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Imeglimin monotherapy in Japanese patients with type 2 diabetes: results from a randomised, 24-week, double-blind, placebo-controlled, phase IIb trial

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BACKGROUND

- Imeglimin is the first in a novel class of glucose-lowering drugs, the glimins.
- Imeglimin is acting on the two key defects in type 2 diabetes mellitus (T2DM) improving both insulin secretion in response to glucose and insulin sensitivity, through a unique mechanism of action targeting mitochondria.

AIMS

- This study was designed to determine the efficacy and safety/tolerability of imeglimin monotherapy at 3 doses compared to placebo in Japanese patients with T2DM after 24 weeks of treatment.

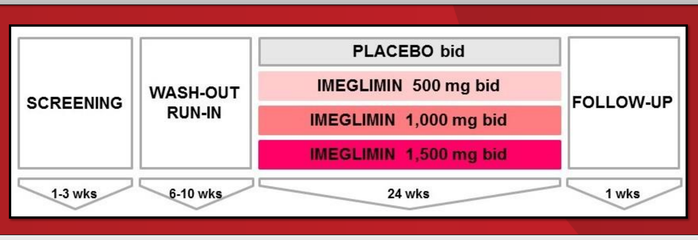
MATERIALS AND METHODS

- This was a randomised, multicenter, double-blind, placebo-controlled dose ranging trial.
- Randomisation in 4 groups through a web-based system and stratified according to:
  - ✓ Baseline glycosylated hemoglobin (HbA1c)
  - ✓ Previous antidiabetic treatment status (naïve patients / patients previously treated by a single oral hypoglycemic agent)

Inclusion criteria

- Japanese adult patients with T2DM naïve or previously treated with monotherapy
- Age ≥ 20 to ≤ 75 years
- BMI ≥ 18.5 kg/m²
- eGFR (MDRD) ≥ 50 mL/min at Screening and ≥ 45 mL/min at pre-randomisation visit

Study design



Endpoints

- Primary efficacy endpoint: Placebo-adjusted dose-dependent reduction in HbA1c from baseline after 24 weeks of treatment, evaluated in all randomised treated patients with at least one post-baseline assessment
- Secondary endpoints included:
  - ✓ Changes in fasting plasma glucose (FPG)
  - ✓ Percentage of responders (HbA1c < 7 %)
  - ✓ HOMA-B
  - ✓ Safety and tolerability

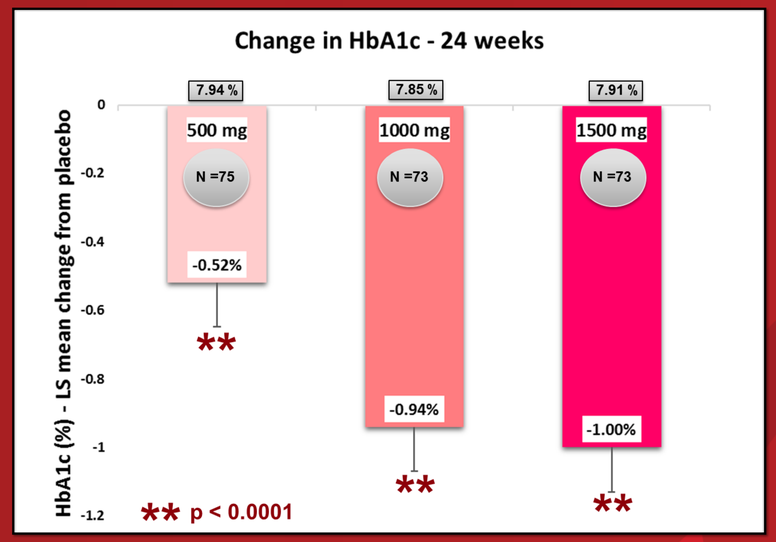
RESULTS

- 299 patients were randomised. 296 were analyzed in the full analysis set.
- Table 1. Baseline Characteristics

	Placebo N = 75	Imeglimin 500mg N = 75	Imeglimin 1000mg N = 73	Imeglimin 1500mg N = 73
Gender				
- Men, n (%)	49 (65%)	49 (65%)	48 (66%)	52 (71%)
- Women, n (%)	26 (35%)	26 (35%)	25 (34%)	21 (29%)
Age (years), mean (SD)	60.2 (9.5)	58.7 (8.5)	59.9 (10.0)	57.6 (10.8)
Body Weight (kg), mean (SD)	70.4 (14.8)	68.5 (15.2)	67.6 (12.5)	73.3 (15.6)
BMI (kg/m²), mean (SD)	25.8 (4.5)	25.2 (4.6)	25.1 (3.9)	26.8 (4.4)
Waist Circumference (cm)	90.9 (11.2)	89.3 (11.2)	89.1 (9.9)	92.6 (11.1)
Diabetes Duration (y)	6.26 (6.3)	7.3 (6.3)	6.25 (5.5)	5.28 (5.8)
HbA1c (%), mean (SD)	7.89 (0.7)	7.94 (0.7)	7.85 (0.6)	7.91 (0.6)
FPG (mg/dL), mean (SD)	160.4 (30.4)	164.5 (31.7)	163.4 (31)	164.8 (31.5)
eGFR (ml/min), mean (SD)	73.4 (13.1)	73.8 (12.6)	75.1 (12)	75.2 (15.2)

Efficacy

- Primary endpoint was met:
  - ✓ Statistically significant dose-dependent placebo-subtracted decrease in HbA1c at the 3 doses with maximal effect at the 2 top doses.



- The secondary endpoints showed:
  - ✓ Significant placebo-subtracted reductions in FPG at the 3 doses (–24.6 mg/dL at 1,000 mg and 1,500 mg bid).
  - ✓ A significantly greater proportion of responders patients with HbA1c <7% at week 24 (33% at 1,000 mg bid and 1,500 mg bid versus 8% for placebo group).
  - ✓ A significantly increase in HOMA-B at all doses versus placebo

Safety

- Overall good safety and tolerability of imeglimin at all doses versus placebo
- No SUSAR and no related SAE
- Similar incidence of TEAEs considered related to the study drug for the 2 lower doses versus placebo
- Slight increase of TEAEs considered related to the study drug for the dose of 1,500 mg bid versus placebo partly due to an increase in the incidence of gastrointestinal AEs.

- Significant decrease in main hepatic enzymes (ALT & GGT) at 1,000 mg bid and 1,500 mg bid versus placebo
- Weight neutral
- No documented hypoglycemia

- Table 2. Overview of safety

	Placebo N = 75	Imeglimin 500 mg N = 75	Imeglimin 1000 mg N = 74	Imeglimin 1500 mg N = 75
Any Adverse Event (AE)	57 (76.0%)	57 (76.0%)	54 (73.0%)	58 (77.3%)
Any Non-TEAE	20 (26.7%)	31 (41.3%)	17 (23.0%)	26 (34.7%)
Any TEAE	51 (68.0%)	51 (68.0%)	46 (62.2%)	55 (73.3%)
Severity of TEAE				
Mild	49 (65.3%)	51 (68.0%)	44 (59.5%)	52 (69.3%)
Moderate	6 (8.0%)	3 (4.0%)	4 (5.4%)	9 (12.0%)
Severe	0	0	4 (5.4%)	1 (1.3%)
Relationship of TEAE to study drug				
Related to Study Drug	6 (8.0%)	4 (5.3%)	4 (5.4%)	18 (24.0%)
Not Related to Study Drug	48 (64.0%)	49 (65.3%)	43 (58.1%)	47 (62.7%)
TEAE leading to interruption /withdrawal of study drug	10 (13.3%)	2 (2.7%)	5 (6.8%)	5 (6.7%)
Any Serious Adverse Event (SAE)				
Any Non-Treatment-Emergent SAE	0	0	1 (1.4%)	0
Any Treatment Emergent SAE	1 (1.3%)	0	4 (5.4%)	1 (1.3%)
TE SAE leading to death	0	0	0	1 (1.3%)

CONCLUSION

This study confirms imeglimin strong efficacy, very good safety and tolerability profile in Japanese T2DM patients. The dose of 1,000 mg bid showed a maximal efficacy with a similar safety and tolerability profile compared to placebo. This study suggests that the dose of 1,000 mg bid of imeglimin is the optimal dose for phase III program in Japan.

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