



Clinical trial results:

A 24-Week International, Multi-center, Randomized, Parallel-group, Double-blind Trial to Evaluate Metformin Extended Release Monotherapy Compared to Metformin Immediate Release Monotherapy in Adult Subjects with Type 2 Diabetes who have Inadequate Glycemic Control with Diet and Exercise

Summary

EudraCT number	2012-004531-23
Trial protocol	CZ DE HU GB PL
Global end of trial date	01 June 2016

Results information

Result version number	v1 (current)
This version publication date	16 June 2017
First version publication date	16 June 2017

Trial information

Trial identification

Sponsor protocol code	CV181-206
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb International Corporation
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.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	01 June 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine if monotherapy with 2000 mg metformin extended release is non-inferior to monotherapy with 2000 mg immediate release in adult patients with type 2 diabetes who have inadequate glycemic control with diet and exercise

Protection of trial subjects:

The study was conducted in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 May 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects**Subjects enrolled per country**

Country: Number of subjects enrolled	Czech Republic: 47
Country: Number of subjects enrolled	Canada: 169
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Hungary: 270
Country: Number of subjects enrolled	Poland: 138
Country: Number of subjects enrolled	Puerto Rico: 95
Country: Number of subjects enrolled	Romania: 345
Country: Number of subjects enrolled	South Africa: 118
Country: Number of subjects enrolled	United Kingdom: 89
Country: Number of subjects enrolled	United States: 439
Worldwide total number of subjects	1736
EEA total number of subjects	915

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)	1366
From 65 to 84 years	365
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

1736 enrolled at 148 study sites in North America, Europe, and South Africa. Lead in period=794. Reasons not entered: 1 AE, 17 WC, 4 lost to FU, 3 NC, 911 SC, 4 ARS, 1 other. Adverse event=-AE, Withdrew consent=WC, Follow-up=FU, poor/non-compliance=NC, No longer met study criteria=SC, Administrative reason by sponsor=ARS.

Pre-assignment

Screening details:

570 completed lead-in period and were eligible for randomization. 568 randomized. Non-randomized: 1 AE, 27 WC, 3 lost to FU, 7 NC, 159 SC, 8 ARS, 3 other.

Period 1

Period 1 title	Double Blind Treatment - All treated
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Blinding implementation details:

Randomized subjects who took at least one dose of double-blind study medication in the treatment group to which they were randomized.

Arms

Are arms mutually exclusive?	Yes
Arm title	Metformin XR

Arm description:

Subjects received Metformin XR and Placebo matching with Metformin XR Metformin Extended Release (XR) 500 mg tablets (500-2000 mg per day) by mouth twice daily (BID) for 24 weeks Placebo matching with Metformin XR 0 mg tablets by mouth twice daily (BID) for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Placebo for Metformin Hydrochloride Modified Release (Metformin XR)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo for Metformin XR modified release is a plain, white to off-white, capsule-shaped, biconvex tablet. Subjects randomized to double-blind treatment with metformin XR were titrated from 500 mg orally once daily (evening) to 2000 mg orally once daily (evening) over the first 3 weeks of the 24-week double-blind treatment period (as tolerated). In order to maintain blinding, subjects received 4 metformin XR tablets daily in the evening (combination of active and placebo) throughout the 24-week double-blind treatment period. Subjects randomized to treatment with metformin XR also received placebo tablets for metformin IR throughout the 24-week double-blind treatment period (2 tablets each morning and 2 tablets each evening).

Investigational medicinal product name	Metformin Hydrochloride Modified Release (Metformin XR)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Metformin XR modified release is a plain, white to off-white, capsule-shaped, biconvex tablet. Subjects randomized to double-blind treatment with metformin XR were titrated from 500 mg orally once daily (evening) to 2000 mg orally once daily (evening) over the first 3 weeks of the 24-week double-blind treatment period (as tolerated). In order to maintain blinding, subjects received 4 metformin XR tablets

daily in the evening (combination of active and placebo) throughout the 24-week double-blind treatment period. Subjects randomized to treatment with metformin XR also received placebo tablets for metformin IR throughout the 24-week double-blind treatment period (2 tablets each morning and 2 tablets each evening).

Arm title	Metformin IR
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Arm description:

Subjects received Metformin IR and Placebo matching with Metformin IR. Metformin Immediate Release (IR) 500 mg tablets (500-2000 mg per day) by mouth twice daily (BID) for 24 weeks Placebo matching with Metformin IR 0 mg tablets by mouth twice daily (BID) for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Metformin Hydrochloride (Metformin IR)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Metformin IR is a white to off-white, round, biconvex, bevel-edged film-coated tablet with no markings. Subjects randomized to double-blind treatment with metformin IR were titrated from 500 mg orally daily (morning) to a total daily dose of 2000 mg orally (divided between morning and evening) over the first 3 weeks of the 24-week double-blind treatment period (as tolerated). In order to maintain blinding, subjects received 4 metformin IR tablets daily (2 tablets each morning and 2 tablets each evening; combination of active and placebo) throughout the 24-week double-blind treatment period. Subjects randomized to treatment with metformin IR also received placebo tablets for metformin XR throughout the 24-week double-blind treatment period (4 tablets each evening).

Investigational medicinal product name	Placebo for Metformin Hydrochloride (Metformin IR)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo for Metformin IR is a white to off-white, round, biconvex, bevel-edged film-coated tablet with no markings. Subjects randomized to double-blind treatment with metformin IR were titrated from 500 mg orally daily (morning) to a total daily dose of 2000 mg orally (divided between morning and evening) over the first 3 weeks of the 24-week double-blind treatment period (as tolerated). In order to maintain blinding, subjects received 4 metformin IR tablets daily (2 tablets each morning and 2 tablets each evening; combination of active and placebo) throughout the 24-week double-blind treatment period. Subjects randomized to treatment with metformin IR also received placebo tablets for metformin XR throughout the 24-week double-blind treatment period (4 tablets each evening).

Number of subjects in period 1	Metformin XR	Metformin IR
Started	283	285
Completed	268	271
Not completed	15	14
Removed due to site non-compliance	15	14

Period 2

Period 2 title	Double Blind - Compliant Randomized
Is this the baseline period?	Yes ^[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
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Arm title	Metformin XR
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Arm description:

Subjects received Metformin XR and Placebo matching with Metformin XR Metformin Extended Release (XR) 500 mg tablets (500-2000 mg per day) by mouth twice daily (BID) for 24 weeks Placebo matching with Metformin XR 0 mg tablets by mouth twice daily (BID) for 24 weeks. Population includes all randomized subjects who took at least one dose of double-blind study medication in the treatment group to which they were randomized, excluding 15 randomized subjects due to site non-compliance.

Arm type	Experimental
Investigational medicinal product name	Placebo for Metformin Hydrochloride Modified Release (Metformin XR)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo for Metformin XR modified release is a plain, white to off-white, capsule-shaped, biconvex tablet. Subjects randomized to double-blind treatment with metformin XR were titrated from 500 mg orally once daily (evening) to 2000 mg orally once daily (evening) over the first 3 weeks of the 24-week double-blind treatment period (as tolerated). In order to maintain blinding, subjects received 4 metformin XR tablets daily in the evening (combination of active and placebo) throughout the 24-week double-blind treatment period. Subjects randomized to treatment with metformin XR also received placebo tablets for metformin IR throughout the 24-week double-blind treatment period (2 tablets each morning and 2 tablets each evening).

Investigational medicinal product name	Metformin Hydrochloride Modified Release (Metformin XR)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Metformin XR modified release is a plain, white to off-white, capsule-shaped, biconvex tablet. Subjects randomized to double-blind treatment with metformin XR were titrated from 500 mg orally once daily (evening) to 2000 mg orally once daily (evening) over the first 3 weeks of the 24-week double-blind treatment period (as tolerated). In order to maintain blinding, subjects received 4 metformin XR tablets daily in the evening (combination of active and placebo) throughout the 24-week double-blind treatment period. Subjects randomized to treatment with metformin XR also received placebo tablets for metformin IR throughout the 24-week double-blind treatment period (2 tablets each morning and 2 tablets each evening).

Arm title	Metformin IR
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Arm description:

Subjects received Metformin IR and Placebo matching with Metformin IR. Metformin Immediate Release (IR) 500 mg tablets (500-2000 mg per day) by mouth twice daily (BID) for 24 weeks Placebo matching with Metformin IR 0 mg tablets by mouth twice daily (BID) for 24 weeks. Population includes all randomized subjects who took at least one dose of double-blind study medication in the treatment group to which they were randomized, excluding 14 randomized subjects due to site non-compliance.

Arm type	Experimental
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Investigational medicinal product name	Metformin Hydrochloride (Metformin IR)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Metformin IR is a white to off-white, round, biconvex, bevel-edged film-coated tablet with no markings. Subjects randomized to double-blind treatment with metformin IR were titrated from 500 mg orally daily (morning) to a total daily dose of 2000 mg orally (divided between morning and evening) over the first 3 weeks of the 24-week double-blind treatment period (as tolerated). In order to maintain blinding, subjects received 4 metformin IR tablets daily (2 tablets each morning and 2 tablets each evening; combination of active and placebo) throughout the 24-week double-blind treatment period. Subjects randomized to treatment with metformin IR also received placebo tablets for metformin XR throughout the 24-week double-blind treatment period (4 tablets each evening).

Investigational medicinal product name	Placebo for Metformin Hydrochloride (Metformin IR)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo for Metformin IR is a white to off-white, round, biconvex, bevel-edged film-coated tablet with no markings. Subjects randomized to double-blind treatment with metformin IR were titrated from 500 mg orally daily (morning) to a total daily dose of 2000 mg orally (divided between morning and evening) over the first 3 weeks of the 24-week double-blind treatment period (as tolerated). In order to maintain blinding, subjects received 4 metformin IR tablets daily (2 tablets each morning and 2 tablets each evening; combination of active and placebo) throughout the 24-week double-blind treatment period. Subjects randomized to treatment with metformin IR also received placebo tablets for metformin XR throughout the 24-week double-blind treatment period (4 tablets each evening).

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline period only refers to those randomized and treated subjects from compliant sites.

Number of subjects in period 2^[2]	Metformin XR	Metformin IR
Started	268	271
Completed	245	245
Not completed	23	26
Adverse event, serious fatal	1	-
Subject Withdrew Consent	4	5
Adverse event, non-fatal	6	1
Other	6	10
Subject Request to Discontinue Treatment	2	-
Poor/Non-compliance	1	-
Lost to follow-up	3	10

Notes:

[2] - 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: Out of 1736 subjects who were enrolled only 568 subjects were treated.

Period 3

Period 3 title	Off Treatment Follow-Up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Metformin XR

Arm description:

Subjects did not received any treatment during the off-treatment follow-up period. These subjects originally received Metformin XR and Placebo matching with Metformin XR Metformin Extended Release (XR) 500 mg tablets (500-2000 mg per day) by mouth twice daily (BID) for 24 weeks Placebo matching with Metformin XR 0 mg tablets by mouth twice daily (BID) for 24 weeks.

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Metformin IR

Arm description:

Subjects did not received any treatment during the off-treatment follow-up period. These subjects originally received Metformin IR and Placebo matching with Metformin IR. Metformin Immediate Release (IR) 500 mg tablets (500-2000 mg per day) by mouth twice daily (BID) for 24 weeks Placebo matching with Metformin IR 0 mg tablets by mouth twice daily (BID) for 24 weeks.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 3^[3]	Metformin XR	Metformin IR
Started	9	1
Completed	6	1
Not completed	3	0
Subject Withdrew Consent	1	-
Other	2	-

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all subjects entered the Follow-Up period.

Baseline characteristics

Reporting groups

Reporting group title	Metformin XR
Reporting group description:	
Subjects received Metformin XR and Placebo matching with Metformin XR Metformin Extended Release (XR) 500 mg tablets (500-2000 mg per day) by mouth twice daily (BID) for 24 weeks Placebo matching with Metformin XR 0 mg tablets by mouth twice daily (BID) for 24 weeks. Population includes all randomized subjects who took at least one dose of double-blind study medication in the treatment group to which they were randomized, excluding 15 randomized subjects due to site non-compliance.	
Reporting group title	Metformin IR
Reporting group description:	
Subjects received Metformin IR and Placebo matching with Metformin IR. Metformin Immediate Release (IR) 500 mg tablets (500-2000 mg per day) by mouth twice daily (BID) for 24 weeks Placebo matching with Metformin IR 0 mg tablets by mouth twice daily (BID) for 24 weeks. Population includes all randomized subjects who took at least one dose of double-blind study medication in the treatment group to which they were randomized, excluding 14 randomized subjects due to site non-compliance.	

Reporting group values	Metformin XR	Metformin IR	Total
Number of subjects	268	271	539
Age Categorical			
Units: Subjects			
< 65 years	198	226	424
>= 65 years	70	45	115
Age Continuous			
Units: years			
arithmetic mean	56.8	55.3	
standard deviation	± 10.69	± 10.34	-
Gender, Male/Female			
Units: Subjects			
Female	122	122	244
Male	146	149	295
Race/Ethnicity, Customized			
Units: Subjects			
White	227	225	452
Black or African American	22	19	41
Asian	17	20	37
Other	2	7	9

End points

End points reporting groups

Reporting group title	Metformin XR
Reporting group description: Subjects received Metformin XR and Placebo matching with Metformin XR Metformin Extended Release (XR) 500 mg tablets (500-2000 mg per day) by mouth twice daily (BID) for 24 weeks Placebo matching with Metformin XR 0 mg tablets by mouth twice daily (BID) for 24 weeks.	
Reporting group title	Metformin IR
Reporting group description: Subjects received Metformin IR and Placebo matching with Metformin IR. Metformin Immediate Release (IR) 500 mg tablets (500-2000 mg per day) by mouth twice daily (BID) for 24 weeks Placebo matching with Metformin IR 0 mg tablets by mouth twice daily (BID) for 24 weeks.	
Reporting group title	Metformin XR
Reporting group description: Subjects received Metformin XR and Placebo matching with Metformin XR Metformin Extended Release (XR) 500 mg tablets (500-2000 mg per day) by mouth twice daily (BID) for 24 weeks Placebo matching with Metformin XR 0 mg tablets by mouth twice daily (BID) for 24 weeks. Population includes all randomized subjects who took at least one dose of double-blind study medication in the treatment group to which they were randomized, excluding 15 randomized subjects due to site non-compliance.	
Reporting group title	Metformin IR
Reporting group description: Subjects received Metformin IR and Placebo matching with Metformin IR. Metformin Immediate Release (IR) 500 mg tablets (500-2000 mg per day) by mouth twice daily (BID) for 24 weeks Placebo matching with Metformin IR 0 mg tablets by mouth twice daily (BID) for 24 weeks. Population includes all randomized subjects who took at least one dose of double-blind study medication in the treatment group to which they were randomized, excluding 14 randomized subjects due to site non-compliance.	
Reporting group title	Metformin XR
Reporting group description: Subjects did not received any treatment during the off-treatment follow-up period. These subjects originally received Metformin XR and Placebo matching with Metformin XR Metformin Extended Release (XR) 500 mg tablets (500-2000 mg per day) by mouth twice daily (BID) for 24 weeks Placebo matching with Metformin XR 0 mg tablets by mouth twice daily (BID) for 24 weeks.	
Reporting group title	Metformin IR
Reporting group description: Subjects did not received any treatment during the off-treatment follow-up period. These subjects originally received Metformin IR and Placebo matching with Metformin IR. Metformin Immediate Release (IR) 500 mg tablets (500-2000 mg per day) by mouth twice daily (BID) for 24 weeks Placebo matching with Metformin IR 0 mg tablets by mouth twice daily (BID) for 24 weeks.	

Primary: Adjusted mean change from baseline in HbA1c

End point title	Adjusted mean change from baseline in HbA1c
End point description: Mean change in glycated hemoglobin (HbA1c) from baseline to Week 24 in the double-blind treatment period.	
End point type	Primary
End point timeframe: Week 24	

End point values	Metformin XR	Metformin IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	237		
Units: percent				
arithmetic mean (standard error)	-0.93 (± 0.0485)	-0.96 (± 0.048)		

Statistical analyses

Statistical analysis title	Adjusted mean change from baseline in HbA1c
Comparison groups	Metformin XR v Metformin IR
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.17
Variability estimate	Standard error of the mean
Dispersion value	0.0687

Primary: Number of Subjects With Death, Serious Adverse Events (SAEs), SAEs Related to Study Therapy, SAEs Leading to Discontinuation, Adverse Events (AEs) Related to Study Therapy, and AEs Leading to Discontinuation

End point title	Number of Subjects With Death, Serious Adverse Events (SAEs), SAEs Related to Study Therapy, SAEs Leading to Discontinuation, Adverse Events (AEs) Related to Study Therapy, and AEs Leading to Discontinuation ^[1]
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End point description:

SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. Treatment-related=having certain, probable, possible, or missing relationship to study drug. Treated subjects; All subjects who took at least one dose of double-blind study medication in the treatment group they were randomized to unless subjects had never received the double-blind study medication they were randomized. Those subjects were included in the treatment group based on the first treatment received.

End point type	Primary
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End point timeframe:

Date of first dose (Day 1) up to 30 post last dose of study drug (approx. 28 weeks)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive summary statistics were planned for this outcome measure.

End point values	Metformin XR	Metformin IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	283	285		
Units: subjects				
Death	1	0		
SAE	8	10		
SAEs Related to Study Therapy	1	1		
SAEs Leading to Discontinuation	0	1		
AEs Related to Study Therapy	30	25		
AEs Leading to Discontinuation	10	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in fasting plasma glucose (FPG)

End point title	Mean change in fasting plasma glucose (FPG)
End point description:	
The mean change in fasting plasma glucose (FPG) from baseline to Week 24 in the double-blind treatment period was assessed. The lack of glycemic control criteria for initiation of rescue medication during Week 12 to Week 24 was having a FPG > 200 mg/dL (11.1 mmol/L). mg/dL = milligrams per deciliter; mmol/L = millimole per Liter	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	Metformin XR	Metformin IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	229		
Units: mg/dL				
arithmetic mean (standard error)	-21.1 (± 1.803)	-20.6 (± 1.789)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in Mean Daily Glucose (MDG)

End point title	Mean change in Mean Daily Glucose (MDG)
End point description:	
The mean change in Mean Daily Glucose (MDG) from baseline to Week 24 in the double-blind treatment period was assessed. Prior to the Day 1 visit (between Week -1 and Day 1) and in the week before the Week 24/Study Termination and Rescue or Early Treatment Termination visit, subjects performed 7-point finger stick blood glucose monitoring (before and 2 hours after 3 meals per day, and at bedtime) for 3 consecutive days in order to determine their MDG.	

End point type	Secondary
End point timeframe:	
Week 24	

End point values	Metformin XR	Metformin IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	218		
Units: mg/dL				
arithmetic mean (standard error)	-24.68 (\pm 1.5813)	-27.05 (\pm 1.555)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of subjects with HbA1c < 7%

End point title	Percent of subjects with HbA1c < 7%
End point description:	
Percent of subjects achieving a therapeutic glycemic response (defined as HbA1c < 7.0%) at Week 24 in the double-blind treatment period.	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	Metformin XR	Metformin IR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	237		
Units: percent of subjects				
number (confidence interval 95%)	70.9 (65.5 to 76.3)	72 (66.3 to 77.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days after the last dose of the study drug

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Metformin IR
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Reporting group description:

Metformin Immediate Release (IR) 500 mg, tablets (500-2000 mg per day), orally, BID and Placebo matching with Metformin IR 0 mg, tablets, orally, BID for 24 weeks.

Reporting group title	Metformin XR
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Reporting group description:

Metformin Extended Release (XR) 500 mg, tablets (500-2000 mg per day), orally, twice daily (BID) and placebo matching with Metformin XR 0 mg, tablets, orally, BID for 24 weeks.

Serious adverse events	Metformin IR	Metformin XR	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 285 (3.51%)	8 / 283 (2.83%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma in situ			
subjects affected / exposed	0 / 285 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic adenoma			
subjects affected / exposed	1 / 285 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 285 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Delayed recovery from anaesthesia subjects affected / exposed	0 / 285 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration subjects affected / exposed	1 / 285 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose subjects affected / exposed	0 / 285 (0.00%)	2 / 283 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders Angina unstable subjects affected / exposed	0 / 285 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders Cerebral haemorrhage subjects affected / exposed	0 / 285 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction subjects affected / exposed	1 / 285 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders Hypocoagulable state subjects affected / exposed	0 / 285 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders Diplopia			

subjects affected / exposed	1 / 285 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 285 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 285 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 285 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 285 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 285 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Ureterolithiasis			
subjects affected / exposed	1 / 285 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pulmonary tuberculosis			

subjects affected / exposed	1 / 285 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 285 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 285 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Metformin IR	Metformin XR	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 285 (11.58%)	39 / 283 (13.78%)	
Investigations			
Glomerular filtration rate decreased			
subjects affected / exposed	13 / 285 (4.56%)	14 / 283 (4.95%)	
occurrences (all)	15	18	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	22 / 285 (7.72%)	25 / 283 (8.83%)	
occurrences (all)	36	32	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 April 2013	This amendment clarified the language for the enrollment period and the lead-in period.
08 August 2013	<p>This amendment added the following exclusion criteria:</p> <ol style="list-style-type: none">1) Moderate or severe impairment of renal function defined as eGFR < 60 mL/min/1.73 m² (estimated by MDRD)2) Administration of any other investigational drug or participation in any interventional clinical study within 30 days of planned screening to this study3) Subject is a participating investigator, study coordinator, employee of an investigator or immediate family member of any of the aforementioned) <p>Additionally, this amendment revised language for discontinuation due to increased serum creatinine; added criteria for discontinuation of study drug due to impairment of renal function based on eGFR; and clarified that a 12-lead ECG would be obtained during the Lead-in Period.</p>
19 June 2014	This amendment revised the inclusion enrollment and randomization criteria for HbA1c (lower limit of HbA1c was changed from $\geq 7.2\%$ to $\geq 7.0\%$, and the upper limit was changed from $\leq 9.0\%$ to $\leq 9.2\%$), clarified the definition of "treatment naïve" for inclusion criteria, allowed for optional pre-screening, and clarified the IVRS contact at Week -1.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported