Safety, Tolerability, PK, and PD of Elecoglipron, an Oral Small-Molecule GLP-1 Receptor Agonist, in Chinese Adults Living with Obesity or Overweight with or without Type 2 Diabetes

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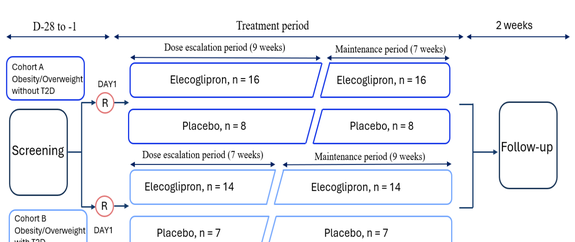
INTRODUCTION

- Elecoglipron (AZD5004/ECC5004) is an oral small-molecule GLP-1 receptor agonist (RA), administered once daily without food or fluid restriction, in development for glycemic control in T2D, and obesity or overweight with co-morbidities. [1]
- In previous Phase 1 studies, elecoglipron was shown to have a safety and tolerability profile comparable to the GLP-1 RA class, target engagement of the GLP-1 receptor, and a pharmacokinetic (PK) profile compatible with once-daily dosing, which was not significantly different between fed and fasted states. [2,3]
- This Phase 1b study aimed to evaluate the safety, tolerability, PK, and pharmacodynamics (PD) in Chinese adults living with obesity or overweight, with or without T2D, over a 16-week treatment period.

METHODS

- This is a Phase 1b, randomized, double-blind, placebo-controlled, parallel-group study (Figure 1).
- Cohort A enrolled participants with overweight/obesity (27 kg/m^2 ≤ BMI ≤ 35 kg/m^2), Cohort B enrolled participants with both overweight/obesity (BMI of ≥ 24 kg/m^2) and T2D (7.0% ≤ HbA1c ≤ 10.5% with allowable metformin as background therapy).
- Participation in the study lasted for up to 22 weeks for Cohort A and Cohort B in total, and all participants would receive elecoglipron or placebo with a dose-escalated to 75 mg once daily.
- The analysis for pharmacodynamics (exploratory endpoint) in both cohorts is performed using mixed models for repeated measures (MMRM). The LS mean difference is calculated between the elecoglipron group and the placebo group in the respective cohort, and the corresponding 95% CI is also provided.

Figure 1 Phase 1b Study design



RESULTS

Participant disposition and demographics

- In Cohort A, 33 participants were screened, 24 randomized, and all participants completed the study.
- In Cohort B, 42 participants were screened, 21 randomized, and 20 (95.2%) completed the study. One participant in the Placebo group discontinued treatment and withdrew from the study due to participant decision.
- Baseline characteristics were comparable between treatment groups for each cohort (Table 1).

Table 1 Baseline characteristics for Cohort A and Cohort B

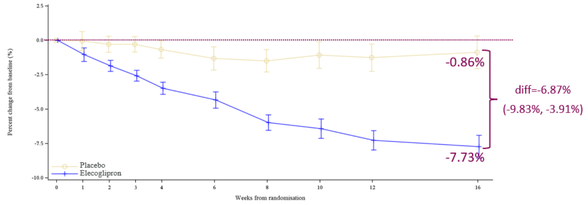
	Cohort A: Overweight/Obesity without T2D	
	Placebo (N=8)	Elecoglipron (N=16)
Age (y)	33.5 ± 6.59	35.7 ± 6.87
Males	5 (62.5%)	8 (50%)
Weight (kg)	85.96 ± 15.39	87.13 ± 10.37
BMI (kg/m^2)	30.10 ± 2.75	30.43 ± 2.11
HbA1c (%)	5.19 ± 0.35	5.38 ± 0.36
	Cohort B: Overweight/Obesity with T2D	
	Placebo (N=7)	**Elecoglipron (N=14)**
Age (y)	48.0 ± 15.83	46.2 ± 13.19
Males	3 (42.9%)	7 (50%)
Weight (kg)	80.70 ± 19.59	82.51 ± 15.48
BMI (kg/m^2)	29.73 ± 5.16	29.96 ± 5.45
HbA1c (%)	7.99 ± 1.16	7.89 ± 0.97
Time since Dx of T2D (y)	4.59 ± 3.79	3.26 ± 2.78

Continuous variables are presented as mean ± standard deviation (SD), and categorical variables as numbers (n) and percentages (%).

Pharmacodynamics (exploratory endpoint)

- In Cohort A, elecoglipron treatment led to reductions in body weight at Week 16 compared with placebo. LS mean differences were -6.87% for percent weight change (Figure 2), -6.11 kg for absolute weight change.

Figure 2 Percent change from baseline in body weight at Week 16 (efficacy estimand) for Cohort A



- In Cohort B, elecoglipron also demonstrated weight loss and glycemic control at Week 16, with LS mean differences of -6.21% for percent weight change (Figure 3), -5.25 kg for absolute weight change, and -1.39% for HbA1c change from baseline (Figure 4).

Figure 3 Percent change from baseline in body weight at Week 16 (efficacy estimand) for Cohort B

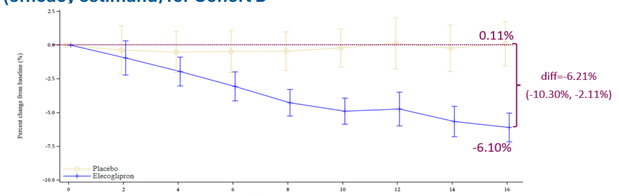
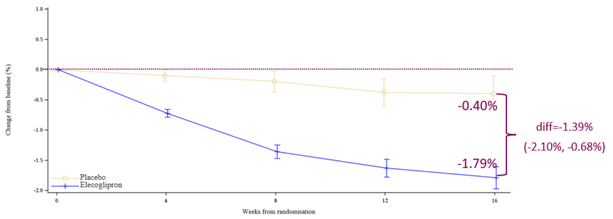


Figure 4 Change from baseline in HbA1c at Week 16 (efficacy estimand) for Cohort B



Safety and tolerability

- Most TEAEs were mild in severity, and no AEs led to treatment discontinuation.
- 1 SAE was reported in elecoglipron group in Cohort A, assessed as unrelated to treatment. No SAE reported in Cohort B.
- Gastrointestinal AEs were mostly mild to moderate, consistent with the GLP-1 RA class profile.
- No hepatic safety signal was observed and no cases of severe hypoglycemia.

Table 2 GI AE in Cohort A

Variable, n(%)	Cohort A: Overweight/Obesity without T2D	
	Placebo (n=8)	Elecoglipron (n=16)
Gastrointestinal disorders*		
Nausea	0	7 (43.8)
Vomiting	1 (12.5)	5 (31.3)
Constipation	1 (12.5)	4 (25.0)
Diarrhea	2 (25.0)	4 (25.0)
Eructation	0	3 (18.8)
Abdominal distension	0	2 (12.5)
Flatulence	0	2 (12.5)

* Only events with ≥ 2 subjects experiencing GI AE are presented.

Table 3 GI AE in Cohort B

Variable, n (%)	Cohort B: Overweight/Obesity with T2D	
	Placebo (n=7)	Elecoglipron (n=14)
Gastrointestinal disorders*		
Nausea	0	4 (28.6)
Vomiting	0	3 (21.4)
Abdominal distension	0	2 (14.3)

* Only events with ≥ 2 subjects experiencing GI AE are presented.

Pharmacokinetics

- Dose-dependent increases in C_{max} and AUC were observed across the dose range evaluated.
- Geometric mean steady-state $t_{1/2}$ was 17.0 hours at the maximum dose level.

CONCLUSIONS

- Treatment with elecoglipron showed clinically meaningful reductions in body weight among adults with obesity or overweight, regardless of T2D status, and meaningful glycemic improvements in participants with T2D were observed.
- Elecoglipron was generally well-tolerated, with no new safety signals identified.
- Elecoglipron exposure was increased after dose escalation in both Cohort A and Cohort B. The pharmacokinetic profile supports the suitability of elecoglipron as a once-daily regimen. [4]
- Phase 2b VISTA and SOLSTICE studies are now completed. Elecoglipron will advance to Phase 3. [4,5]

References
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Disclosures
YY and PF has no conflicts of interest. WC,JX, QL, JP, JZ and BZ are employees and equity holders of Eccogene. XM, TL, HL, and XZ are employees and stockholders of AstraZeneca.

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