg, oral, twice daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Dapagliflozin 5mg BID Plus Metformin	Dapagliflozin 5mg, oral, twice daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Dapagliflozin 10mg OD Plus Metformin	Dapagliflozin 10mg, oral, once daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Placebo Plus Metformin	Placebo plus Metformin, oral, twice daily, >=1500mg total daily dose

Measured Values

	Dapagliflozin 2.5mg BID Plus Metformin	Dapagliflozin 5mg BID Plus Metformin	Dapagliflozin 10mg OD Plus Metformin	Placebo Plus Metformin
Number of Participants Analyzed	99	99	98	101
Adjusted Mean Change in Fasting Plasma Glucose (FPG) From Baseline to Week 1 [units: mg/dL] Least Squares Mean (Standard Error)	-13.7 (2.657)	-14.7 (2.672)	-15.5 (2.634)	2.0 (2.584)

Statistical Analysis 1 for Adjusted Mean Change in Fasting Plasma Glucose (FPG) From Baseline to Week 1

Statistical Analysis Overview	Comparison Groups	Dapagliflozin 2.5mg BID Plus Metformin, Placebo Plus Metformin
	Comments	The null hypothesis is given as H0: mean(treat) minus mean(placebo) = 0 versus HA: mean(treat) minus mean(placebo) =/= 0 (with alpha = 0.05, two-sided)
	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). Key secondary endpoints are tested following a hierarchical closed testing procedure within treatment group for treatment groups tested significantly different from placebo for the primary endpoint.
	Method	ANCOVA
	Comments	with treatment group (all treatment groups included) and stratum (HbA1c <7.0% vs >=7.0% at randomization) as effect and baseline value as covariate.
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-15.7
	Confidence Interval	(2-Sided) 95% -21.7 to -9.7
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.040
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Adjusted Mean Change in Fasting Plasma Glucose (FPG) From Baseline to Week 1

Statistical Analysis Overview	Comparison Groups	Dapagliflozin 5mg BID Plus Metformin, Placebo Plus Metformin
	Comments	The null hypothesis is given as H0: mean(treat) minus mean(placebo) = 0 versus HA: mean(treat) minus mean(placebo) =/= 0 (with alpha = 0.05, two-sided)
	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). Key secondary endpoints are tested following a hierarchical closed testing procedure within treatment group for treatment groups tested significantly different from placebo for the primary endpoint.
	Method	ANCOVA
	Comments	with treatment group (all treatment groups included) and stratum (HbA1c <7.0% vs >=7.0% at randomization) as effect and baseline value as covariate.

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-16.7
	Confidence Interval	(2-Sided) 95% -22.7 to -10.7
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.039
	Estimation Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Adjusted Mean Change in Fasting Plasma Glucose (FPG) From Baseline to Week 16
Measure Description	To compare the change from baseline in fasting plasma glucose (FPG) achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment.
Time Frame	Baseline to Week 16
Safety Issue?	No

Analysis Population Description

Full Analysis Set, participants with non-missing baseline and Week 16 (LOCF) values

Reporting Groups

	Description
Dapagliflozin 2.5mg BID Plus Metformin	Dapagliflozin 2.5mg, oral, twice daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Dapagliflozin 5mg BID Plus Metformin	Dapagliflozin 5mg, oral, twice daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Dapagliflozin 10mg OD Plus Metformin	Dapagliflozin 10mg, oral, once daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Placebo Plus Metformin	Placebo plus Metformin, oral, twice daily, >=1500mg total daily dose

Measured Values

	Dapagliflozin 2.5mg BID Plus Metformin	Dapagliflozin 5mg BID Plus Metformin	Dapagliflozin 10mg OD Plus Metformin	Placebo Plus Metformin
Number of Participants Analyzed	100	99	98	101
Adjusted Mean Change in Fasting Plasma Glucose (FPG) From Baseline to Week 16 [units: mg/dL] Least Squares Mean (Standard Error)	-20.8 (2.738)	-25.6 (2.759)	-20.4 (2.720)	-10.4 (2.669)

Statistical Analysis 1 for Adjusted Mean Change in Fasting Plasma Glucose (FPG) From Baseline to Week 16

Statistical Analysis Overview	Comparison Groups	Dapagliflozin 2.5mg BID Plus Metformin, Placebo Plus Metformin
	Comments	The null hypothesis is given as H0: mean(treat) minus mean(placebo) = 0 versus HA: mean(treat) minus mean(placebo) =/= 0 (with alpha = 0.05, two-sided)
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0010
	Comments	significant at alpha=0.05 (2-sided). Key secondary endpoints are tested following a hierarchical closed testing procedure within treatment group for treatment groups tested significantly different from placebo for the primary endpoint.
	Method	ANCOVA
	Comments	with treatment group (all treatment groups included) and stratum (HbA1c <7.0% vs >=7.0% at randomization) as effect and baseline value as covariate.

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-10.4
	Confidence Interval	(2-Sided) 95% -16.5 to -4.2
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.132
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Adjusted Mean Change in Fasting Plasma Glucose (FPG) From Baseline to Week 16

Statistical Analysis Overview	Comparison Groups	Dapagliflozin 5mg BID Plus Metformin, Placebo Plus Metformin
	Comments	The null hypothesis is given as H0: mean(treat) minus mean(placebo) = 0 versus HA: mean(treat) minus mean(placebo) =/= 0 (with alpha = 0.05, two-sided)
	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). Key secondary endpoints are tested following a hierarchical closed testing procedure within treatment group for treatment groups tested significantly different from placebo for the primary endpoint.
	Method	ANCOVA
	Comments	with treatment group (all treatment groups included) and stratum (HbA1c <7.0% vs >=7.0% at randomization) as effect and baseline value as covariate.

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-15.3
	Confidence Interval	(2-Sided) 95% -21.4 to -9.1
	Parameter Dispersion	Type: Standard Error of the mean Value: 3.139
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Proportion of Participants With HbA1c<7.0% at Week 16, in Participants Who Had HbA1c ≥7.0% at Baseline.
Measure Description	To compare the adjusted proportions controlling for baseline HbA1c [acc. to Zhang, Tsiatis & Davidian and Davidian, Tsiatis, Zhang & Lu] of participants with HbA1c <7.0% achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5 mg BID) co-administered with metformin versus placebo co-administered with metformin after 16 weeks of double-blind treatment, in patients who had HbA1c ≥7.0% at baseline.
Time Frame	Baseline to Week 16
Safety Issue?	No

Analysis Population Description

Full Analysis Set, participants with non-missing baseline and Week 16 (LOCF) values

Reporting Groups

	Description
Dapagliflozin 2.5mg BID Plus Metformin	Dapagliflozin 2.5mg, oral, twice daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Dapagliflozin 5mg BID Plus Metformin	Dapagliflozin 5mg, oral, twice daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Dapagliflozin 10mg OD Plus Metformin	Dapagliflozin 10mg, oral, once daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Placebo Plus Metformin	Placebo plus Metformin, oral, twice daily, >=1500mg total daily dose

Measured Values

	Dapagliflozin 2.5mg BID Plus Metformin	Dapagliflozin 5mg BID Plus Metformin	Dapagliflozin 10mg OD Plus Metformin	Placebo Plus Metformin
Number of Participants Analyzed	89	90	81	87
Proportion of Participants With HbA1c<7.0% at Week 16, in Participants Who Had HbA1c ≥7.0% at Baseline. [units: Percentage of participants] Least Squares Mean (95% Confidence Interval)	33.6 (24.6 to 42.5)	38.2 (29.1 to 47.3)	28.1 (19.0 to 37.1)	21.4 (13.2 to 29.6)

Statistical Analysis 1 for Proportion of Participants With HbA1c<7.0% at Week 16, in Participants Who Had HbA1c ≥7.0% at Baseline.

Statistical Analysis Overview	Comparison Groups	Dapagliflozin 2.5mg BID Plus Metformin, Placebo Plus Metformin
	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	0.0455
	Comments	significant at alpha=0.05 (2-sided). Key secondary endpoints are tested following a hierarchical closed testing procedure within treatment group for treatment groups tested significantly different from placebo for the primary endpoint.
	Method	Regression, Logistic
	Comments	Methodology of Zhang, Tsiatis & Davidian and Davidian, Tsiatis, Zhang & Lu, with adjustment for baseline value.

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	12.2
	Confidence Interval	(2-Sided) 95% 0.2 to 24.1
	Parameter Dispersion	Type: Standard Error of the mean Value: 6.097
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Proportion of Participants With HbA1c<7.0% at Week 16, in Participants Who Had HbA1c ≥7.0% at Baseline.

Statistical Analysis Overview	Comparison Groups	Dapagliflozin 5mg BID Plus Metformin, Placebo Plus Metformin
	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	0.0062
	Comments	significant at alpha=0.05 (2-sided). Key secondary endpoints are tested following a hierarchical closed testing procedure within treatment group for treatment groups tested significantly different from placebo for the primary endpoint.
	Method	Regression, Logistic
	Comments	Methodology of Zhang, Tsiatis & Davidian and Davidian, Tsiatis, Zhang & Lu, with adjustment for baseline value.

Method of Estimation	Estimation Parameter	Risk Difference (RD)
	Estimated Value	16.8
	Confidence Interval	(2-Sided) 95% 4.8 to 28.9
	Parameter Dispersion	Type: Standard Error of the mean Value: 6.153
	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 16 weeks double-blind treatment period plus 4 days / 30 days or up to follow-up visit 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 2.5mg BID Plus Metformin	Dapagliflozin 2.5mg, oral, twice daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Dapagliflozin 5mg BID Plus Metformin	Dapagliflozin 5mg, oral, twice daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Dapagliflozin 10mg OD Plus Metformin	Dapagliflozin 10mg, oral, once daily plus Metformin, oral, twice daily, >=1500mg total daily dose
Placebo Plus Metformin	Placebo plus Metformin, oral, twice daily, >=1500mg total daily dose

Serious Adverse Events

	Dapagliflozin 2.5mg BID Plus Metformin	Dapagliflozin 5mg BID Plus Metformin	Dapagliflozin 10mg OD Plus Metformin	Placebo Plus Metformin
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	4/100 (4%)	1/100 (1%)	2/99 (2.02%)	0/101 (0%)
Cardiac disorders				
CARDIAC FAILURE [A] †	0/100 (0%)	1/100 (1%)	0/99 (0%)	0/101 (0%)
SICK SINUS SYNDROME [A] †	0/100 (0%)	0/100 (0%)	1/99 (1.01%)	0/101 (0%)
Infections and infestations				
ENDOMETRITIS [A] †	1/100 (1%)	0/100 (0%)	0/99 (0%)	0/101 (0%)
Respiratory, thoracic and mediastinal disorders				
EPISTAXIS [A] †	1/100 (1%)	0/100 (0%)	0/99 (0%)	0/101 (0%)
HAEMOPTYSIS [A] †	1/100 (1%)	0/100 (0%)	0/99 (0%)	0/101 (0%)
Vascular disorders				
FEMORAL ARTERY OCCLUSION [A] †	1/100 (1%)	0/100 (0%)	0/99 (0%)	0/101 (0%)

	Dapagliflozin 2.5mg BID Plus Metformin	Dapagliflozin 5mg BID Plus Metformin	Dapagliflozin 10mg OD Plus Metformin	Placebo Plus Metformin
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
HYPERTENSIVE CRISIS [A] †	0/100 (0%)	0/100 (0%)	1/99 (1.01%)	0/101 (0%)

† 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 2.5mg BID Plus Metformin	Dapagliflozin 5mg BID Plus Metformin	Dapagliflozin 10mg OD Plus Metformin	Placebo Plus Metformin
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	8/100 (8%)	0/100 (0%)	6/99 (6.06%)	9/101 (8.91%)
Infections and infestations				
INFLUENZA [A] †	5/100 (5%)	0/100 (0%)	2/99 (2.02%)	3/101 (2.97%)
Vascular disorders				
HYPERTENSION [A] †	3/100 (3%)	0/100 (0%)	4/99 (4.04%)	6/101 (5.94%)

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

Limitations and Caveats

For participants who did not complete 16 weeks LOCF (last observation carried forward) was used.

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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