



Clinical trial results:

A Multicenter, Randomized, Double-Blind, Active Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Add-On Therapy With Saxagliptin and Dapagliflozin Added to Metformin Compared to Add-On Therapy With Saxagliptin in Combination With Metformin or Dapagliflozin in Combination With Metformin in Subjects With Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Alone

Summary

EudraCT number	2012-000679-18
Trial protocol	PL IT
Global end of trial date	17 January 2014

Results information

Result version number	v1 (current)
This version publication date	26 May 2016
First version publication date	26 May 2016

Trial information

Trial identification

Sponsor protocol code	CV181-169
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01606007
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca Pharmaceuticals
Sponsor organisation address	Astrazeneca AB, Södertälje, Sweden,
Public contact	Eva Johnsson, AstraZeneca Pharmaceuticals, +46 +46 31 7762484, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Eva Johnsson, AstraZeneca Pharmaceuticals, +46 +46 31 7762484, ClinicalTrialTransparency@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 January 2014
Global end of trial reached?	Yes
Global end of trial date	17 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Mean change from baseline in HbA1c at Week 24 [Time Frame: Baseline (Week 0) and at Week 24] [Designated as safety issue: No]

Protection of trial subjects:

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff.

Background therapy:

Metformin

Evidence for comparator:

Drug: Saxagliptin

Drug: Metformin XR

Drug: Dapagliflozin

Drug: Placebo matching with Dapagliflozin

Drug: Placebo matching with Saxagliptin

Actual start date of recruitment	05 June 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 759
Country: Number of subjects enrolled	Canada: 51
Country: Number of subjects enrolled	Mexico: 173
Country: Number of subjects enrolled	Puerto Rico: 32
Country: Number of subjects enrolled	Poland: 36
Country: Number of subjects enrolled	Romania: 81
Country: Number of subjects enrolled	Korea, Republic of: 16
Country: Number of subjects enrolled	South Africa: 134
Worldwide total number of subjects	1282
EEA total number of subjects	117

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1089
From 65 to 84 years	193
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrollment: 1282 subjects

Pre-assignment

Screening details:

Lead-in: 639 subjects

Period 1

Period 1 title	Double-blind Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1: Saxagliptin+Metformin XR+Placebo

Arm description:

Drug: Saxagliptin Tablets, Oral, 5mg , Once daily, 24 weeks Other Names: Onglyza Drug: Metformin XR Tablets, Oral, $\geq 1500\text{mg}/\leq 2000\text{mg}$, Once daily, 24 weeks Other Names: Glucophage XR Drug: Placebo matching with Dapagliflozin Tablets, Oral, 0mg, Once daily, 24 weeks

Arm type	Active comparator
Investigational medicinal product name	Saxagliptin+Metformin XR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Saxagliptin Tablets, Oral, 5mg , Once daily, 24 weeks Other Names: Onglyza Drug: Metformin XR Tablets, Oral, $\geq 1500\text{mg}/\leq 2000\text{mg}$, Once daily, 24 weeks Other Names: Glucophage XR Drug: Placebo matching with Dapagliflozin Tablets, Oral, 0mg, Once daily, 24 weeks

Arm title	Arm 2: Dapagliflozin+Metformin XR+Placebo
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Arm description:

Drug: Metformin XR Tablets, Oral, $\geq 1500\text{mg}/\leq 2000\text{mg}$, Once daily, 24 weeks Other Names: Glucophage XR Drug: Dapagliflozin Tablets, Oral, 10mg , Once daily, 24 weeks Other Names: BMS512148 Drug: Placebo matching with Saxagliptin Tablets, Oral, 0mg, Once daily, 24 weeks

Arm type	Active comparator
Investigational medicinal product name	Dapagliflozin+Metformin XR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Tablet
Routes of administration	Oral use

Dosage and administration details:

Metformin XR Tablets, Oral, $\geq 1500\text{mg}/\leq 2000\text{mg}$, Once daily, 24 weeks Other Names: Glucophage XR Drug: Dapagliflozin Tablets, Oral, 10mg , Once daily, 24 weeks Other Names: BMS512148 Drug: Placebo matching with Saxagliptin Tablets, Oral, 0mg, Once daily, 24 weeks

Arm title	Arm 3: Saxagliptin+Dapagliflozin+Metformin XR
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Arm description:

Drug: Saxagliptin Tablets, Oral, 5mg , Once daily, 24 weeks Other Names: Onglyza Drug: Metformin XR Tablets, Oral, $\geq 1500\text{mg}/\leq 2000\text{mg}$, Once daily, 24 weeks Other Names: Glucophage XR Drug: Dapagliflozin Tablets, Oral, 10mg , Once daily, 24 weeks Other Names: BMS512148

Arm type	Experimental
Investigational medicinal product name	Saxagliptin+Dapagliflozin+Metformin XR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet, Tablet
Routes of administration	Oral use

Dosage and administration details:

Saxagliptin Tablets, Oral, 5mg , Once daily, 24 weeks Other Names: Onglyza Drug: Metformin XR Tablets, Oral, $\geq 1500\text{mg}/\leq 2000\text{mg}$, Once daily, 24 weeks Other Names: Glucophage XR Drug: Dapagliflozin Tablets, Oral, 10mg , Once daily, 24 weeks

Number of subjects in period 1^[1]	Arm 1: Saxagliptin+Metformin XR+Placebo	Arm 2: Dapagliflozin+Metformin XR+Placebo	Arm 3: Saxagliptin+Dapagliflozin+Metformin XR
Started	176	179	179
Completed	161	160	169
Not completed	15	19	10
Consent withdrawn by subject	8	6	1
Reason 'Other' in the protocol	-	1	1
Adverse event, non-fatal	-	1	1
Pregnancy	-	1	1
discontinue study treatment	-	2	1
Lost to follow-up	6	8	5
poor or non-compliance	1	-	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: System bug.

Enrollment = 1282 subjects

Entered "Lead-in" period = 639 subjects

Completed "Lead-in" period = 540 subjects

Entered "Double-blind treatment" period = 534 subjects

Completed "Double-blind treatment" period = 490 subjects

Baseline characteristics

Reporting groups

Reporting group title	Arm 1: Saxagliptin+Metformin XR+Placebo
Reporting group description:	
Drug: Saxagliptin Tablets, Oral, 5mg , Once daily, 24 weeks Other Names: Onglyza Drug: Metformin XR Tablets, Oral, $\geq 1500\text{mg}/\leq 2000\text{mg}$, Once daily, 24 weeks Other Names: Glucophage XR Drug: Placebo matching with Dapagliflozin Tablets, Oral, 0mg, Once daily, 24 weeks	
Reporting group title	Arm 2: Dapagliflozin+Metformin XR+Placebo
Reporting group description:	
Drug: Metformin XR Tablets, Oral, $\geq 1500\text{mg}/\leq 2000\text{mg}$, Once daily, 24 weeks Other Names: Glucophage XR Drug: Dapagliflozin Tablets, Oral, 10mg , Once daily, 24 weeks Other Names: BMS512148 Drug: Placebo matching with Saxagliptin Tablets, Oral, 0mg, Once daily, 24 weeks	
Reporting group title	Arm 3: Saxagliptin+Dapagliflozin+Metformin XR
Reporting group description:	
Drug: Saxagliptin Tablets, Oral, 5mg , Once daily, 24 weeks Other Names: Onglyza Drug: Metformin XR Tablets, Oral, $\geq 1500\text{mg}/\leq 2000\text{mg}$, Once daily, 24 weeks Other Names: Glucophage XR Drug: Dapagliflozin Tablets, Oral, 10mg , Once daily, 24 weeks Other Names: BMS512148	

Reporting group values	Arm 1: Saxagliptin+Metformin XR+Placebo	Arm 2: Dapagliflozin+Metformin XR+Placebo	Arm 3: Saxagliptin+Dapagliflozin+Metformin XR
Number of subjects	176	179	179
Age categorical			
Units: Subjects			
Adults (18-64 years)	148	158	160
From ≥ 65 years	28	21	19
Age continuous			
Units: years			
arithmetic mean	54.6	53.5	53.4
standard deviation	± 9.63	± 9.67	± 9.84
Gender, Male/Female			
Units: participants			
Female	82	90	94
Male	94	89	85
Age, Customized			
Units: Subjects			
<65 years	148	158	160
≥ 65 years	28	21	19
Race/Ethnicity, Customized			
Units: Subjects			
White	121	131	120
Black african/american	22	16	22
Asian	11	10	12
Other	22	22	25

Reporting group values	Total		
Number of subjects	534		
Age categorical			
Units: Subjects			
Adults (18-64 years)	466		

From >= 65 years	68		
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Age continuous Units: years arithmetic mean standard deviation	-		
Gender, Male/Female Units: participants			
Female	266		
Male	268		
Age, Customized Units: Subjects			
<65 years	466		
>=65 years	68		
Race/Ethnicity, Customized Units: Subjects			
White	372		
Black african/american	60		
Asian	33		
Other	69		

Subject analysis sets

Subject analysis set title	Randomized and Treated Subjects Data Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Data from all randomized subjects who took at least one dose of double-blind study medication during the double-blind period was included in the Randomized Subjects Data Set. When the Randomized Subjects Data Set is used, subjects are presented in the treatment group to which they were randomized at the start of the double-blind treatment period, even if the treatment they received was different.

Reporting group values	Randomized and Treated Subjects Data Set		
Number of subjects	534		
Age categorical Units: Subjects			
Adults (18-64 years)	466		
From >= 65 years	68		
Age continuous Units: years arithmetic mean standard deviation	53.8 ± 9.71		
Gender, Male/Female Units: participants			
Female	266		
Male	268		
Age, Customized Units: Subjects			
<65 years	466		
>=65 years	68		

Race/Ethnicity, Customized			
Units: Subjects			
White	372		
Black african/american	60		
Asian	33		
Other	69		

End points

End points reporting groups

Reporting group title	Arm 1: Saxagliptin+Metformin XR+Placebo
Reporting group description: Drug: Saxagliptin Tablets, Oral, 5mg , Once daily, 24 weeks Other Names: Onglyza Drug: Metformin XR Tablets, Oral, $\geq 1500\text{mg}/\leq 2000\text{mg}$, Once daily, 24 weeks Other Names: Glucophage XR Drug: Placebo matching with Dapagliflozin Tablets, Oral, 0mg, Once daily, 24 weeks	
Reporting group title	Arm 2: Dapagliflozin+Metformin XR+Placebo
Reporting group description: Drug: Metformin XR Tablets, Oral, $\geq 1500\text{mg}/\leq 2000\text{mg}$, Once daily, 24 weeks Other Names: Glucophage XR Drug: Dapagliflozin Tablets, Oral, 10mg , Once daily, 24 weeks Other Names: BMS512148 Drug: Placebo matching with Saxagliptin Tablets, Oral, 0mg, Once daily, 24 weeks	
Reporting group title	Arm 3: Saxagliptin+Dapagliflozin+Metformin XR
Reporting group description: Drug: Saxagliptin Tablets, Oral, 5mg , Once daily, 24 weeks Other Names: Onglyza Drug: Metformin XR Tablets, Oral, $\geq 1500\text{mg}/\leq 2000\text{mg}$, Once daily, 24 weeks Other Names: Glucophage XR Drug: Dapagliflozin Tablets, Oral, 10mg , Once daily, 24 weeks Other Names: BMS512148	
Subject analysis set title	Randomized and Treated Subjects Data Set
Subject analysis set type	Intention-to-treat
Subject analysis set description: Data from all randomized subjects who took at least one dose of double-blind study medication during the double-blind period was included in the Randomized Subjects Data Set. When the Randomized Subjects Data Set is used, subjects are presented in the treatment group to which they were randomized at the start of the double-blind treatment period, even if the treatment they received was different.	

Primary: Mean change from baseline in HbA1c at Week 24

End point title	Mean change from baseline in HbA1c at Week 24
End point description:	
End point type	Primary
End point timeframe: Baseline (Week 0) and at Week 24	

End point values	Arm 1: Saxagliptin+Metformin XR+Placebo	Arm 2: Dapagliflozin+Metformin XR+Placebo	Arm 3: Saxagliptin+Dapagliflozin+Metformin XR	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	143	151	158	
Units: % HbA1c				
least squares mean (confidence interval 95%)	-0.88 (-1.03 to -0.72)	-1.2 (-1.35 to -1.04)	-1.47 (-1.62 to -1.31)	

Statistical analyses

Statistical analysis title	Mean change from baseline in HbA1c
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Statistical analysis description:

Adjusted mean change from baseline in HbA1c at Week 24

Comparison groups	Arm 1: Saxagliptin+Metformin XR+Placebo v Arm 3: Saxagliptin+Dapagliflozin+Metformin XR
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	-0.37
Variability estimate	Standard error of the mean
Dispersion value	0.1112

Statistical analysis title

Mean change from baseline in HbA1c

Statistical analysis description:

Adjusted mean change from baseline in HbA1c at Week 24

Comparison groups	Arm 2: Dapagliflozin+Metformin XR+Placebo v Arm 3: Saxagliptin+Dapagliflozin+Metformin XR
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0166
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	-0.05
Variability estimate	Standard error of the mean
Dispersion value	0.1108

Secondary: Mean change from baseline in 2-hour post-prandial glucose (PPG) during a liquid meal test (2-h MTT)

End point title	Mean change from baseline in 2-hour post-prandial glucose (PPG) during a liquid meal test (2-h MTT)
End point description:	
End point type	Secondary

End point timeframe:

Baseline (Week 0) and at Week 24

End point values	Arm 1: Saxagliptin+Metformin XR+Placebo	Arm 2: Dapagliflozin+Metformin XR+Placebo	Arm 3: Saxagliptin+Dapagliflozin+Metformin XR	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	147	144	154	
Units: MG/DL PPG				
least squares mean (confidence interval 95%)	-35.6 (-42.5 to -28.7)	-70.4 (-77.4 to -63.5)	-79.6 (-86.3 to -72.8)	

Statistical analyses

Statistical analysis title	Mean change from baseline in PPG
Statistical analysis description: Adjusted mean change from baseline in 2-hour PPG during a liquid meal test (2-h MTT)	
Comparison groups	Arm 1: Saxagliptin+Metformin XR+Placebo v Arm 3: Saxagliptin+Dapagliflozin+Metformin XR
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.7
upper limit	-34.3
Variability estimate	Standard error of the mean
Dispersion value	4.914

Statistical analysis title	Mean change from baseline in PPG
Statistical analysis description: Adjusted mean change from baseline in 2-hour PPG during a liquid meal test (2-h MTT)	
Comparison groups	Arm 2: Dapagliflozin+Metformin XR+Placebo v Arm 3: Saxagliptin+Dapagliflozin+Metformin XR

Number of subjects included in analysis	298
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0639
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-9.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.8
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	4.923

Secondary: Mean change from baseline in fasting plasma glucose (FPG)

End point title	Mean change from baseline in fasting plasma glucose (FPG)
End point description:	
End point type	Secondary
End point timeframe:	
Baseline (Week 0) and at Week 24	

End point values	Arm 1: Saxagliptin+Metformin XR+Placebo	Arm 2: Dapagliflozin+Metformin XR+Placebo	Arm 3: Saxagliptin+Dapagliflozin+Metformin XR	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	142	148	155	
Units: mg/dL				
least squares mean (confidence interval 95%)	-14 (-19.6 to -8.4)	-31.7 (-37.3 to -26.2)	-37.8 (-43.2 to -32.3)	

Statistical analyses

Statistical analysis title	Mean change from baseline in FPG
Statistical analysis description:	
Adjusted mean change from baseline in fasting plasma glucose (FPG)	
Comparison groups	Arm 1: Saxagliptin+Metformin XR+Placebo v Arm 3: Saxagliptin+Dapagliflozin+Metformin XR

Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-23.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.6
upper limit	-15.9
Variability estimate	Standard error of the mean
Dispersion value	3.988

Statistical analysis title	Mean change from baseline in FPG
Statistical analysis description:	
Adjusted mean change from baseline in fasting plasma glucose (FPG)	
Comparison groups	Arm 2: Dapagliflozin+Metformin XR+Placebo v Arm 3: Saxagliptin+Dapagliflozin+Metformin XR
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-6.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.8
upper limit	1.7
Variability estimate	Standard error of the mean
Dispersion value	3.957

Secondary: Number of subjects achieving glycemic response defined as Glycosylated hemoglobin (HbA1c) < 7%

End point title	Number of subjects achieving glycemic response defined as Glycosylated hemoglobin (HbA1c) < 7%
End point description:	
End point type	Secondary
End point timeframe:	
At Week 24	

End point values	Arm 1: Saxagliptin+Metformin XR+Placebo	Arm 2: Dapagliflozin+Metformin XR+Placebo	Arm 3: Saxagliptin+Dapagliflozin+Metformin XR	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	175	173	177	
Units: Participants	29	40	74	

Statistical analyses

Statistical analysis title	Glycemic response HbA1c < 7%
Statistical analysis description:	
Number of subjects achieving glycemic response defined as Glycosylated hemoglobin (HbA1c) < 7%	
Comparison groups	Arm 1: Saxagliptin+Metformin XR+Placebo v Arm 3: Saxagliptin+Dapagliflozin+Metformin XR
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	23.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.7
upper limit	31.5
Variability estimate	Standard error of the mean
Dispersion value	4.282

Statistical analysis title	Glycemic response HbA1c < 7%
Statistical analysis description:	
Number of subjects achieving glycemic response defined as Glycosylated hemoglobin (HbA1c) < 7%	
Comparison groups	Arm 2: Dapagliflozin+Metformin XR+Placebo v Arm 3: Saxagliptin+Dapagliflozin+Metformin XR
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	19.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.1
upper limit	28.1
Variability estimate	Standard error of the mean
Dispersion value	4.587

Secondary: Mean change from baseline in body weight at Week 24 with the addition of Saxagliptin and Dapagliflozin to Metformin vs. the addition of placebo and Saxagliptin to Metformin

End point title	Mean change from baseline in body weight at Week 24 with the addition of Saxagliptin and Dapagliflozin to Metformin vs. the addition of placebo and Saxagliptin to Metformin
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End point description:

End point type	Secondary
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End point timeframe:

Baseline (Week 0) and at Week 24

End point values	Arm 1: Saxagliptin+Metformin XR+Placebo	Arm 2: Dapagliflozin+Metformin XR+Placebo	Arm 3: Saxagliptin+Dapagliflozin+Metformin XR	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	145	152	159	
Units: Body weight Kg				
least squares mean (confidence interval 95%)	0 (-0.48 to 0.49)	-2.39 (-2.87 to -1.91)	-2.05 (-2.52 to -1.58)	

Statistical analyses

Statistical analysis title	Mean change from baseline in body weight
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Statistical analysis description:

Adjust mean change from baseline in body weight at Week 24 with the addition of Saxagliptin and Dapagliflozin to Metformin vs. the addition of placebo and Saxagliptin to Metformin

Comparison groups	Arm 1: Saxagliptin+Metformin XR+Placebo v Arm 3: Saxagliptin+Dapagliflozin+Metformin XR
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.73
upper limit	-1.37
Variability estimate	Standard error of the mean
Dispersion value	0.3451

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

24 weeks

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	SAXA + MET
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Reporting group description:

Drug: Saxagliptin Tablets, Oral, 5mg , Once daily, 24 weeks Other Names: Onglyza Drug: Metformin XR Tablets, Oral, $\geq 1500\text{mg}/\leq 2000\text{mg}$, Once daily, 24 weeks Other Names: Glucophage XR Drug: Placebo matching with Dapagliflozin Tablets, Oral, 0mg, Once daily, 24 weeks

Reporting group title	SAXA + DAPA + MET
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Reporting group description:

Drug: Saxagliptin Tablets, Oral, 5mg , Once daily, 24 weeks Other Names: Onglyza Drug: Metformin XR Tablets, Oral, $\geq 1500\text{mg}/\leq 2000\text{mg}$, Once daily, 24 weeks Other Names: Glucophage XR Drug: Dapagliflozin Tablets, Oral, 10mg , Once daily, 24 weeks Other Names: BMS512148

Reporting group title	DAPA + MET
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Reporting group description:

Drug: Metformin XR Tablets, Oral, $\geq 1500\text{mg}/\leq 2000\text{mg}$, Once daily, 24 weeks Other Names: Glucophage XR Drug: Dapagliflozin Tablets, Oral, 10mg , Once daily, 24 weeks Other Names: BMS512148 Drug: Placebo matching with Saxagliptin Tablets, Oral, 0mg, Once daily, 24 weeks

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: There are no non-serious adverse events presented due to the 5% cut-off.

Serious adverse events	SAXA + MET	SAXA + DAPA + MET	DAPA + MET
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 176 (3.41%)	2 / 179 (1.12%)	2 / 179 (1.12%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) GASTRIC NEOPLASM			
subjects affected / exposed	0 / 176 (0.00%)	1 / 179 (0.56%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications PATELLA FRACTURE			
subjects affected / exposed	1 / 176 (0.57%)	0 / 179 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders DEEP VEIN THROMBOSIS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 176 (0.57%) 0 / 1 0 / 0	0 / 179 (0.00%) 0 / 0 0 / 0	0 / 179 (0.00%) 0 / 0 0 / 0
Cardiac disorders ACUTE MYOCARDIAL INFARCTION subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 176 (0.00%) 0 / 0 0 / 0	1 / 179 (0.56%) 0 / 1 0 / 0	0 / 179 (0.00%) 0 / 0 0 / 0
Nervous system disorders TRANSIENT ISCHAEMIC ATTACK subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 176 (0.00%) 0 / 0 0 / 0	0 / 179 (0.00%) 0 / 0 0 / 0	1 / 179 (0.56%) 0 / 1 0 / 0
General disorders and administration site conditions CHEST PAIN subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 176 (0.57%) 0 / 1 0 / 0	0 / 179 (0.00%) 0 / 0 0 / 0	0 / 179 (0.00%) 0 / 0 0 / 0
Gastrointestinal disorders PANCREATITIS CHRONIC subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 176 (0.00%) 0 / 0 0 / 0	1 / 179 (0.56%) 0 / 1 0 / 0	0 / 179 (0.00%) 0 / 0 0 / 0
UMBILICAL HERNIA subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 176 (0.57%) 0 / 1 0 / 0	0 / 179 (0.00%) 0 / 0 0 / 0	0 / 179 (0.00%) 0 / 0 0 / 0
Reproductive system and breast disorders BENIGN PROSTATIC HYPERPLASIA subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 176 (0.00%) 0 / 0 0 / 0	0 / 179 (0.00%) 0 / 0 0 / 0	1 / 179 (0.56%) 0 / 1 0 / 0
Respiratory, thoracic and mediastinal			

disorders			
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 176 (0.57%)	0 / 179 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
ARTHRITIS			
subjects affected / exposed	1 / 176 (0.57%)	0 / 179 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
TOOTH INFECTION			
subjects affected / exposed	1 / 176 (0.57%)	0 / 179 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
HYPERKALAEMIA			
subjects affected / exposed	1 / 176 (0.57%)	0 / 179 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	SAXA + MET	SAXA + DAPA + MET	DAPA + MET
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 176 (0.00%)	0 / 179 (0.00%)	0 / 179 (0.00%)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 April 2012	1 Amendment: The objective of this Amendment is to permit the collection and storage of blood samples
11 September 2012	Amendment 02 is to make clarifications and to correct the

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported