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RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFECTS OF IMEGLIMIN ON INSULIN SECRETION DURING A HYPERGLYCEMIC CLAMP IN TYPE 2 DIABETIC SUBJECTS

PROTOCOL NUMBER: PXL008-006

Investigational Products:	Imeglimin
Study Phase:	2
Study Start Date:	18-Apr-2012 (First visit of the first subject)
Study Completion Date:	25-May-2013 (Last visit of the last subject)
EudraCT number:	2011-004086-32
Results version number:	1

1 SPONSOR

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2 OBJECTIVES

2.1 Primary Objective

To assess the insulin secretion during a hyperglycemic clamp after 7 (+3) day administration of imeglimin versus placebo in type 2 diabetic subjects.

2.2 Secondary Objectives

- To assess other metabolic parameters after 7 (+3) day administration of imeglimin versus placebo in type 2 diabetic subjects,

- To assess the safety and tolerability after 7 (+3) day administration of imeglimin versus placebo in type 2 diabetic subjects,

- To assess some pharmacokinetic parameters of imeglimin after 7 (+3) day administration of imeglimin in type 2 diabetic subjects.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan – Description

This was a two-centre, randomized, double-blind, placebo-controlled, parallel group study, in type 2 diabetic subjects, previously treated with metformin monotherapy for at least 12 weeks before screening visit, to evaluate the effect of imeglimin on β cell function.

After approval of amendment n°2, eligible T2DM subjects were either naïve of treatment or treated with an anti-diabetic monotherapy including either metformin or DPPIV inhibitors or alpha glucosidase inhibitors with stable doses for the 12 weeks prior to screening.

For the sake of homogeneity, no other antidiabetic treatments were authorised.

After the V1 selection visit (performed in one of the two centres), eligible subjects were informed by telephone and invited to stop their anti-diabetic treatment for the following 2 weeks (wash-out period). During this period, blood glucose was to be checked using a glucometer at least twice a

week. A blood glucose monitoring device (glucometer) was given to subjects who did not already have one. The disposable material required for the glucose monitoring was provided by the Sponsor for the duration of the study. During the second week of the wash-out period, a fasting plasma glucose measurement was taken at the centre in which the subject attended his selection visit. The results were sent to the investigator for interpretation. At the end of this wash-out period subjects with fasting plasma glucose values below 240 mg/dL (13.3 mM) could be randomized.

The inclusion and exclusion criteria were checked and the subjects were randomized. The subjects were supplied with study treatment for 7 (+3) days, either imeglimin (1500 mg twice per day) or a placebo (3 tablets twice per day) under double blind conditions.

On D7 (+3) after the first dose of treatment, these subjects attended centre 001 for visit 3 after an overnight fasting, in order to have the hyperglycemic clamp procedure. The subjects took the last dose of imeglimin or placebo in the morning of visit 3, 2 hours before the beginning of the clamp procedure.

At the end of the clamp procedure, the subjects left the study with an appropriate anti-diabetic treatment

3.2 Selection of Study Population – Main inclusion criteria

- Subjects with type 2 diabetes, male or female.
- Subject previously treated with metformin for at least 12 weeks prior to screening up to the approval of amendment n°2, and then naïve subjects or subjects previously treated with monotherapy including:
  - Metformin,
  - DPPIV inhibitors,
  - Alpha-glucosidase inhibitors
- At stable dose during the 12 weeks prior to screening.
- Creatinine clearance according to the MDRD formula: ≥ 60 mL/min.
- Age: ≥ 18 and ≤ 75 years.
- Body Mass Index (BMI): ≥ 25 and ≤ 35 kg/m² up to the approval of amendment n°3 and then ≥ 20 and ≤ 40 kg/m².
- HbA1c: ≥ 6.5% and ≤ 7.5% up to the approval of amendment n°3 and then ≥ 6.0% and ≤ 8.0% at selection visit V1.
- Fasting plasma glucose values ≤ 240 mg/dL at the end of the wash-out period.
- Concomitant treatment authorised, stable for at least 2 weeks prior to randomization (start of wash-out).

- Acceptable method of contraception for women of child-bearing potential.
- Signature of written consent by the subject before the start of any study-related activities.

3.3 Treatments

Test product, dose, mode of administration:
Name of the compound: Imeglimin
Pharmaceutical form: 500 mg tablet
Dose per administration: 1500 mg
Mode of administration: 3 tablets of 500 mg orally twice a day during 7 days (+3)

Reference product, dose, mode of administration:
Name of the compound: Placebo
Pharmaceutical form: tablet
Dose per administration: NA
Mode of administration: 3 tablets orally twice a day during 7 days (+3)

4 STUDY SUBJECTS

4.1 Disposition of Subjects

33 subjects were randomized (18 subjects in Imeglimin group and 15 subjects in placebo group). 30 subjects completed the study (15 subjects in Imeglimin group and 15 subjects in placebo group).

4.2 Baseline Characteristics

Table 1 Demographic data

Demography	Statistics	1500 mg Imeglimin (N=15)	Placebo (N=15)
Age (years)	Mean±SD	60.7±8.1	60.5±8.6
Gender			
Male	N(%)	11(73.3)	12(80.0)
Female	N(%)	4(26.7)	3(20.0)
BMI (kg/cm²)	Mean±SD	28.97±3.46	30.29±4.42
Ethnic origin			
Caucasian	N(%)	14(93.3)	15(100.0)
Black	N(%)	1(6.7)	0(0.0)

BMI: body mass index, SD: standard deviation

5 EFFICACY EVALUATION

5.1 Primary endpoint

Table 2 AUC and iAUC$_{(0\text{-}45\ min)}$ of insulin secretion: Descriptive statistics by treatment group and comparative statistics – Intent to treat set (N = 30)

	1500 mg Imeglimin (N=15)	Placebo (N=15)	p value*
AUC (0-45 min) of insulin secretion (min x pmol/L)			
N	15	15	0.048
Mean±SD	14956.8±9978.6	8227.5±3878.8	
SEM	2576.5	1001.5	
Min/Median/Max	2804/12708.5/39483	4015/7891.8/18569	
iAUC (0-45 min) of insulin secretion (min x pmol/L)			
N	15	15	0.066
Mean±SD	9609.9±8604.9	4522.8±2576.8	
SEM	2221.8	665.3	
Min/Median/Max	1112/6702.3/34069	1454/3817.5/10991	

* Log data two-sample t test

5.2 Secondary endpoints

5.2.1 Fasting metabolic parameters

There was no significant difference between the 2 groups (placebo vs. imeglimin) in mean fasting concentrations change (V3-V2) for glucose, insulin, C-peptide and glucagon.

5.2.2 AUC$_{(0\text{-}10\ min)}$, first phase of insulin and C-peptide secretion in response to hyperglycemia

Table 3 AUC$_{(0\text{-}10\ min)}$ of insulin and C-peptide secretion: Descriptive statistics by treatment group and comparative statistics – Intent to treat set (N = 30)

	Statistics	1500 mg Imeglimin (N=15)	Placebo (N=15)	p value*
AUC$_{(0\text{-}10\ min)}$ of insulin secretion (min x pmol/L)	N	15	15	0.022
	Mean±SD	2359.0±2345.5	977.8±512.6	
	SEM	605.6	132.3	
	Min/Median/Max	447/1892.0/9110	273/783.7/2346	
AUC$_{(0\text{-}10\ min)}$ of C-peptide secretion (min x nmol/L)	N	15	15	0.049
	Mean±SD	14.6±7.7	10.1±3.1	
	SEM	2.0	0.8	
	Min/Median/Max	6/13.6/36	5/9.7/18	

* Log data two-sample t test

5.2.3 $AUC_{(10\text{-}45\ min)}$, second phase of insulin and C-peptide in response to hyperglycemia

Table 4 $AUC_{(10\text{-}45\ min)}$ of insulin and C-peptide secretion: Descriptive statistics by treatment group and comparative statistics – Intent to treat set (N = 30)

	Statistics	1500 mg Imeglimin (N=15)	Placebo (N=15)	p value
$AUC_{(10\text{-}45\ min)}$ of insulin secretion (min x pmol/L)	N	15	15	0.057*
	Mean±SD	12597.8±7925.6	7249.7±3399.3	
	SEM	2046.4	877.7	
	Min/Median/Max	2357/10322.3/30373	3743/6837.0/16224	
$AUC_{(10\text{-}45\ min)}$ of C-peptide secretion (min x nmol/L)	N	15	15	0.040**
	Mean±SD	69.5±24.7	53.6±14.7	
	SEM	6.4	3.8	
	Min/Median/Max	30/66.8/109	30/52.1/88	

* Log data two-sample t test
**Raw data two-sample t test

5.2.4 $AUC_{(45\text{-}55\ min)}$, maximal secretory capacities of insulin and C-peptide in response to Arginine infusion

Table 5 $AUC_{(45\text{-}55\ min)}$ of insulin and C-peptide secretion: Descriptive statistics by treatment group and comparative statistics – Intent to treat set (N = 30)

	Statistics	1500 mg Imeglimin (N=15)	Placebo (N=15)	p value
$AUC_{(45\text{-}55\ min)}$ of insulin secretion (min x pmol/L)	N	15	15	0.070
	Mean±SD	14301.3±8243.4	8809.1±3488.1	
	SEM	2128.4	900.6	
	Min/Median/Max	2463/12048.7/33614	4005/7969.3/17430	
$AUC_{(45\text{-}55\ min)}$ of C-peptide secretion (min x nmol/L)	N	15	15	0.026
	Mean±SD	42.8±14.7	32.5±8.1	
	SEM	3.8	2.1	
	Min/Median/Max	16/42.0/65	19/31.5/48	

* Log data two-sample t test
**Raw data two-sample t test

5.2.5 iAUC$_{(0\text{-}45\ min)}$, Glucacon secretion throughout the first 45 minutes of the hyperglycemic clamp

Table 6 iAUC$_{(0\text{-}45\ min)}$ of glucacon secretion: Descriptive statistics by treatment group and comparative statistics – Intent to treat set (N=30)

	Statistics	1500 mg Imeglimin (N=15)	Placebo (N=15)	p value*
iAUC$_{(0\text{-}45\ min)}$ of glucagon secretion (min x ng/L)	N	15	15	0.391
	Mean±SD	-1358.3±1758.4	-1407.0±1117.2	
	SEM	454.0	288.4	
	Min/Median/Max	-5010/-499.5/53	-3523/-1101.0/-158	

* Two-sample Wilcoxon test

5.2.6 Insulin hepatic extraction

Table 7 Hepatic extraction - AUC$_{(0\text{-}45\ min)}$ of insulin secretion / AUC$_{(0\text{-}45\ min)}$ of C-peptide ratio: Descriptive statistics by treatment group and comparative statistics – Intent to treat set (N=30)

	Statistics	1500 mg Imeglimin (N=15)	Placebo (N=15)	p value*
Hepatic extraction	N	15	15	0.059
	Mean±SD	0.162±0.065	0.125±0.024	
	SEM	0.017	0.006	
	Min/Median/Max	0.08/0.156/0.35	0.08/0.129/0.18	

* Log data two-sample t test

6 Safety Evaluation

During the overall study period, 9/33 (27.3%) subjects reported the occurrence of 16 adverse events. Fifteen (15) of these were treatment emergent adverse events (TEAEs) and 1 was non treatment emergent (tonsillitis). Among the TEAEs, 14 TEAE in 7 subjects were experienced after imeglimin intake and 1 TEAE in 1 subject after placebo intake. All were of mild to moderate intensity.

Table 8 Number of subjects with at least one emergent adverse event by system organ class (SOC) and preferred term by treatment group - Safety Set (N=33)

		1500 mg Imeglimin			Placebo			All		
System Organ Class	Preferred Term	NAE (1)	n (2)	% (3)	NAE (1)	n (2)	% (3)	NAE (1)	n (2)	% (3)
All SOCs	All PTs	14	7	38.9	1	1	6.7	15	8	24.2
Cardiac disorders	All PTs	1	1	5.6	.	.	.	1	1	3.0
	Atrial fibrillation	1	1	5.6	.	.	.	1	1	3.0
Gastrointestinal disorders	All PTs	4	4	22.2	.	.	.	4	4	12.1
	Diarrhoea	2	2	11.1	.	.	.	2	2	6.1
	Epigastric discomfort	1	1	5.6	.	.	.	1	1	3.0
	Vomiting	1	1	5.6	.	.	.	1	1	3.0
Infections and infestations	All PTs	2	2	11.1	.	.	.	2	2	6.1
	Gastroenteritis	**2**	2	11.1	.	.	.	2	2	6.1
Nervous system disorders	All PTs	7	2	11.1	.	.	.	7	2	6.1
	Dizziness	6	1	5.6	.	.	.	6	1	3.0
	Syncope	1	1	5.6	.	.	.	1	1	3.0
Vascular disorders	All PTs	.	.	.	1	1	6.7	1	1	3.0
	Thrombophlebitis superficial	.	.	.	1	1	6.7	1	1	3.0

(1) Number of adverse events
(2) Number of subjects with at least one adverse event
(3) (n / N)*100 (N: number of subjects by treatment) = % of subject with at least one AE

The relationship to study drug was considered as probably related for 5 TEAEs in 4 subjects: 2 episodes of diarrhoea, 1 episode of gastroenteritis, 1 episode of vomiting and 1 episode of epigastric discomfort. All were reported after imeglimin intake.

One serious adverse event (hospitalisation for gastroenteritis) was reported in the imeglimin group and was considered to be unrelated to study drug intake.

No clinically relevant findings were observed in clinical examination, laboratory parameters or vital signs.