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The Efficacy and Safety of Imeglimin as Add-on Therapy in Patients With Type 2 Diabetes Inadequately Controlled With Metformin Monotherapy

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Background

- Imeglimin is the first in a new Tetrahydrotriazine-containing class of oral anti-diabetic agents, the glimins, which in preclinical studies has been shown to target the insulin resistant organs, liver and skeletal muscle, and the pancreas[1].
- In Phase I/II studies, imeglimin was shown to have comparable efficacy to metformin in regulating glycemia[2].
- Metformin alone is frequently insufficient to maintain glycemic goals, therefore many patients require multiple pharmacotherapies for optimal disease management[3].

Objectives

- This Phase II study examined the efficacy, safety and tolerability of imeglimin in combination with metformin in patients with T2D inadequately controlled with metformin alone.

Research Design and Methods

- This 12-week, multi-center, randomized, double-blind, placebo controlled, parallel-group study included subjects with T2D inadequately controlled with a daily dose of 1500-2000 mg metformin.
- Following a 2-week single-blind run-in period under previous metformin treatment and placebo, subjects were randomized 1:1 to receive 1500mg BID imeglimin or placebo, in addition to their lead-in dose of metformin for 12 weeks.
- After the add-on treatment period, subjects were followed up for 1 week and received a single-blind placebo alongside their previous metformin treatment.
- The primary efficacy endpoint of the study was change in A1C from baseline to week 12.
- Secondary end points included changes from baseline in FPG, and pro-insulin/insulin ratio.
- The percentage of responders achieving an A1C < 7% and a decrease from baseline ≥ 0.5% at week 12 was calculated.
- Pre-specified subgroup analysis was performed to determine the effect of baseline A1C on the change in A1C from baseline to week 12.
- The safety and tolerability of 12-week treatment with imeglimin versus placebo was assessed, and adverse events were categorized by relation to treatment and severity.

Results

Patients

- A total of 156 subjects were randomized to receive study treatment. The ITT population contained 155 subjects; 77 subjects received imeglimin and 78 subjects received placebo.
- Average metformin doses remained the same throughout the study; 1,901 mg in the metformin-imeglimin group and 1,914 mg in the metformin-placebo group.
- Baseline demographic characteristics were similar between the two treatment arms (Table 1).

Efficacy

- Metformin-imeglimin treatment was associated with a significant reduction in A1C from baseline at week 12 compared with metformin-placebo (-0.65% and -0.21% respectively) (P=0.001) (Figure 1).
- A statistically significant greater proportion of responders achieved a decrease in A1C ≥ 0.5% with metformin-imeglimin (63.6%) compared with metformin-placebo (36.4%) (P=0.001).
- 14.3% of subjects receiving metformin-imeglimin achieved an A1C < 7% compared with 3.8% of subjects receiving metformin-placebo (P=0.04)
- Metformin-imeglimin reduced mean A1C from baseline to week 12 by 0.41%, 0.68% and 0.78% for pre-specified baseline A1C subgroup measurements <8.0%, 8.0% to 9.0% and > 9.0%, respectively. Greater reductions in mean A1C were observed in each A1C subgroup with metformin-imeglimin compared with metformin-placebo (Figure 2).
- Metformin-imeglimin decreased mean FPG levels from baseline to week 12 by -0.91 mmol/L, compared with a 0.36 mmol/L increase in the metformin-placebo treatment arm (P<0.001).
- At the end of treatment, metformin-imeglimin had decreased the mean pro-insulin/insulin ratio from baseline by -4.79, compared with an increase of 13.42 observed with metformin-placebo (P=0.007) (Figure 3).

Safety

- Imeglimin as an add-on treatment to metformin was generally well tolerated with a comparable safety profile to the metformin-placebo group.
- 18 subjects (23.1%) in the metformin-imeglimin group and 15 subjects (19.2%) in the metformin-placebo group experienced treatment-emergent adverse events (TEAE), most of which were mild in intensity (Table 2).
- The most frequent treatment-related TEAEs in the metformin-imeglimin group were gastrointestinal (GI) disorders; however these were transient and did not require any dose adjustment.
- Two subjects in the metformin-imeglimin group had TEAEs that led to withdrawal from the study: hyperglycemia (not investigational medicinal product (IMP)-related) and severe watery stool (IMP-related).
- No serious adverse events were reported in the metformin-imeglimin treatment group, compared with three subjects in the metformin-placebo group (discal hernia, myocardial infarction and unstable angina).

Discussion

- Metformin-imeglimin progressively reduced mean A1C from baseline over the treatment period with no evidence of plateau, suggesting further improvements might be expected beyond 12 weeks.
- Subgroup analysis based on stratifications of A1C baseline measurements concluded reductions in A1C were greater within increasing baseline levels, as seen with other glucose lowering medications[4].
- Imeglimin add-on treatment to metformin reduced the pro-insulin/insulin ratio, suggesting that imeglimin may have a beneficial effect on β cell function. Further studies will be needed to determine if such an effect may translate to β cell protection over-time, as suggested in in vitro studies where imeglimin reduced β cell apoptosis induced by various stresses such as cytokine and high glucose conditions[1].
- The GI adverse events observed in the metformin-imeglimin group are typically experienced with metformin monotherapy more than any other oral anti-diabetic medication[5], but GI side effects have not been observed with imeglimin monotherapy.

Conclusions

- Twice-daily imeglimin combined with metformin for 12 weeks resulted in improved A1C and FPG.
- Imeglimin may protect β cell function as indicated by a reduced pro-insulin/insulin ratio.
- Addition of imeglimin to metformin was generally well tolerated with no serious adverse events or cardiovascular events reported.
- This Phase II study demonstrates that first in class imeglimin may be a safe and effective therapy combined with metformin as a new treatment for T2D.

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Table 1: Demographics and Baseline Characteristics (Safety Population)

Characteristic	Statistic/Category	Metformin + Imeglimin N=78	Metformin + Placebo N=78
Age (years)	N Mean (SD) Min - Max	78 56.2 (7.7) 33 - 70	78 55.1 (7.2) 34 - 69
Gender	Male Female	49 (62.8%) 29 (37.2%)	48 (61.5%) 30 (38.5%)
Ethnicity	Caucasian	78 (100.0%)	78 (100.0%)
Weight (kg)	Mean (SD) Min - Max	95.69 (17.00) 56.0 - 131.0	92.97 (14.65) 63.0 - 133.5
Waist Circumference (cm)	Mean (SD) Min - Max	108.17 (12.15) 76.0 - 140.0	107.97 (12.24) 75.0 - 152.0
BMI (kg/m2)	Mean (SD) Min - Max	32.63 (4.64) 22.9 - 39.8	33.11 (4.52) 23.7 - 40.2
HbA1C (%)	Mean (SD) Min-Max	8.5 (0.72) 7.1-10.2	8.6 (0.73) 7.3-10.2
FPG (mmol/L)	Mean (SD) Min-Max	10.39 (2.48) 6.4-18.9	10.39 (2.48) 6.4-18.9
Metformin Dose (mg)	Mean	1,901	1,914
Duration of Diabetes (years)	Mean (SD) Min-Max	4.63 (3.28) 0.2-17.1	4.45 (3.03) 0.2-13.9

Table 2: Summary of Adverse Events (Safety Population)

	Metformin + Imeglimin 1500mg BID N=78		Metformin + Placebo N=78	
	E	N (%)	E	N (%)
Any TEAEs	43	18 (23.1)	28	15 (19.2)
Related TEAEs	18	8 (10.3)	1	1 (1.3)
Cardiovascular	0	0 (0.0)	1	1 (1.3)
Gastrointestinal	12	7 (9.0)	0	0 (0.0)
Metabolism	4	1 (1.3)	0	0 (0.0)
CNS	4	1 (1.3)	0	0 (0.0)
Skin and subcutaneous	4	1 (1.3)	0	0 (0.0)
SAEs	0	0 (0.0)	3	3 (3.8)
Cardiac disorders	0	0 (0.0)	2	2 (2.6)
Musculo-skeletal	0	0 (0.0)	1	1 (1.3)
Any EAC adjudicated cardiovascular events	0	0 (0.0)	4	2 (2.6)
TEAE leading to withdrawal	2	2 (2.6)	1	1 (1.3)

E = number of events; EAC = Event Adjudication Committee; N = number of subjects exposed; n = number of subjects with AEs; SAE = serious adverse event; TEAE = treatment-emergent AE

Figure 1: Effect of Metformin-Imeglimin Versus Metformin-Placebo: A1C Reductions from Baseline Over the 12 Week Treatment Period

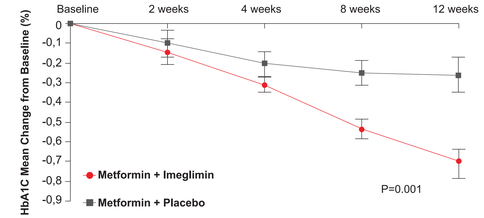


Figure 2: Change from Baseline to Week 12 for Subjects with Baseline A1C (%) Measurements < 8.0%, 8.0% to 9.0% and > 9.0%

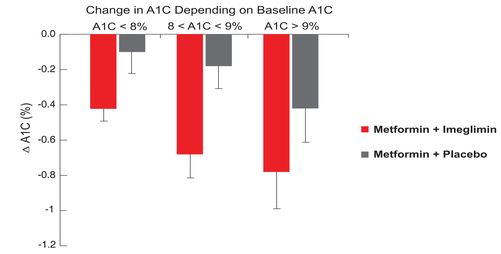
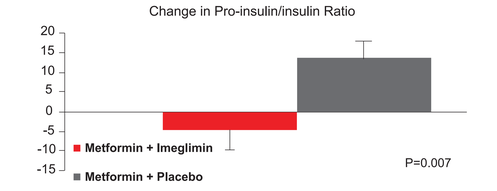


Figure 3: Change in Pro-insulin/insulin Ratio from Baseline to Week 12



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