Clinical trial results:
A randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of one dose of imeglimin versus placebo after 18 weeks of treatment in subjects with type 2 diabetes mellitus

Summary

EudraCT number	2013-001539-35
Trial protocol	HU LV
Global end of trial date	23 October 2014

Results information

Result version number	v1 (current)
This version publication date	27 October 2021
First version publication date	27 October 2021

Trial information

Trial identification

Sponsor protocol code	PXL008-009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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 S.A., +33 437372010, pascale.fouqueray@poxelpharma.com
Scientific contact	Pascale Fouqueray, POXEL S.A., +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	24 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of imeglimin versus placebo on glucose tolerance during a 3-hour Oral Glucose Tolerance Test (OGTT) after 18 weeks of treatment in type 2 diabetic subjects.

Protection of trial subjects:

Subjects 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. The subject's written informed consent to participate in the study must have been given before any study-related activities were carried out. Whenever important new information became available that was relevant to the subject's consent, the written subject information sheet and any other written information provided to subjects were revised by the Sponsor and submitted again to the IEC/IRB for review and favourable opinion. The agreed, revised information was forwarded to each subject in the study. The Investigator explained the changes to the previous version and the subject was asked to sign the new version. Subjects were free to discontinue the study at any time without giving their reasons.
To overcome the risk to expose T2DM subjects to inappropriate glycaemic levels, some proactive measures were implemented. First, the upper level of HbA1c inclusion criteria at randomisation was limited to 9.5% to avoid highly uncontrolled subjects entering the study. 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. Thresholds were defined following the Food and Drug Administration (FDA) guidance to withdraw subjects whose glycaemic parameters continued to deteriorate during the study period so that rescue therapy could be initiated.

Background therapy:

No background therapy was allowed during the study.

Evidence for comparator:

This mechanistic study was designed to evaluate the efficacy of imeglimin on both fasting and postprandial glycaemic control compared to placebo after 18 weeks of treatment duration, and their respective participation in decreasing HbA1c.

Actual start date of recruitment	12 August 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	Hungary: 26
Country: Number of subjects enrolled	Latvia: 19
Country: Number of subjects enrolled	Romania: 14
Worldwide total number of subjects	59
EEA total number of subjects	59

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)	50
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Among the 13 sites initiated, this study was conducted at 9 recruiting centres in 3 countries (4 centres in Hungary, 2 centres in Latvia, and 3 centres in Romania). Four sites were inactive (1 centre in Hungary and 3 in Romania).
First subject screened: 12Aug2013 - Last subject randomized: 11Jun2014

Pre-assignment

Screening details:

Subjects were screened within 3 weeks, followed by a 4-week single blind placebo wash-out period.

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

Arms

Are arms mutually exclusive?	Yes
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 for 18 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:

3 tablets of placebo twice daily for 18 weeks

Number of subjects in period 1	Imeglimin 1500 mg twice daily	Placebo
Started	30	29
Completed	25	18
Not completed	5	11
Consent withdrawn by subject	4	-
Adverse event, non-fatal	-	1
Lack of efficacy	1	9
Protocol deviation	-	1

Baseline characteristics

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

Reporting group values	Imeglimin 1500 mg twice daily	Placebo	Total
Number of subjects	30	29	59
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	58.4	54.3	
standard deviation	± 8.0	± 8.9	-
Gender categorical			
Units: Subjects			
Female	18	13	31
Male	12	16	28
BMI			
Units: kg/m²			
arithmetic mean	32.83	32.91	
standard deviation	± 4.95	± 4.26	-
HbA1c			
Units: percent			
arithmetic mean	8.12	8.14	
standard deviation	± 0.56	± 0.61	-
Fasting Plasma Glucose			
Units: mmol/L			
arithmetic mean	11.33	10.25	
standard deviation	± 2.53	± 1.92	-

End points

End points reporting groups

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

Primary: Change in glucose AUC during the 3-hour OGTT from baseline to Week 18 versus placebo

End point title	Change in glucose AUC during the 3-hour OGTT from baseline to Week 18 versus placebo
End point description:	

End point type	Primary
End point timeframe:	
Baseline to Week 18 (End of Treatment)	

End point values	Imeglimin 1500 mg twice daily	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	28		
Units: mmol/L·min				
arithmetic mean (standard deviation)	-800.1 (± 620.0)	-257.3 (± 586.2)		

Statistical analyses

Statistical analysis title	Imeglimin 1500 mg bid versus Placebo
Statistical analysis description:	
Change from baseline to Week 18 in glucose AUC during the OGTT was assessed with an analysis of covariance (ANCOVA) model, with country and treatment effect fitted as factors and baseline AUC glucose fitted as a covariate. This analysis was performed on the ITT population using LOCF.	
Comparison groups	Imeglimin 1500 mg twice daily v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-429.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-678
upper limit	181.3
Variability estimate	Standard error of the mean
Dispersion value	123.7

Secondary: Change in HbA1c from baseline to Week 18 versus placebo

End point title	Change in HbA1c from baseline to Week 18 versus placebo
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to Week 18 (End of Treatment)	

End point values	Imeglimin 1500 mg twice daily	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	28		
Units: percent				
arithmetic mean (standard deviation)	-0.44 (± 0.76)	0.16 (± 1.00)		

Statistical analyses

Statistical analysis title	Imeglimin 1500 mg bid versus Placebo
Statistical analysis description:	
Change from baseline to Week 18 was to be assessed with an ANCOVA model with country and treatment effect fitted as factors and baseline HbA1c fitted as a covariate. The analysis was performed on the ITT population using LOCF (when applicable).	
Comparison groups	Imeglimin 1500 mg twice daily v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.11
upper limit	-0.14

Variability estimate	Standard error of the mean
Dispersion value	0.24

Secondary: Change in Predose FPG from baseline to Week 18 versus placebo

End point title	Change in Predose FPG from baseline to Week 18 versus placebo

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 18 (End of Treatment)

End point values	Imeglimin 1500 mg twice daily	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	28		
Units: mmol/L				
arithmetic mean (standard deviation)	-1.77 (± 2.42)	-0.41 (± 1.91)		

Statistical analyses

Statistical analysis title	Imeglimin 1500 mg bid versus Placebo

Statistical analysis description:

Change from baseline to Week 18 was to be assessed with an ANCOVA model with country and treatment effect fitted as factors and baseline predose FPG as a covariate. The analysis was performed on the ITT population using LOCF (when applicable).

Comparison groups	Imeglimin 1500 mg twice daily v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.092
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.97
upper limit	0.15
Variability estimate	Standard error of the mean
Dispersion value	0.53

Secondary: Change in Postdose FPG from baseline to Week 18 versus placebo	
End point title	Change in Postdose FPG from baseline to Week 18 versus placebo

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 18 (End of Treatment)

End point values	Imeglimin 1500 mg twice daily	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	28		
Units: mmol/L				
arithmetic mean (standard deviation)	-2.26 (± 2.60)	-0.53 (± 1.71)		

Statistical analyses

Statistical analysis title	Imeglimin 1500 mg bid versus Placebo

Statistical analysis description:

Change from baseline to Week 18 was to be assessed with an ANCOVA model with country and treatment effect fitted as factors and baseline Postdose FPG fitted as a covariate. The analysis was performed on the ITT population using LOCF (when applicable).

Comparison groups	Imeglimin 1500 mg twice daily v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.25
upper limit	-0.18
Variability estimate	Standard error of the mean
Dispersion value	0.52

Secondary: Change in Rate sensitivity from baseline to Week 18 versus placebo	
End point title	Change in Rate sensitivity from baseline to Week 18 versus placebo

End point description:

End point type	Secondary
End point timeframe:	
Baseline to Week 18 (End of Treatment)	

End point values	Imeglimin 1500 mg twice daily	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	28		
Units: pmol.m^-2.mM^-1				
arithmetic mean (standard deviation)	223.20 (± 385.75)	39.20 (± 273.54)		

Statistical analyses

Statistical analysis title	Imeglimin 1500 mg bid versus Placebo
Comparison groups	Imeglimin 1500 mg twice daily v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.051
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	183.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.17
upper limit	367.67
Variability estimate	Standard error of the mean
Dispersion value	91.86

Secondary: Change in insulinogenic index from baseline to Week 18 versus placebo

End point title	Change in insulinogenic index from baseline to Week 18 versus placebo
End point description:	

End point type	Secondary
End point timeframe:	
Baseline to Week 18 (End of Treatment)	

End point values	Imeglimin 1500 mg twice daily	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	28		
Units: not applicable				
arithmetic mean (standard deviation)	2.57 (± 2.40)	0.69 (± 2.89)		

Statistical analyses

Statistical analysis title	Imeglimin 1500 mg bid versus Placebo
Comparison groups	Imeglimin 1500 mg twice daily v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	3.34
Variability estimate	Standard error of the mean
Dispersion value	0.77

Secondary: Change in glucose sensitivity from baseline to Week 18 versus placebo

End point title	Change in glucose sensitivity from baseline to Week 18 versus placebo

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 18 (End of Treatment)

End point values	Imeglimin 1500 mg twice daily	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	28		
Units: pmol.min^-1.m^-2.mM^-1				
arithmetic mean (standard deviation)	14.98 (± 18.50)	0.96 (± 13.22)		

Statistical analyses

Statistical analysis title	Imeglimin 1500 mg bid versus Placebo
Comparison groups	Imeglimin 1500 mg twice daily v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	12.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.2
upper limit	20.3
Variability estimate	Standard error of the mean
Dispersion value	4.01

Secondary: Change in Stumvoll index from baseline to Week 18 versus placebo	
End point title	Change in Stumvoll index from baseline to Week 18 versus placebo
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to Week 18 (End of Treatment)	

End point values	Imeglimin 1500 mg twice daily	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	28		
Units: No unit				
arithmetic mean (standard deviation)	0.0188 (± 0.0139)	0.0056 (± 0.0150)		

Statistical analyses

Statistical analysis title	Imeglimin 1500 mg bid versus Placebo
Comparison groups	Imeglimin 1500 mg twice daily v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.0133
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0058
upper limit	0.0208
Variability estimate	Standard error of the mean
Dispersion value	0.0037

Secondary: Change in incremental AUC 0-180 C-Peptide / incremental AUC 0-180 Glucose from baseline to Week 18 versus placebo

End point title	Change in incremental AUC 0-180 C-Peptide / incremental AUC 0-180 Glucose from baseline to Week 18 versus placebo

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 18

End point values	Imeglimin 1500 mg twice daily	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	28		
Units: No unit				
arithmetic mean (standard deviation)	0.119 (± 0.132)	0.028 (± 0.058)		

Statistical analyses

Statistical analysis title	Imeglimin 1500 mg bid versus Placebo
Comparison groups	Imeglimin 1500 mg twice daily v Placebo

Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.091
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.033
upper limit	0.149
Variability estimate	Standard error of the mean
Dispersion value	0.029

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	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

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

Serious adverse events	Imeglimin 1500 mg twice daily	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meigs' syndrome			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Imeglimin 1500 mg twice daily	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 30 (20.00%)	14 / 29 (48.28%)	
Cardiac disorders			
Left ventricular hypertrophy			
subjects affected / exposed	2 / 30 (6.67%)	0 / 29 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Diabetic neuropathy			
subjects affected / exposed	0 / 30 (0.00%)	3 / 29 (10.34%)	
occurrences (all)	0	3	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	5 / 30 (16.67%)	12 / 29 (41.38%)	
occurrences (all)	7	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 December 2013	The purpose of this amendment was: - To change 1 study procedure (OGTT at 6 weeks became optional). - To change 1 inclusion criteria (broaden HbA1c eligible lower range, without affecting subject's safety and efficacy assessment). - To clarify the CGM procedure. - To correct inconsistencies in the protocol. - To include administrative changes.
29 April 2014	The purpose of this amendment was: - To include administrative change concerning the laboratory assigned for bioanalysis. - To extend the study period due to recruitment being slower than expected. - To update the title and contact details of the Sponsor's Medical Responsible Person.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported