Clinical trial results:
A randomized, double-blind, placebo-controlled, parallel groups study to investigate the safety and tolerability, efficacy, pharmacokinetics and pharmacodynamics of three BI 187004 doses given once daily as mono-therapy and of the highest BI 187004 dose given once daily as add on treatment to metformin over 28 days in patients with type 2 diabetes mellitus

Summary

EudraCT number	2013-003646-16
Trial protocol	DE
Global end of trial date	02 August 2015

Results information

Result version number	v1 (current)
This version publication date	13 August 2016
First version publication date	13 August 2016

Trial information

Trial identification

Sponsor protocol code	1307.4

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02150824
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim , +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim , +1 8002430127, clintriage.rdg@boehringer-ingelheim.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	10 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 July 2015
Global end of trial reached?	Yes
Global end of trial date	02 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the current study is to investigate the safety and tolerability of a once daily oral dose of 20 mg, 80 mg or 240 mg BI 187004 as mono-therapy and 240 mg BI 187004 on a stable metformin background over 28 days in patients with type 2 diabetes mellitus.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 July 2014
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	Germany: 103
Worldwide total number of subjects	103
EEA total number of subjects	103

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)	72
From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a randomised,double-blind,placebo-controlled study with parallel groups to investigate the safety, tolerability, efficacy, pharmacokinetics&pharmacodynamics of BI 187004 administered as once daily oral dose of 20mg,80mg or 240mg monotherapy,or as 240mg add-on to a metformin background,over 28 days in patients with type 2 diabetes mellitus.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in trial. Subjects attended specialist sites to ensure that they (the subjects) met all implemented inclusion/exclusion criteria. Subjects were not to be randomised to trial drug if any of the specific entry criteria was violated. In this study,216 enrolled &103 entered & treated.

Period 1

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

Blinding implementation details:

This is a randomised, placebo-controlled, double-blind and parallel-group study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 oral antidiabetic drug (OAD) (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered placebo tablet(s) once daily over 28 days.

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

Dosage and administration details:

Subject were orally administered placebo tablet(s) once daily over 28 days.

Arm title	20 mg BI 187004

Arm description:

The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 20 mg BI 187004 tablet once daily over 28 days.

Arm type	Experimental
Investigational medicinal product name	BI 187004 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were orally administered 20 mg BI 187004 tablet once daily over 28 days.

Arm title	80 mg BI 187004

Arm description:

The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 80 mg BI 187004 tablet once daily over 28 days.

Arm type	Experimental
Investigational medicinal product name	BI 187004 80mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were orally administered 80 mg BI 187004 tablet once daily over 28 days.

Arm title	240 mg BI 187004

Arm description:

The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 240 mg BI 187004 once daily over 28 days.

Arm type	Experimental
Investigational medicinal product name	BI 187004 240mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were orally administered 240 mg BI 187004 once daily over 28 days.

Arm title	Placebo + met

Arm description:

The patients on a stable background monotherapy treatment with metformin for at least 12 weeks prior to the study and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered placebo tablets once daily over 28 days with metformin as background therapy.

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

Dosage and administration details:

The patients were orally administered placebo tablets once daily over 28 days.

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

Dosage and administration details:

The patients were orally administered Metformin as a background therapy once daily over 28 days.

Arm title	240 mg BI 187004 + met

Arm description:

The patients on a stable background monotherapy treatment with metformin for at least 12 weeks prior to the study and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 240 mg BI 187004 once daily over 28 days with metformin as background therapy.

Arm type	Experimental
Investigational medicinal product name	240 mg BI 187004
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The patients on a stable background monotherapy treatment with metformin and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 240 mg BI 187004 once daily over 28 days.

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

Dosage and administration details:

The patients were orally administered Metformin as a background therapy once daily over 28 days.

Number of subjects in period 1	Placebo	20 mg BI 187004	80 mg BI 187004
Started	15	16	16
Completed	15	16	16

Number of subjects in period 1	240 mg BI 187004	Placebo + met	240 mg BI 187004 + met
Started	15	21	20
Completed	15	21	20

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 oral antidiabetic drug (OAD) (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered placebo tablet(s) once daily over 28 days.	
Reporting group title	20 mg BI 187004
Reporting group description:	
The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 20 mg BI 187004 tablet once daily over 28 days.	
Reporting group title	80 mg BI 187004
Reporting group description:	
The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 80 mg BI 187004 tablet once daily over 28 days.	
Reporting group title	240 mg BI 187004
Reporting group description:	
The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 240 mg BI 187004 once daily over 28 days.	
Reporting group title	Placebo + met
Reporting group description:	
The patients on a stable background monotherapy treatment with metformin for at least 12 weeks prior to the study and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered placebo tablets once daily over 28 days with metformin as background therapy.	
Reporting group title	240 mg BI 187004 + met
Reporting group description:	
The patients on a stable background monotherapy treatment with metformin for at least 12 weeks prior to the study and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 240 mg BI 187004 once daily over 28 days with metformin as background therapy.	

Reporting group values	Placebo	20 mg BI 187004	80 mg BI 187004
Number of subjects	15	16	16
Age categorical Units: Subjects			

Age continuous			
Treated Set(TS): The patients who were treated with ≥1 dose of study medication were all included in the Treated Set.			
Units: years			
arithmetic mean	57.6	58.6	59.4
standard deviation	± 7.3	± 11.6	± 8.6
Gender categorical Units: Subjects			
Female	4	3	5
Male	11	13	11

Reporting group values	240 mg BI 187004	Placebo + met	240 mg BI 187004 + met
Number of subjects	15	21	20
Age categorical Units: Subjects			

Age continuous			
Treated Set(TS): The patients who were treated with ≥1 dose of study medication were all included in the Treated Set.			
Units: years			
arithmetic mean	55.7	57.2	62.1
standard deviation	± 7.8	± 9.8	± 7.8
Gender categorical Units: Subjects			
Female	3	5	2
Male	12	16	18

Reporting group values	Total		
Number of subjects	103		
Age categorical Units: Subjects			

Age continuous			
Treated Set(TS): The patients who were treated with ≥1 dose of study medication were all included in the Treated Set.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	22		
Male	81		

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 oral antidiabetic drug (OAD) (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered placebo tablet(s) once daily over 28 days.

Reporting group title	20 mg BI 187004

Reporting group description:

The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 20 mg BI 187004 tablet once daily over 28 days.

Reporting group title	80 mg BI 187004

Reporting group description:

The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 80 mg BI 187004 tablet once daily over 28 days.

Reporting group title	240 mg BI 187004

Reporting group description:

The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 240 mg BI 187004 once daily over 28 days.

Reporting group title	Placebo + met

Reporting group description:

The patients on a stable background monotherapy treatment with metformin for at least 12 weeks prior to the study and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered placebo tablets once daily over 28 days with metformin as background therapy.

Reporting group title	240 mg BI 187004 + met

Reporting group description:

The patients on a stable background monotherapy treatment with metformin for at least 12 weeks prior to the study and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 240 mg BI 187004 once daily over 28 days with metformin as background therapy.

Primary: The percentage of patients with drug-related AEs

End point title	The percentage of patients with drug-related AEs[1]

End point description:

The percentage of patients with drug-related AEs.

End point type	Primary

End point timeframe:

from first drug administration until 14 days after the last drug administration, up to 42 days.

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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis test were tested.

End point values	Placebo	20 mg BI 187004	80 mg BI 187004	240 mg BI 187004
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[2]	16[3]	16[4]	15[5]
Units: Percentage of participants				
number (not applicable)	33.3	0	31.3	26.7

Notes:

[2] - Treated Set

[3] - Treated Set

[4] - Treated Set

[5] - Treated Set

End point values	Placebo + met	240 mg BI 187004 + met		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[6]	20[7]		
Units: Percentage of participants				
number (not applicable)	19	30		

Notes:

[6] - Treated Set

[7] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in FPG after 28 days of treatment

End point title	Change from baseline in FPG after 28 days of treatment

End point description:

Change from baseline in fasting plasma glucose (FPG) after 28 days of treatment.The ANCOVA model was used to calculate the least squares mean and standard error.

Observed case analysis for FPG (OC-G): This method was used to impute the missing values.

The number of participants analysed displays the number of participants with available data at the timepoint of interest.

End point type	Secondary

End point timeframe:

Baseline and Day 29

End point values	Placebo	20 mg BI 187004	80 mg BI 187004	240 mg BI 187004
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[8]	16[9]	16[10]	14[11]
Units: mg/dL				
least squares mean (standard error)	0.9 (± 5.2)	6.6 (± 5)	8 (± 5)	6.8 (± 5.4)

Notes:

[8] - TS (OC-G)

[9] - TS (OC-G)

[10] - TS (OC-G)

[11] - TS (OC-G)

End point values	Placebo + met	240 mg BI 187004 + met		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[12]	20[13]		
Units: mg/dL				
least squares mean (standard error)	4.5 (± 4.4)	6.1 (± 4.5)		

Notes:

[12] - TS (OC-G)

[13] - TS (OC-G)

Statistical analyses

Statistical analysis title	All groups

Statistical analysis description:

The statistical model used for the analysis of change from baseline (Day 1 of Visit 3) in FPG after 28 days of treatment was an Analysis of Covariance (ANCOVA) model. In model, the treatment was considered as a categorical effect, baseline FPG was included as a continuous covariate. Missing FPG values after 28 days of treatment were not replaced, whereas values after the potential introduction of another antidiabetic drug were not included in the primary analysis.

Comparison groups	Placebo v 20 mg BI 187004 v 80 mg BI 187004 v 240 mg BI 187004 v Placebo + met v 240 mg BI 187004 + met
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9414
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

from first drug administration until 14 days after the last drug administration, upto 42 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered placebo tablet(s) once daily over 28 days.

Reporting group title	20 mg BI 187004

Reporting group description:

The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 20 mg BI 187004 tablet once daily over 28 days.

Reporting group title	80 mg BI 187004

Reporting group description:

The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 80 mg BI 187004 tablet once daily over 28 days.

Reporting group title	240 mg BI 187004

Reporting group description:

The patients untreated (therapy-naïve patients or patients with no antidiabetic treatment within 4 weeks prior to giving informed consent) or previously treated with 1 OAD (underwent a 28-day wash-out period) and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 240 mg BI 187004 once daily over 28 days.

Reporting group title	Placebo + met

Reporting group description:

The patients on a stable background monotherapy treatment with metformin for at least 12 weeks prior to the study and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered placebo tablets once daily over 28 days with metformin as background therapy.

Reporting group title	240 mg BI 187004 + met

Reporting group description:

The patients on a stable background monotherapy treatment with metformin for at least 12 weeks prior to the study and who successfully completed the placebo run-in period of 2 weeks were randomised and orally administered 240 mg BI 187004 once daily over 28 days with metformin as background therapy.

Serious adverse events	Placebo	20 mg BI 187004	80 mg BI 187004
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	240 mg BI 187004	Placebo + met	240 mg BI 187004 + met
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Placebo	20 mg BI 187004	80 mg BI 187004
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 15 (86.67%)	14 / 16 (87.50%)	15 / 16 (93.75%)
Vascular disorders			
Flushing			
subjects affected / exposed	10 / 15 (66.67%)	14 / 16 (87.50%)	12 / 16 (75.00%)
occurrences (all)	10	14	12
Orthostatic hypotension			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Peripheral coldness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Feeling abnormal			

subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Listless			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Mood swings			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			

subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	6 / 16 (37.50%)
occurrences (all)	1	0	8
Hypogeusia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Epigastric discomfort			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dermatitis contact			

subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Rash generalised			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	2 / 15 (13.33%)	0 / 16 (0.00%)	2 / 16 (12.50%)
occurrences (all)	2	0	2
Musculoskeletal pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Adenoviral conjunctivitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	1 / 15 (6.67%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			

Hyperglycaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Polydipsia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	240 mg BI 187004	Placebo + met	240 mg BI 187004 + met
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)	18 / 21 (85.71%)	18 / 20 (90.00%)
Vascular disorders			
Flushing			
subjects affected / exposed	14 / 15 (93.33%)	17 / 21 (80.95%)	14 / 20 (70.00%)
occurrences (all)	14	17	14
Orthostatic hypotension			
subjects affected / exposed	0 / 15 (0.00%)	2 / 21 (9.52%)	2 / 20 (10.00%)
occurrences (all)	0	3	3
Peripheral coldness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Feeling abnormal			
subjects affected / exposed	1 / 15 (6.67%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Peripheral swelling			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Listless			
subjects affected / exposed	1 / 15 (6.67%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Mood swings			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 15 (6.67%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	1 / 15 (6.67%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 21 (4.76%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	2 / 15 (13.33%)	0 / 21 (0.00%)	3 / 20 (15.00%)
occurrences (all)	2	0	3
Hypogeusia			

subjects affected / exposed	1 / 15 (6.67%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	3 / 20 (15.00%)
occurrences (all)	0	0	4
Epigastric discomfort			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 21 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Toothache			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	1 / 15 (6.67%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	1 / 15 (6.67%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Eczema			

subjects affected / exposed	1 / 15 (6.67%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Rash generalised			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Adenoviral conjunctivitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 15 (6.67%)	3 / 21 (14.29%)	3 / 20 (15.00%)
occurrences (all)	1	3	3
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Polydipsia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 June 2014	A new statement has been added to clarify on the meaning of the original sentence and make sure it is clear that all statins are allowed as co-medications regardless of their inhibition on the CYP3A4. As proposed and agreed with regulatory bodies, the blood glucose threshold for the initiation of rescue therapy has been lowered. Thus all instances of 270 mg/dL were replaced with 240 mg/dl. The text "(with the exception of GLP-1 receptor agonist)" was added to clarify GLP-1 analogues, though injectable antidiabetics, are allowed rescue medications. As proposed and agreed with Central EC , a process has been added to verify if it is medically acceptable for a patient to continue its participation when more repeated values greater than 140 mg/dL are detected. The clear guidance on where to find detailed instructions on how to handle the urine samples for pharmacodynamic assessments and on how to collect the weight of the containers was added.
05 September 2014	Flow chart &all other relevant sections of protocol were updated,In order to provide reliable results, prior to testing cortisol,ACTH &other pituitary axis hormones,resting time of approximately 30 minutes (min) was implemented &In order to accommodate the resting time,60 min window has been introduced & also time interval for the test was increase. An exclusion criterion has been updated based on a publication referenced in protocol.The conversion from mg/dl to mmol/L for blood glucose levels has been changed from 15.0 to 13,3. The µg/l values for cortisol & pg/ml values for Adrenocorticotrophin hormone(ACTH) were removed.The plasma cortisol cut-off point has been updated from 595 nmol/L to 377 nmol/L. A clarification on how to handle the 3 supine measurements &how to perform the comparison to individual standing measurements was updated.
01 April 2015	Change in sample size was updated. In Sampling flow chart the typographical error was corrected and updated that the Day 28 3:00 am sample for WMG is meant to be at a specific point in time and not relative to the study drug intake. In order to minimized or prevented any bias during the interim analysis as certain functions within Boehringer Ingelheim will be required to be unblinded. It was updated that though certain patient will be unblinded, the unblinded information will not be shared or disclosed with team members that have a significant influence in the conduct of the study. Therefore, any bias will be minimized or prevented. The scope and purpose of the interim analysis was updated. The clarification was provided to emphasize that symptom compatible with low blood pressure or sudden changes in blood pressure are enough to declare the orthostatic test as abnormal. The definition of Postural Orthostatic Tachycardia Syndrome was updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported