Clinical trial results:
A double blind, double dummy, randomised, multi-centre study to assess the tolerability and efficacy profile of vildagliptin compared to gliclazide as dual therapy with metformin in Muslim patients with type 2 diabetes fasting during Ramadan

Summary

EudraCT number	2011-005499-41
Trial protocol	DK ES GB
Global end of trial date	05 September 2013

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	24 July 2015

Trial information

Trial identification

Sponsor protocol code	CLAF237A2411

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01758380
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

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	05 September 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate in Muslim patients with T2DM who plan to fast during the Ramadan fasting period:

The proportion of patients with at least one HE (Hypoglycaemic event) is lower in the vildagliptin plus metformin arm compared to the gliclazide plus metformin arm during the Ramadan fasting period.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial. Basal insulin could be used as rescue medication at the discretion of the investigator any time during the study after randomization for those patients who were not achieving a satisfactory therapeutic effect.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 January 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	Denmark: 1
Country: Number of subjects enrolled	Egypt: 86
Country: Number of subjects enrolled	Germany: 37
Country: Number of subjects enrolled	Indonesia: 38
Country: Number of subjects enrolled	Jordan: 35
Country: Number of subjects enrolled	Kuwait: 13
Country: Number of subjects enrolled	Lebanon: 85
Country: Number of subjects enrolled	Malaysia: 21
Country: Number of subjects enrolled	Russian Federation: 50
Country: Number of subjects enrolled	Saudi Arabia: 13
Country: Number of subjects enrolled	Singapore: 31
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	Tunisia: 57
Country: Number of subjects enrolled	Turkey: 25
Country: Number of subjects enrolled	United Arab Emirates: 10

Country: Number of subjects enrolled	United Kingdom: 31
Worldwide total number of subjects	557
EEA total number of subjects	93

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)	491
From 65 to 84 years	66
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A screening period of up to 4 weeks was used to ensure the entry criteria are met and allowing test results to be received and evaluated.

Period 1

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

Blinding implementation details:

The identity of the treatments was concealed by the use of study drugs that were identical in packaging, labeling, schedule of administration and appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Vildagliptin (50 mg bid) + Metformin

Arm description:

Metformin 1500-2500 mg daily plus vildagliptin 50 mg bid plus gliclazide placebo (in multiples of 80 mg only). The overall treatment duration consisted of a ≥ 8 week pre-Ramadan stabilization period, the 4-week Ramadan period and a post-Ramadan period of ≤ 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Metformin 500 mg tablets 1500-2500 mg daily for the ≥ 8 week pre-Ramadan stabilization period, the 4-week Ramadan period and a post-Ramadan period of ≤ 4 weeks.

Investigational medicinal product name	Vildagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vildagliptin 50 mg tablets twice a day (bid) for the ≥ 8 week pre-Ramadan stabilization period, the 4-week Ramadan period and a post-Ramadan period of ≤ 4 weeks.

Investigational medicinal product name	Gliclazide placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Gliclazide 80 mg matching placebo capsules administered at an equivalent dose to previous sulfonylurea treatment or adjusted in accordance with international or local guidelines, for the ≥ 8 week pre-Ramadan stabilization period, the 4-week Ramadan period and a post-Ramadan period of ≤ 4 weeks.

Arm title	Gliclazide (80-320 mg/d) + Metformin

Arm description:

Metformin 1500-2500 mg daily plus gliclazide 80-320 mg/d (in multiples of 80 mg only) plus vildagliptin 50 mg placebo.

Arm type	Experimental
Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Metformin 500 mg tablets 1500-2500 mg daily for the ≥ 8 week pre-Ramadan stabilization period, the 4-week Ramadan period and a post-Ramadan period of ≤ 4 weeks.

Investigational medicinal product name	Vildagliptin Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vildagliptin 50 mg matching placebo tablets twice a day (bid) for the ≥ 8 week pre-Ramadan stabilization period, the 4-week Ramadan period and a post-Ramadan period of ≤ 4 weeks.

Investigational medicinal product name	Gliclazide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Gliclazide 80-320 mg/d (80 mg capsules) administered at an equivalent dose to previous sulfonylurea treatment or adjusted in accordance with international or local guidelines, for the ≥ 8 week pre-Ramadan stabilization period, the 4-week Ramadan period and a post-Ramadan period of ≤ 4 weeks.

Number of subjects in period 1	Vildagliptin (50 mg bid) + Metformin	Gliclazide (80-320 mg/d) + Metformin
Started	279	278
Completed	239	239
Not completed	40	39
Consent withdrawn by subject	14	13
Adverse event, non-fatal	8	10
Unsatisfactory therapeutic effect	2	1
Administrative problems	9	7
Lost to follow-up	7	7
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Vildagliptin (50 mg bid) + Metformin
Reporting group description:	
Metformin 1500-2500 mg daily plus vildagliptin 50 mg bid plus gliclazide placebo (in multiples of 80 mg only). The overall treatment duration consisted of a ≥ 8 week pre-Ramadan stabilization period, the 4-week Ramadan period and a post-Ramadan period of ≤ 4 weeks.	
Reporting group title	Gliclazide (80-320 mg/d) + Metformin
Reporting group description:	
Metformin 1500-2500 mg daily plus gliclazide 80-320 mg/d (in multiples of 80 mg only) plus vildagliptin 50 mg placebo.	

Reporting group values	Vildagliptin (50 mg bid) + Metformin	Gliclazide (80-320 mg/d) + Metformin	Total
Number of subjects	279	278	557
Age categorical Units: Subjects			
<65	248	243	491
≥65	31	35	66
Age continuous Units: years			
arithmetic mean	54.6	54.3	
standard deviation	± 9.28	± 9.07	-
Gender categorical Units: Subjects			
Female	147	150	297
Male	132	128	260

End points

End points reporting groups

Reporting group title	Vildagliptin (50 mg bid) + Metformin

Reporting group description:

Metformin 1500-2500 mg daily plus vildagliptin 50 mg bid plus gliclazide placebo (in multiples of 80 mg only). The overall treatment duration consisted of a ≥ 8 week pre-Ramadan stabilization period, the 4-week Ramadan period and a post-Ramadan period of ≤ 4 weeks.

Reporting group title	Gliclazide (80-320 mg/d) + Metformin

Reporting group description:

Metformin 1500-2500 mg daily plus gliclazide 80-320 mg/d (in multiples of 80 mg only) plus vildagliptin 50 mg placebo.

Subject analysis set title	Vildagliptin (50 mg bid) + Metformin Per Protocol Set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

The PPS consisted of all randomized patients that received at least one dose of study medication and fasted at least 10 days or stopped fasting due to hypoglycemia during the Ramadan fasting period, and had no major protocol deviations and had taken study medication for at least 10 days during Ramadan.

Subject analysis set title	Gliclazide (80-320 mg/d) + Metformin Per Protocol Set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

The PPS consisted of all randomized patients that received at least one dose of study medication and fasted at least 10 days or stopped fasting due to hypoglycemia during the Ramadan fasting period, and had no major protocol deviations and had taken study medication for at least 10 days during Ramadan.

Subject analysis set title	Vildagliptin (50 mg bid) + Metformin Safety Set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

The SAF consisted of all randomized patients that received at least one dose of study medication.

Subject analysis set title	Gliclazide (80-320 mg/d) + Metformin Safety Set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

The SAF consisted of all randomized patients that received at least one dose of study medication.

Subject analysis set title	Vildagliptin (50 mg bid) + Metformin Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS consisted of all randomized patients that received at least one dose of study medication.

Subject analysis set title	Gliclazide (80-320 mg/d) + Metformin Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS consisted of all randomized patients that received at least one dose of study medication.

Primary: Percentage of Participants Reporting at Least One Hypoglycemic Event (HE) During the Ramadan Fasting Period While Not on Rescue Medication

End point title	Percentage of Participants Reporting at Least One Hypoglycemic Event (HE) During the Ramadan Fasting Period While Not on Rescue Medication

End point description:

HEs are defined as:
a) symptoms suggestive of hypoglycemia, where the patient is able to initiate self-treatment and plasma glucose measurement is < 3.9 mmol/L (grade 1 HEs),
b) symptoms suggestive of hypoglycemia, where the patient is able to initiate self-treatment and no plasma glucose measurement is available (suspected grade 1 HEs),
c) symptoms suggestive of hypoglycemia, where the patient is unable to initiate self-treatment and plasma glucose measurement is <3.9 mmol/L (grade 2 HEs),
d) symptoms suggestive of hypoglycemia, where the patient is unable to initiate self-treatment and no

plasma glucose measurement is available (suspected grade 2 HEs),
e) Plasma glucose measurement < 3.9 mmol/L without symptoms (asymptomatic HEs).

End point type	Primary

End point timeframe:

1 month

End point values	Vildagliptin (50 mg bid) + Metformin Per Protocol Set (PPS)	Gliclazide (80-320 mg/d) + Metformin Per Protocol Set (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	234	230		
Units: percentage of participants				
number (confidence interval 95%)	6 (3.31 to 9.83)	8.7 (5.39 to 13.11)		

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Vildagliptin (50 mg bid) + Metformin Per Protocol Set (PPS) v Gliclazide (80-320 mg/d) + Metformin Per Protocol Set (PPS)
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.173
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.06

Secondary: Change from Pre-Ramadan to Post-Ramadan HbA1c (Glycosylated Hemoglobin / Hemoglobin A1c)

End point title	Change from Pre-Ramadan to Post-Ramadan HbA1c (Glycosylated Hemoglobin / Hemoglobin A1c)

End point description:

Pre-Ramadan is the measurement obtained at Visit 3 (within 4 weeks before start of Ramadam). Post-Ramadan is defined as the final available post-baseline HbA1c measurement obtained at any visit (scheduled or unscheduled) during or after Ramadan, prior to or at the start of rescue medication use, up to final scheduled visit (Visit 4). The endpoint (for PPS) was defined as the final HbA1c measurement obtained during or after Ramadan, prior to or at the initiation of rescue medication.

End point type	Secondary

End point timeframe:

Visit 3 (anytime from week -4 to day -1 before start of Ramadan) to visit 4 (within 4 weeks post-

Ramadan fasting period) (minimum 4.5 weeks to maximum 12 weeks).

End point values	Vildagliptin (50 mg bid) + Metformin Per Protocol Set (PPS)	Gliclazide (80-320 mg/d) + Metformin Per Protocol Set (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	224[1]	218[2]		
Units: HbA1c				
least squares mean (standard error)	0.05 (± 0.04)	-0.03 (± 0.04)		

Notes:

[1] - Number of participants with observations at both Pre-Ramadan and Post-Ramadan.

[2] - Number of participants with observations at both Pre-Ramadan and Post-Ramadan.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Endpoint in Glycosylated Hemoglobin (HbA1c)

End point title	Change from Baseline to Endpoint in Glycosylated Hemoglobin (HbA1c)

End point description:

Endpoint is defined as the visit 4 (post-Ramadan) measurement or the last observation obtained during or after Ramadan, prior to or at initiation of rescue medication. Baseline HbA1c was the measurement obtained on the day of randomization (Visit 2), or the closest prior measurement to Visit 2 (including scheduled and unscheduled visits) if the Visit 2 measurement was missing. Post-Ramadan is defined as the final available post baseline HbA1c measurement obtained at any visit (scheduled or unscheduled) during or after Ramadan, prior to or at the start of rescue medication.

End point type	Secondary

End point timeframe:

Baseline to visit 4 (within 4 weeks post-Ramadan fasting period) (minimum 12.5 weeks to maximum 30 weeks)

End point values	Vildagliptin (50 mg bid) + Metformin Per Protocol Set (PPS)	Gliclazide (80-320 mg/d) + Metformin Per Protocol Set (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	227[3]	220[4]		
Units: HbA1c				
least squares mean (standard error)	-0.01 (± 0.05)	-0.13 (± 0.05)		

Notes:

[3] - Number of participants with observations at both Baseline and Post-Ramadan.

[4] - Number of participants with observations at both Baseline and Post-Ramadan.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants achieving composite endpoint from Pre- to Post-Ramadan prior to the start of rescue medication

End point title	Percentage of Participants achieving composite endpoint from Pre- to Post-Ramadan prior to the start of rescue medication

End point description:

The composite endpoint was defined as change in HbA1c pre- to post-Ramadan not larger than 0.3% and no HEs during the Ramadan fasting period.

End point type	Secondary

End point timeframe:

Visit 3 (anytime from week -4 to day -1 before start of Ramadan) to visit 4 (within 4 weeks post-Ramadan fasting period) (minimum 4.5 weeks to maximum 12 weeks) for HbA1c; and during 1 month (Ramadan) for HEs

End point values	Vildagliptin (50 mg bid) + Metformin Per Protocol Set (PPS)	Gliclazide (80-320 mg/d) + Metformin Per Protocol Set (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	234	230		
Units: percentage of participants				
number (not applicable)	79.5	74.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Amplitude of Glycemic Excursions (MAGE) to Measure Glucose Fluctuations During the Day

End point title	Mean Amplitude of Glycemic Excursions (MAGE) to Measure Glucose Fluctuations During the Day

End point description:

MAGE was to be assessed in a selected subgroup of patients. Analysis was not done due lack of enough evaluable data.

End point type	Secondary

End point timeframe:

72 hours

End point values	Vildagliptin (50 mg bid) + Metformin Per Protocol Set (PPS)	Gliclazide (80-320 mg/d) + Metformin Per Protocol Set (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[5]	0[6]		
Units: no units				
arithmetic mean (standard deviation)	()	()		

Notes:

[5] - Not done due to lack of enough evaluable data.

[6] - Not done due to lack of enough evaluable data.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Pre-Ramadan to Post-Ramadan Body Weight

End point title	Change from Pre-Ramadan to Post-Ramadan Body Weight

End point description:

Baseline body weight was the measurement obtained on the day of randomization (Visit 2), or the closest prior measurement to Visit 2 (including scheduled and unscheduled visits) if the Visit 2 measurement was missing. Post-Ramadan is defined as the final available post-baseline measurement of body weight obtained at any visit (scheduled or unscheduled) during or after Ramadan, prior to or at the start of rescue medication use, up to final scheduled visit (Visit 4). The endpoint (for PPS) was defined as the final body weight measurement obtained during or after Ramadan, prior to or at the initiation of rescue medication.

End point type	Secondary

End point timeframe:

Visit 3 (anytime from week -4 to day -1 before start of Ramadan) to visit 4 (within 4 weeks post-Ramadan fasting period) (minimum 4.5 weeks to maximum 12 weeks)

End point values	Vildagliptin (50 mg bid) + Metformin Per Protocol Set (PPS)	Gliclazide (80-320 mg/d) + Metformin Per Protocol Set (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	231[7]	226[8]		
Units: kg				
least squares mean (standard error)	-1.06 (± 0.15)	-1.06 (± 0.15)		

Notes:

[7] - Number of participants with observations at both pre-Ramadan and post- Ramadan.

[8] - Number of participants with observations at both pre-Ramadan and post- Ramadan.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days Fasted During the Ramadan Fasting Period

End point title	Number of Days Fasted During the Ramadan Fasting Period

End point description:

End point type	Secondary

End point timeframe:

1 month

End point values	Vildagliptin (50 mg bid) + Metformin Safety Set (SAF)	Gliclazide (80-320 mg/d) + Metformin Safety Set (SAF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	241[9]	242[10]		
Units: days				
arithmetic mean (standard deviation)	28.3 (± 3.03)	28.1 (± 3.83)		

Notes:

[9] - Safety Set participants with observations on the number of days fasted during Ramadan.

[10] - Safety Set participants with observations on the number of days fasted during Ramadan.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Having at Least 1 Unscheduled Visit to the Health Care Professional (HCP)

End point title	Percentage of Participants Having at Least 1 Unscheduled Visit to the Health Care Professional (HCP)

End point description:

End point type	Secondary

End point timeframe:

Between the pre- Ramadan visit (Visit 3) and the post-Ramadan visit (Visit 4)/end of study

End point values	Vildagliptin (50 mg bid) + Metformin Full Analysis Set (FAS)	Gliclazide (80-320 mg/d) + Metformin Full Analysis Set (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	273	274		
Units: percentage of participants				
number (not applicable)	1.5	3.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Treatment Adherence During the Ramadan Fasting Period

End point title	Overall Treatment Adherence During the Ramadan Fasting Period

End point description:

Treatment adherence (%) was defined as: [number of days during Ramadan fasting period *

(recommended therapy (metformin, vildagliptin, gliclazide) daily dose during Ramadan period) – (number of missed doses during Ramadan period)] *100/ [number of days during Ramadan fasting period * (recommended therapy daily dose during Ramadan period)].
Overall adherence (%) was defined as metformin adherence + vildagliptin adherence + gliclazide adherence / 3.

End point type	Secondary

End point timeframe:

Number of days from start of Ramadan to the Ramadan end period date (minimum 4.5 weeks to maximum 12 weeks).

End point values	Vildagliptin (50 mg bid) + Metformin Safety Set (SAF)	Gliclazide (80-320 mg/d) + Metformin Safety Set (SAF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	273	274		
Units: percentage				
arithmetic mean (standard deviation)	96.7 (± 10.4)	95.8 (± 11.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Serious or Clinically Significant Adverse Events (AEs)

End point title	Percentage of Participants with Serious or Clinically Significant Adverse Events (AEs)

End point description:

End point type	Secondary

End point timeframe:

Baseline to visit 4 (within 4 weeks post-Ramadan fasting period) (minimum 12.5 weeks to maximum 30 weeks)

End point values	Vildagliptin (50 mg bid) + Metformin Safety Set (SAF)	Gliclazide (80-320 mg/d) + Metformin Safety Set (SAF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	273	274		
Units: percentage of participants				
number (not applicable)				
Deaths	0	0		
Serious AEs	2.2	1.5		
Discontinuation due to AEs	2.9	4		

AEs causing dose adjustment or drug interruption	2.6	3.6		
AEs of predefined risk	5.5	9.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Severe Hypoglycemia or Hypoglycemic Events that Occurred During the Ramadan Fasting Period

End point title	Percentage of Participants with Severe Hypoglycemia or Hypoglycemic Events that Occurred During the Ramadan Fasting Period

End point description:

Severe hypoglycemia and hypoglycemic events are defined as suspected grade 2 (requiring 3rd party assistance).

End point type	Secondary

End point timeframe:

1 month

End point values	Vildagliptin (50 mg bid) + Metformin Per Protocol Set (PPS)	Gliclazide (80-320 mg/d) + Metformin Per Protocol Set (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	234	230		
Units: percentage of participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Vildagliptin (50 mg bid) + Metformin

Reporting group description:

Metformin 1500-2500 mg daily plus vildagliptin 50 mg bid plus gliclazide placebo (in multiples of 80 mg only). The overall treatment duration consisted of a ≥ 8 week pre-Ramadan stabilization period, the 4-week Ramadan period and a post-Ramadan period of ≤ 4 weeks.

Reporting group title	Gliclazide (80-320 mg/d) + Metformin

Reporting group description:

Metformin 1500-2500 mg daily plus gliclazide 80-320 mg/d (in multiples of 80 mg only) plus vildagliptin 50 mg placebo.

Serious adverse events	Vildagliptin (50 mg bid) + Metformin	Gliclazide (80-320 mg/d) + Metformin	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 273 (2.20%)	4 / 274 (1.46%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 273 (0.37%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	2 / 273 (0.73%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 273 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Anal fissure			
subjects affected / exposed	0 / 273 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	1 / 273 (0.37%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 273 (0.37%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 273 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	1 / 273 (0.37%)	0 / 274 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 273 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 273 (0.00%)	1 / 274 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Vildagliptin (50 mg bid) + Metformin	Gliclazide (80-320 mg/d) + Metformin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 273 (17.22%)	56 / 274 (20.44%)	
Investigations			
Blood pressure increased			
subjects affected / exposed	3 / 273 (1.10%)	3 / 274 (1.09%)	
occurrences (all)	3	3	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 273 (1.10%)	2 / 274 (0.73%)	
occurrences (all)	3	2	
Cardiac disorders			
Palpitations			
subjects affected / exposed	3 / 273 (1.10%)	1 / 274 (0.36%)	
occurrences (all)	4	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 273 (1.83%)	4 / 274 (1.46%)	
occurrences (all)	6	5	
Headache			
subjects affected / exposed	3 / 273 (1.10%)	11 / 274 (4.01%)	
occurrences (all)	3	14	
Lethargy			
subjects affected / exposed	3 / 273 (1.10%)	0 / 274 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 273 (0.37%)	3 / 274 (1.09%)	
occurrences (all)	1	3	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 273 (0.73%)	3 / 274 (1.09%)	
occurrences (all)	2	3	
Abdominal pain			

subjects affected / exposed	0 / 273 (0.00%)	3 / 274 (1.09%)	
occurrences (all)	0	4	
Abdominal pain upper			
subjects affected / exposed	5 / 273 (1.83%)	2 / 274 (0.73%)	
occurrences (all)	5	2	
Constipation			
subjects affected / exposed	5 / 273 (1.83%)	1 / 274 (0.36%)	
occurrences (all)	6	1	
Diarrhoea			
subjects affected / exposed	11 / 273 (4.03%)	12 / 274 (4.38%)	
occurrences (all)	13	15	
Flatulence			
subjects affected / exposed	3 / 273 (1.10%)	0 / 274 (0.00%)	
occurrences (all)	3	0	
Nausea			
subjects affected / exposed	7 / 273 (2.56%)	7 / 274 (2.55%)	
occurrences (all)	9	8	
Vomiting			
subjects affected / exposed	3 / 273 (1.10%)	2 / 274 (0.73%)	
occurrences (all)	3	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 273 (0.37%)	7 / 274 (2.55%)	
occurrences (all)	1	10	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 273 (0.37%)	4 / 274 (1.46%)	
occurrences (all)	1	4	
Upper respiratory tract infection			
subjects affected / exposed	4 / 273 (1.47%)	4 / 274 (1.46%)	
occurrences (all)	4	4	
Nasopharyngitis			
subjects affected / exposed	1 / 273 (0.37%)	3 / 274 (1.09%)	
occurrences (all)	1	3	
Metabolism and nutrition disorders			

Hyperglycaemia			
subjects affected / exposed	2 / 273 (0.73%)	4 / 274 (1.46%)	
occurrences (all)	2	4	
Vitamin D deficiency			
subjects affected / exposed	3 / 273 (1.10%)	1 / 274 (0.36%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 May 2013	When the study was designed, a very short recruitment period was envisioned. Enrolling patients within a very narrow time window would have ensured that all patients have a very similar overall study duration (i.e., from randomization (Visit 2) to last visit (Visit 4)). This was an important consideration for a reliable efficacy assessment over the entire treatment period. However, during the operational set-up phase of the study it became obvious that a longer time frame would be required to successfully complete recruitment: a large number of patients (>550) had to be enrolled in a very short period of time and due to the fixed start date of Ramadan no extension of the recruitment period would have been possible. Thus, to limit the risk of incomplete enrollment and to facilitate the study operationally, the time window for enrollment was markedly increased compared to the initial predictions, and patients therefore entered the study over a ~4 months period. Consequently, the time period from randomization to last visit varied considerably between patients (from ~13 to ~29 weeks). Given the different individual study durations, there was also a significant risk that the mean treatment duration may no longer be balanced between the treatments arms. In addition, from a clinical perspective, this may likely have an impact on the stability of treatment in the now extended pre-Ramadan period, with a higher probability of dose adjustments. Taken together, all these factors impact the validity/robustness of the non-inferiority (NI) assessment of the HbA1c changes from randomization to the last visit between treatments, which was a co-primary endpoint in the original protocol. Thus it was decided to focus the primary objective on the most important and new aspect of this study, i.e., to test in an interventional, double-blind setting the hypothesis of a lower incidence of hypoglycemia with vildagliptin versus SUs during the key study period of Ramadan.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported