Imeglimin, a novel glimin oral anti-diabetic, exhibits good glycemic control in Type 2 diabetic patients

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Background

There are three main defects associated with Type 2 diabetes (T2D): excessive hepatic glucose production, impaired peripheral glucose uptake by skeletal muscle, and insufficient insulin secretion/β-cell death.[1,2] Currently there are numerous anti-diabetic drugs available, however these target one or two, but not all three, key defects of T2D. These drugs also have limitations in terms of side effects, particularly weight gain and hypoglycemia, or contraindications that limit their use.[3] Moreover, there is evidence that only about 56% of patients achieve and maintain an HbA_{1c} of <7.0%. Therefore, there is an unmet medical need for new agents that provide sustained efficacy with very good tolerability and safety. Imeglimin is the first in a new glimin class of oral anti-diabetic agents that targets insulin resistant organs, addresses β-cell failure (Figure 1) and is expected to meet unmet medical needs.

Aim

To investigate the effects of imeglimin on glycemic control compared with metformin in T2D patients.

Materials and Methods

Two phase II studies were conducted to investigate the effects of imeglimin on glycemic control.

Oral Glucose Tolerance Test (OGTT) Study

Design: Randomized, double-blind, double-dummy, three-arm parallel group, oral multiple doses. Subjects were T2D patients:

- Treatment naïve or previous monotherapy with an oral anti-diabetic
- Aged 18–65 years
- Body mass index (BMI) 22 to 40 kg/m^2
- Fasting plasma glucose (FPG) 7.02–13.3 mmol/L (126–240 mg/dL)
- HbA_{1c} 6.5–8.5%.

Patients were randomized to treatment following a 3-week wash out/run-in period. An oral glucose tolerance test (OGTT) was performed: subjects ingested 75 g glucose and blood samples were collected before and 30, 60, 90, 120, and 180 min after glucose ingestion. The OGTT was performed during the wash out/run-in period (after 18 days wash out), and after 25 days of treatment. Treatments: imeglimin 2000 mg once daily (od) in the evening (n=20) or 1000 mg twice daily (bid) (n=19); metformin 850 mg bid (n=19).

The area under the plasma glucose concentration-time curve (AUC_{PG}) was calculated and differences in least square (LS) means with 95% confidence intervals (95% CIs) was assessed between treatments. Analysis used standard statistical tests, such as Student's t-test (paired and unpaired) and the Mann-Whitney U-test.

Phase IIa Study

Design: Randomized, double-blind, double-dummy, controlled multi-center study.
Subjects were T2D patients:

- Treatment naïve or previous monotherapy with an oral anti-diabetic
- Aged 18–70 years
- BMI ≥20 to <40 kg/m^2
- FPG ≥7.8 mmol/L but ≤13.3 mmol/L (≥140 mg/dL but ≤239 mg/dL)
- HbA_{1c} ≤10%

Subjects were randomized to treatment after a three-week single-blind wash out/run-in period. Double-blind treatments: imeglimin 500 mg bid (n=31) or 1500 mg bid (n=31); metformin 850 mg bid (n=33); placebo (n=33); treatment lasted for 8 weeks. Glycemic assessments: AUC up to 6 hours ($AUC_{0\text{-}6h}$) for glucose during a prolonged meal, FPG, and HbA_{1c}.

Results are presented as LS means and standard error of the mean (SEM). Analysis of the primary endpoint ($AUC_{0\text{-}6h}$) was performed using a two-sample unpaired Student's t-test. Statistical analysis was not performed on the secondary endpoints of change in FPG and change in HbA_{1c}.

Results

OGTT Study

Baseline-adjusted changes in the OGTT AUC were -33% for imeglimin bid (p<0.0001), -30% for metformin (p<0.0004), and -10% for imeglimin od (p=0.0305). Between-treatment comparisons for the OGTT AUC_{PG} are summarized in Table 1. The difference was clearly less for imeglimin od compared with metformin (p=0.0041), but was comparable between imeglimin bid and metformin (p=0.8321).

Phase IIa Study

LS mean changes in $AUC_{0\text{-}6h}$ are summarized in Table 2. Differences were statistically significantly different from placebo in the imeglimin 1500 mg bid (p=0.003) and metformin 850 mg bid (p<0.0001) groups, but not in the imeglimin 500 mg bid group (p=0.086). There was no statistically significant difference between imeglimin 1500 mg bid group and metformin group. Decreases in FPG and HbA_{1c} from baseline to the end of treatment were observed in the imeglimin 1500 mg bid and metformin 850 mg bid groups, but only a small decrease in the imeglimin 500 mg bid group was observed (Figure 2; Figure 3). A greater response in all glycemic parameters was observed for treatment-naïve subjects and in those with more severe hyperglycemia (≥8%), although the numbers were small (≤12 in all treatment groups).

Treatment-Emergent Adverse Events (OGTT and Phase IIa Study)

Treatment-emergent adverse events (TEAEs) are summarized for the OGTT and phase IIa studies in Table 3. The percentage of subjects with treatment-related TEAEs was much higher in the OGTT than in the phase IIa study. This is probably due to the differences in study conduct. The OGTT study was conducted at a single center and subjects were assessed every week and questioned about AEs. In contrast, the phase IIa study was conducted across multiple centers and subjects were assessed less frequently.

In the OGTT study, TEAEs related to treatment were experienced by 6 (30%) subjects given imeglimin od, 7 (35%) subjects given imeglimin bid and 13 (68%) subjects given metformin. Most adverse events were of mild intensity.

In the phase IIa study, no TEAEs related to the treatment were reported in the imeglimin 1500 mg bid group. In contrast 3 (10%) subjects who received the 500 mg bid dose had treatment-related TEAEs reported, as did 3 (9%) of placebo subjects and 7 (21%) subjects who received metformin. No treatment-related serious adverse events occurred.

No serious or severe adverse events associated with imeglimin were reported. No clinically significant changes occurred in laboratory parameters, vitals signs, or ECG.

Conclusions

- Imeglimin was as effective as metformin at reducing the AUC_{PG} and $AUC_{0\text{-}6h}$, FPG, and HbA_{1c}.
- There were no safety concerns with imeglimin.
- Imeglimin appears suitable for use as monotherapy at diagnosis of T2D.
- The use of imeglimin may be effective at any stage in the T2D continuum, from diagnosis through to disease complications.
- Due to its unique mode of action, imeglimin may be well suited for combination therapy with most other classes of anti-diabetic agents.
- The safety and tolerability profile of imeglimin makes it suitable for use in sensitive populations such as the elderly and patients with renal impairment.

References

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Table 1: Between Treatment Comparisons of OGTT AUC_{PG} (OGTT Study)

Comparison	Difference in LS Means	95% CI	p-value
Change in AUC_{PG} (unadjusted)			
Imeglimin od vs metformin bid	-0.1658	-0.2518, -0.0798	**0.0003**
Imeglimin bid vs metformin bid	-0.0595	-0.1466, 0.0276	0.1765
Change in AUC_{PG} (adjusted for baseline)			
Imeglimin od vs metformin bid	-0.2843	-0.4746, -0.0940	**0.0041**
Imeglimin bid vs metformin bid	0.0205	-0.1722, 0.2132	0.8321

Table 2: LS Mean Change (SEM) in $AUC_{0\text{-}6h}$ During a Prolonged Meal (Phase IIa Study)

Parameter	Imeglimin 500 mg bid (n=31)	Imeglimin 1500 mg bid (n=31)	Metformin 850 mg bid (n=33)	Placebo (n=33)
Overall	103.4 (158.5)	-365.7 (179.5)	-629.4 (144.7)	463.1 (165.1)
p-value	0.086	**0.003**	**<0.0001**	--
Previous Treatment Experience				
n	4	7	9	12
Naïve	-58.1 (153.8)	-515.9 (349.5)	-627.3 (191.1)	855.7 (159.1)
n	24	23	23	19
Experienced	130.3 (193.27)	-320.1 (216.11)	-612.7 (192.66)	215.2 (245.56)
Baseline HbA_{1c}				
n	4	5	3	7
≥8%	-32.8 (707.69)	-865.6 (408.27)	-1051.8 (113.23)	813.3 (291.91)
n	23	25	38	23
<8%	147.9 (170.25)	-265.8 (200.55)	-566.7 (164.55)	396.5 (206.58)

Table 3: Number (%) of Patients with Treatment-Emergent Adverse Events in the OGTT and Phase IIa Studies

	OGTT Study			Phase IIa Study			
Type of TEAE	Imeglimin 1000 mg od (n=20)	Imeglimin 1000 mg bid (n=20)	Metformin 850 mg bid (n=33)	Imeglimin 500 mg bid (n=31)	Imeglimin 1500 mg bid (n=31)	Metformin 850 mg bid (n=33)	Placebo (n=33)
Overall							
Any TEAE	8 (40)	17 (85)	13 (68)	5 (16)	6 (19)	13 (39)	11 (33)
Any related TEAE	6 (30)	7 (35)	13 (68)	3 (10)	0	7 (21)	3 (9)
Seriousness							
Serious TEAEs	0	1 (5)	0	0	0	0	1 (3)
Related serious TEAEs	0	0	0	0	0	0	0
Discontinuations							
Any TEAEs	0	1 (5)	0	0	0	1 (3)	1 (3)
Any related TEAEs	0	0	0	0	0	1 (3)	0
Deaths							
Any TEAEs	0	0	0	0	0	0	0
Any related TEAEs	0	0	0	0	0	0	0

Figure 1: Imeglimin Targets the Three Key Organs Involved in T2D Pathophysiology

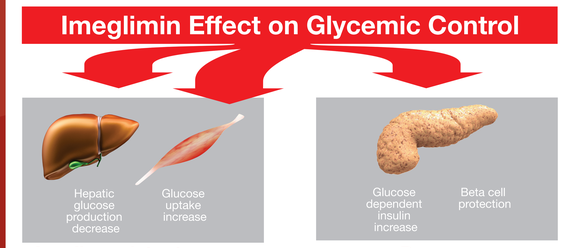


Figure 2: Change in FPG (mmol/L) from Baseline to End of Treatment (Phase IIa Study)

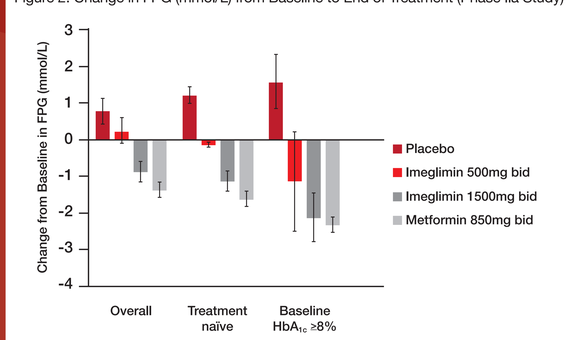
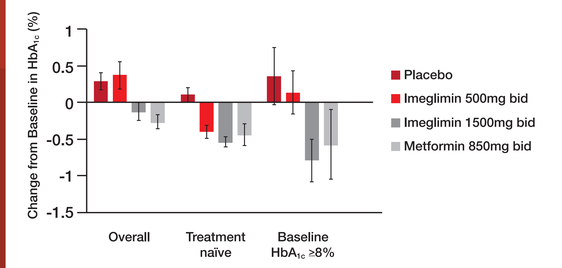


Figure 3: Change in HbA_{1c} (%) from Baseline to End of Treatment (Phase IIa Study)



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