Clinical trial results:
A dose-ranging, randomized, double-blind, placebo-controlled, parallel-group, multi-center study of the efficacy and safety of 4 doses of imeglimin after 24 weeks of treatment in subjects with type 2 diabetes mellitus

Summary

EudraCT number	2012-004045-33
Trial protocol	LV HU EE CZ RO
Global end of trial date	10 July 2014

Results information

Result version number	v1 (current)
This version publication date	26 September 2021
First version publication date	26 September 2021

Trial information

Trial identification

Sponsor protocol code	PXL008-008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01951235
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	POXEL SA
Sponsor organisation address	259/261 avenue Jean Jaurès, LYON, France, 69007
Public contact	Pascale Fouqueray, Poxel SA, 33 437372010,
Scientific contact	Pascale Fouqueray, Poxel SA, +33 437372010, pascale.fouqueray@poxelpharma.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	21 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the dose-response of imeglimin at 4 doses (500 mg, 1000 mg, 1500 mg and 2000 mg bid) compared to placebo in male and female subjects with type 2 diabetes mellitus after 24 weeks of treatment, using glycosylated hemoglobin (HbA1c) as the primary evaluation criterion.

Protection of trial subjects:

Subjects, or their legally acceptable representatives, provided their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits of treatment. The subject information sheet in the local language and prepared in accordance with the ICH GCP guidance was provided by the sponsor for the purpose of obtaining informed consent. Written informed consent was provided at Screening Visit 1 before any study-specific activity and whenever important new information became available that was relevant to the subject's consent. Subjects were free to discontinue the study at any time without giving their reasons.
To overcome the risk to expose subjects with T2DM to an inappropriate glycemic control, some proactive measures were implemented. First, the upper limit of HbA1c inclusion criterion at randomization was limited to 9.5% in order to avoid highly uncontrolled subjects entering the study (see Section 9.3.1). Second, fasting plasma glucose (FPG) was closely monitored throughout the study by the subject (glucometer) and by the investigator at each visit and whenever necessary. Threshold was defined following the Food and Drug Administration (FDA) guidance to withdraw from the study subjects whose glycemic parameters kept deteriorating during the study period in order to initiate rescue therapy.

Background therapy:

No background therapy was allowed during the study.

Evidence for comparator:

The design of this dose-ranging study included a placebo arm in order to compare the efficacy of each dose of imeglimin based on the change in HbA1c values as well as safety and tolerability.

Actual start date of recruitment	25 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	Russian Federation: 28
Country: Number of subjects enrolled	United States: 45
Country: Number of subjects enrolled	Ukraine: 63
Country: Number of subjects enrolled	Romania: 68
Country: Number of subjects enrolled	Czechia: 15
Country: Number of subjects enrolled	Estonia: 31
Country: Number of subjects enrolled	Hungary: 60
Country: Number of subjects enrolled	Latvia: 72

Worldwide total number of subjects	382
EEA total number of subjects	246

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)	283
From 65 to 84 years	99
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at a total of 74 study centers, in the Czech Republic (5 centers), Estonia (6 centers), Hungary (13 centers), Latvia (9 centers), Romania (11 centers), Russia (10 centers), Ukraine (11 centers), and the United States (9 centers).
First subject screened: 25Jan2013 - Last subject screened: 02Dec2013

Pre-assignment

Screening details:

Subjects were screened within 3 weeks, followed by a 3-week placebo run-in period for treatment-naive subjects, or 6-week placebo wash-out/run-in period for subjects previously treated with an oral antidiabetic monotherapy.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Imeglimin 500 mg twice daily

Arm description: -

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

Dosage and administration details:

1×500 mg tablet of imeglimin twice daily plus 3 tablets of placebo twice daily for 24 weeks

Arm title	Imeglimin 1000 mg twice daily

Arm description: -

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

Dosage and administration details:

2×500 mg tablets of imeglimin twice daily plus 2 tablets of placebo twice daily for 24 weeks

Arm title	Imeglimin 1500 mg twice daily

Arm description: -

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

Dosage and administration details:

3×500 mg tablet of imeglimin twice daily plus 1 tablets of placebo twice daily for 24 weeks

Arm title	Imeglimin 2000 mg twice daily
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Imeglimin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

4×500 mg tablet of imeglimin twice daily for 24 weeks

Arm title	Placebo
Arm description: -	
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:

4 tablets of placebo twice daily for 24 weeks

Number of subjects in period 1	Imeglimin 500 mg twice daily	Imeglimin 1000 mg twice daily	Imeglimin 1500 mg twice daily
Started	74	79	74
Completed	63	66	60
Not completed	11	13	14
Consent withdrawn by subject	4	4	8
Intake of non-permitted drug	-	-	1
Adverse event, non-fatal	-	1	2
Other reasons	-	-	2
Not Adequate Treatment Compliance	1	-	-
Exclusion criteria	-	-	-
Lack of efficacy	5	6	-
Protocol deviation	1	2	1

Number of subjects in period 1	Imeglimin 2000 mg twice daily	Placebo
Started	74	81
Completed	61	65
Not completed	13	16

Consent withdrawn by subject	5	7
Intake of non-permitted drug	-	1
Adverse event, non-fatal	3	-
Other reasons	-	1
Not Adequate Treatment Compliance	-	-
Exclusion criteria	-	1
Lack of efficacy	4	6
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Imeglimin 500 mg twice daily
Reporting group description: -	
Reporting group title	Imeglimin 1000 mg twice daily
Reporting group description: -	
Reporting group title	Imeglimin 1500 mg twice daily
Reporting group description: -	
Reporting group title	Imeglimin 2000 mg twice daily
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Imeglimin 500 mg twice daily	Imeglimin 1000 mg twice daily	Imeglimin 1500 mg twice daily
Number of subjects	74	79	74
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	58.1	58.5	58.1
standard deviation	± 10.6	± 8.9	± 8.5
Gender categorical Units: Subjects			
Female	40	54	45
Male	34	25	29
BMI Units: kg/m²			
arithmetic mean	31.8	31.4	32.0
standard deviation	± 4.5	± 4.4	± 4.5
Duration of Diabetes Units: Years			
arithmetic mean	5.2	5.4	6.0
standard deviation	± 4.4	± 4.1	± 5.5
HbA1c Units: percent			
arithmetic mean	7.95	8.09	7.89
standard deviation	± 0.69	± 0.77	± 0.59
Fasting Plasma Glucose (FPG) Units: mmol/L			
arithmetic mean	9.92	10.29	9.99
standard deviation	± 2.80	± 2.14	± 2.18
HOMA-IR Units: n/a			
arithmetic mean	7.3	8.1	8.1
standard deviation	± 4.7	± 5.9	± 6.5

Reporting group values	Imeglimin 2000 mg twice daily	Placebo	Total
Number of subjects	74	81	382
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	59.0	58.2	
standard deviation	± 8.8	± 9.3	-
Gender categorical Units: Subjects			
Female	45	44	228
Male	29	37	154
BMI Units: kg/m²			
arithmetic mean	31.0	30.5	
standard deviation	± 4.5	± 4.2	-
Duration of Diabetes Units: Years			
arithmetic mean	5.7	5.0	
standard deviation	± 5.1	± 4.1	-
HbA1c Units: percent			
arithmetic mean	8.04	7.76	
standard deviation	± 0.74	± 0.62	-
Fasting Plasma Glucose (FPG) Units: mmol/L			
arithmetic mean	9.76	9.63	
standard deviation	± 2.40	± 2.12	-
HOMA-IR Units: n/a			
arithmetic mean	7.6	12.5	
standard deviation	± 5.2	± 48.9	-

End points

End points reporting groups

Reporting group title	Imeglimin 500 mg twice daily
Reporting group description: -	
Reporting group title	Imeglimin 1000 mg twice daily
Reporting group description: -	
Reporting group title	Imeglimin 1500 mg twice daily
Reporting group description: -	
Reporting group title	Imeglimin 2000 mg twice daily
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Placebo-adjusted dose-dependent reduction in HbA1c from baseline to Week 24

End point title	Placebo-adjusted dose-dependent reduction in HbA1c from baseline to Week 24
End point description:	
End point type	Primary
End point timeframe:	
Baseline to Week 24	

End point values	Imeglimin 500 mg twice daily	Imeglimin 1000 mg twice daily	Imeglimin 1500 mg twice daily	Imeglimin 2000 mg twice daily
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72	77	69	69
Units: percent				
least squares mean (standard error)	0.14 (± 0.114)	-0.09 (± 0.111)	-0.43 (± 0.116)	-0.25 (± 0.117)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: percent				
least squares mean (standard error)	0.20 (± 0.109)			

Statistical analyses

Statistical analysis title	Imeglimin 500 mg bid versus Placebo

Statistical analysis description:

Change in HbA1c from baseline to Week 24 was analyzed using an analysis of covariance (ANCOVA) method where the change in HbA1c from baseline to Week 24 was the outcome variable and country and treatment group were fixed effects. HbA1c values at baseline and subjects naïve of treatment/previously treated were included as covariates. This parameter was assessed by using the last observation carried forward (LOCF) imputation of missing values for the ITT population.

Comparison groups	Imeglimin 500 mg twice daily v Placebo
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.698
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.25
Variability estimate	Standard error of the mean
Dispersion value	0.158

Statistical analysis title	Imeglimin 1000 mg bid versus Placebo

Statistical analysis description:

Change in HbA1c from baseline to Week 24 was analyzed using an analysis of covariance (ANCOVA) method where the change in HbA1c from baseline to Week 24 was the outcome variable and country and treatment group were fixed effects. HbA1c values at baseline and subjects naïve of treatment/previously treated were included as covariates. This parameter was assessed by using the last observation carried forward (LOCF) imputation of missing values for the ITT population.

Comparison groups	Placebo v Imeglimin 1000 mg twice daily
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.068
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.287
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	0.02
Variability estimate	Standard error of the mean
Dispersion value	0.156

Statistical analysis title	Imeglimin 1500 mg bid versus Placebo

Statistical analysis description:

Change in HbA1c from baseline to Week 24 was analyzed using an analysis of covariance (ANCOVA) method where the change in HbA1c from baseline to Week 24 was the outcome variable and country and treatment group were fixed effects. HbA1c values at baseline and subjects naïve of treatment/previously treated were included as covariates. This parameter was assessed by using the last observation carried forward (LOCF) imputation of missing values for the ITT population.

Comparison groups	Placebo v Imeglimin 1500 mg twice daily
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.625
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.94
upper limit	-0.31
Variability estimate	Standard error of the mean
Dispersion value	0.159

Statistical analysis title	Imeglimin 2000 mg bid versus Placebo

Statistical analysis description:

Change in HbA1c from baseline to Week 24 was analyzed using an analysis of covariance (ANCOVA) method where the change in HbA1c from baseline to Week 24 was the outcome variable and country and treatment group were fixed effects. HbA1c values at baseline and subjects naïve of treatment/previously treated were included as covariates. This parameter was assessed by using the last observation carried forward (LOCF) imputation of missing values for the ITT population.

Comparison groups	Imeglimin 2000 mg twice daily v Placebo
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.443
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	-0.13
Variability estimate	Standard error of the mean
Dispersion value	0.16

Secondary: Percentage of subjects achieving an HbA1c response

End point title	Percentage of subjects achieving an HbA1c response

End point description:

The percentage of subjects achieving an HbA1c response at Week 24 (ie, HbA1c ≤ 7.0%) who had an

HbA1c value > 7.0% at baseline was compared against placebo using logistic regression analysis. Country, baseline HbA1c value, and subjects naïve of treatment/previously treated were included as covariates.

End point type	Secondary
End point timeframe:	
Baseline to Week 24	

End point values	Imeglimin 500 mg twice daily	Imeglimin 1000 mg twice daily	Imeglimin 1500 mg twice daily	Imeglimin 2000 mg twice daily
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	64	72	68	63
Units: percent				
number (not applicable)	18.1	15.6	33.3	20.3

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: percent				
number (not applicable)	12.5			

Statistical analyses

Statistical analysis title	Imeglimin 500 mg bid versus Placebo
Statistical analysis description:	
Logistic regression	
Comparison groups	Imeglimin 500 mg twice daily v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.101
Method	Regression, Logistic

Statistical analysis title	Imeglimin 1000 mg bid versus Placebo
Statistical analysis description:	
Logistic regression	
Comparison groups	Placebo v Imeglimin 1000 mg twice daily

Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.245
Method	Regression, Logistic

Statistical analysis title	Imeglimin 1500 mg bid versus Placebo
Statistical analysis description: Logistic regression	
Comparison groups	Placebo v Imeglimin 1500 mg twice daily
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Regression, Logistic

Statistical analysis title	Imeglimin 2000 mg bid versus Placebo
Statistical analysis description: Logistic regression	
Comparison groups	Placebo v Imeglimin 2000 mg twice daily
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.124
Method	Regression, Logistic

Secondary: Change in FPG from baseline to Week 24

End point title	Change in FPG from baseline to Week 24

End point description:

Change in FPG from baseline to Week 24 was analyzed using an ANCOVA method where the change in FPG from baseline to Week 24 was the outcome variable and country and treatment group were the fixed effects. The corresponding FPG at baseline and subjects naïve of treatment/previously treated were included as covariates. The standard error of the change from baseline was also included. The adjusted mean difference between each dose level against placebo was presented along with the standard error and a 95% CI. Baseline was the last nonmissing observation at Visit 5 or before. Analysis was performed by LOCF.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Imeglimin 500 mg twice daily	Imeglimin 1000 mg twice daily	Imeglimin 1500 mg twice daily	Imeglimin 2000 mg twice daily
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72	77	69	69
Units: mmol/L				
least squares mean (standard error)	0.368 (± 0.266)	-0.101 (± 0.259)	-0.904 (± 0.272)	-0.269 (± 0.272)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: mmol/L				
least squares mean (standard error)	0.347 (± 0.253)			

Statistical analyses

Statistical analysis title	Imeglimin 500 mg bid versus Placebo
Comparison groups	Imeglimin 500 mg twice daily v Placebo
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.956
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.703
upper limit	0.743
Variability estimate	Standard error of the mean
Dispersion value	0.368

Statistical analysis title	Imeglimin 1000 mg bid versus Placebo
Comparison groups	Placebo v Imeglimin 1000 mg twice daily
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.218
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.448

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.162
upper limit	0.266
Variability estimate	Standard error of the mean
Dispersion value	0.218

Statistical analysis title	Imeglimin 1500 mg bid versus Placebo
Comparison groups	Placebo v Imeglimin 1500 mg twice daily
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.252
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.983
upper limit	-0.52
Variability estimate	Standard error of the mean
Dispersion value	0.372

Statistical analysis title	Imeglimin 2000 mg bid versus Placebo
Comparison groups	Placebo v Imeglimin 2000 mg twice daily
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.098
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.616
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.347
upper limit	0.115
Variability estimate	Standard error of the mean
Dispersion value	0.372

Secondary: Percentage of subjects requiring rescue treatment	
End point title	Percentage of subjects requiring rescue treatment

End point description:

The percentage of subjects requiring rescue treatment, due to a high FPG concentration or high HbA1c percentage, any time between the first dose of double-blind study treatment and Week 24 was summarized. The incidence of subjects requiring rescue treatment by Week 24 was compared for each treatment group against placebo using chi-squared analysis.

End point type	Secondary

End point timeframe:

Any time between the first dose of double-blind study treatment and Week 24.

End point values	Imeglimin 500 mg twice daily	Imeglimin 1000 mg twice daily	Imeglimin 1500 mg twice daily	Imeglimin 2000 mg twice daily
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	74	79	74	74
Units: percent				
number (not applicable)	6.8	7.6	0	5.4

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	81			
Units: percent				
number (not applicable)	7.4			

Statistical analyses

Statistical analysis title	Imeglimin 500 mg bid versus Placebo
Comparison groups	Imeglimin 500 mg twice daily v Placebo
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8748
Method	Chi-squared

Statistical analysis title	Imeglimin 1000 mg bid versus Placebo
Comparison groups	Placebo v Imeglimin 1000 mg twice daily
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9641
Method	Chi-squared

Statistical analysis title	Imeglimin 1500 mg bid versus Placebo
Comparison groups	Placebo v Imeglimin 1500 mg twice daily
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0169
Method	Chi-squared

Statistical analysis title	Imeglimin 2000 mg bid versus Placebo
Comparison groups	Placebo v Imeglimin 2000 mg twice daily
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6123
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Informed Consent Form signature up to to the end of the follow-up period

Adverse event reporting additional description:

Only events that occurred after the first dose intake of the study drug were considered as Treatment Emergent Adverse Events (TEAEs). Only TEAEs are presented in this Section.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Imeglimin 500 mg twice daily
Reporting group description: -	
Reporting group title	Imeglimin 1000 mg twice daily
Reporting group description: -	
Reporting group title	Imeglimin 1500 mg twice daily
Reporting group description: -	
Reporting group title	Imeglimin 2000 mg twice daily
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Imeglimin 500 mg twice daily	Imeglimin 1000 mg twice daily	Imeglimin 1500 mg twice daily
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 74 (0.00%)	2 / 79 (2.53%)	1 / 74 (1.35%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Incisional hernia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 79 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Sciatica			
subjects affected / exposed	0 / 74 (0.00%)	1 / 79 (1.27%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Lung disorder			
subjects affected / exposed	0 / 74 (0.00%)	0 / 79 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gangrene			
subjects affected / exposed	0 / 74 (0.00%)	0 / 79 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orchitis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 79 (1.27%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Imeglimin 2000 mg twice daily	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 74 (0.00%)	1 / 81 (1.23%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Incisional hernia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Sciatica			
subjects affected / exposed	0 / 74 (0.00%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Lung disorder			
subjects affected / exposed	0 / 74 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Gangrene			
subjects affected / exposed	0 / 74 (0.00%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Imeglimin 500 mg twice daily	Imeglimin 1000 mg twice daily	Imeglimin 1500 mg twice daily
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 74 (24.32%)	28 / 79 (35.44%)	20 / 74 (27.03%)
Investigations			
aPTT prolonged			
subjects affected / exposed	1 / 74 (1.35%)	1 / 79 (1.27%)	1 / 74 (1.35%)
occurrences (all)	1	1	1
AST increased			
subjects affected / exposed	2 / 74 (2.70%)	0 / 79 (0.00%)	0 / 74 (0.00%)
occurrences (all)	2	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 74 (1.35%)	0 / 79 (0.00%)	2 / 74 (2.70%)
occurrences (all)	1	0	2
Blood lactic acid increased			
subjects affected / exposed	1 / 74 (1.35%)	5 / 79 (6.33%)	1 / 74 (1.35%)
occurrences (all)	1	5	1
ECG ST segment depression			
subjects affected / exposed	1 / 74 (1.35%)	0 / 79 (0.00%)	1 / 74 (1.35%)
occurrences (all)	1	0	1
ECG T wave inversion			
subjects affected / exposed	0 / 74 (0.00%)	0 / 79 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Nervous system disorders			

Headache			
subjects affected / exposed	2 / 74 (2.70%)	2 / 79 (2.53%)	3 / 74 (4.05%)
occurrences (all)	2	2	3
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 74 (0.00%)	0 / 79 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	2 / 74 (2.70%)	2 / 79 (2.53%)	3 / 74 (4.05%)
occurrences (all)	2	2	3
Dyspepsia			
subjects affected / exposed	0 / 74 (0.00%)	2 / 79 (2.53%)	0 / 74 (0.00%)
occurrences (all)	0	2	0
Nausea			
subjects affected / exposed	1 / 74 (1.35%)	1 / 79 (1.27%)	3 / 74 (4.05%)
occurrences (all)	1	1	3
Vomiting			
subjects affected / exposed	1 / 74 (1.35%)	0 / 79 (0.00%)	1 / 74 (1.35%)
occurrences (all)	1	0	1
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 79 (0.00%)	0 / 74 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	2 / 74 (2.70%)	0 / 79 (0.00%)	1 / 74 (1.35%)
occurrences (all)	2	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 74 (1.35%)	5 / 79 (6.33%)	1 / 74 (1.35%)
occurrences (all)	1	6	1
Nasopharyngitis			
subjects affected / exposed	3 / 74 (4.05%)	2 / 79 (2.53%)	2 / 74 (2.70%)
occurrences (all)	3	3	2
Upper respiratory tract infection			

subjects affected / exposed	1 / 74 (1.35%)	1 / 79 (1.27%)	1 / 74 (1.35%)
occurrences (all)	1	1	1
Urinary tract infection			
subjects affected / exposed	0 / 74 (0.00%)	0 / 79 (0.00%)	2 / 74 (2.70%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	6 / 74 (8.11%)	11 / 79 (13.92%)	2 / 74 (2.70%)
occurrences (all)	7	12	2

Non-serious adverse events	Imeglimin 2000 mg twice daily	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 74 (41.89%)	25 / 81 (30.86%)	
Investigations			
aPTT prolonged			
subjects affected / exposed	2 / 74 (2.70%)	1 / 81 (1.23%)	
occurrences (all)	2	2	
AST increased			
subjects affected / exposed	0 / 74 (0.00%)	0 / 81 (0.00%)	
occurrences (all)	0	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 74 (1.35%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Blood lactic acid increased			
subjects affected / exposed	2 / 74 (2.70%)	1 / 81 (1.23%)	
occurrences (all)	2	1	
ECG ST segment depression			
subjects affected / exposed	0 / 74 (0.00%)	2 / 81 (2.47%)	
occurrences (all)	0	2	
ECG T wave inversion			
subjects affected / exposed	0 / 74 (0.00%)	2 / 81 (2.47%)	
occurrences (all)	0	3	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 74 (2.70%)	2 / 81 (2.47%)	
occurrences (all)	2	3	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 74 (2.70%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Diarrhoea			
subjects affected / exposed	6 / 74 (8.11%)	1 / 81 (1.23%)	
occurrences (all)	10	1	
Dyspepsia			
subjects affected / exposed	2 / 74 (2.70%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	3 / 74 (4.05%)	1 / 81 (1.23%)	
occurrences (all)	4	1	
Vomiting			
subjects affected / exposed	2 / 74 (2.70%)	2 / 81 (2.47%)	
occurrences (all)	2	2	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 74 (0.00%)	2 / 81 (2.47%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 74 (0.00%)	0 / 81 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	5 / 74 (6.76%)	2 / 81 (2.47%)	
occurrences (all)	8	2	
Upper respiratory tract infection			
subjects affected / exposed	0 / 74 (0.00%)	2 / 81 (2.47%)	
occurrences (all)	0	2	
Urinary tract infection			

subjects affected / exposed occurrences (all)	1 / 74 (1.35%) 1	0 / 81 (0.00%) 0	
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	 11 / 74 (14.86%) 11	 11 / 81 (13.58%) 14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2013	Firstly, there was a change in the ECG recording schedule for assessment of the exclusion criterion related to the QT/QTc interval from Randomization Visit 5 to Laboratory Visit 4, in order to make the results available for Randomization Visit 5. Additionally, to simplify this criterion, calculation of the QTc interval was changed to use only the Fridericia's formula. Secondly, a change was made to allow some flexibility in the timeframe for ophthalmology examination. As well as these modifications to the timelines for 2 exclusion criteria, it was also clarified that any overcompliance > 100% of planned study drug intake was required to be reported as a potential overdose in an expedited manner.
02 December 2013	This amendment was to notify the authorities that the ratio of subjects naïve of treatment versus subjects previously treated that were planned to be recruited changed from 30-40% naïve versus 60-70% previously treated, to approximately 25% naïve and approximately 75% previously treated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported