AZD5004/ECC5004, a Small Molecule GLP-1 Receptor Agonist May Be Administered Once Daily Under Fed/Fasted Conditions

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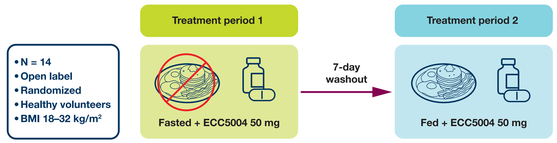
Introduction

- GLP-1 receptor agonists (RAs) are established therapies in type 2 diabetes (T2D), chronic weight management, and cardiovascular risk reduction.[1–3]
- Most GLP-1 RAs are injectable, thereby limiting access to therapy for many patients; the only existing oral preparation needs to be taken under strict fasting conditions.[4,5]
- AZD5004/ECC5004 is an oral small molecule GLP-1 RA in development for glycemic control in T2D and chronic weight management in obesity/overweight.
- In non-clinical studies, ECC5004 engaged the GLP-1 receptor and exhibited fully G-protein biased signaling via cAMP, but not beta-arrestin, with potency equivalent to or greater than that of other small molecule GLP-1 RAs.[6]
- In the Phase 1, first-in-human (FIH) study, ECC5004 was shown to have a safety and tolerability profile comparable to the GLP-1 RA class, a pharmacokinetic (PK) profile compatible with once daily dosing, and target engagement of the GLP-1 receptor.[6,7]
- In this Phase 1 study, we aimed to evaluate the PK profile of ECC5004 under fed and fasted conditions.

Methods

- An open-label, randomized, single-dose study was performed in 14 healthy participants under fasted (> 10 hours) conditions, or following a standardized high-fat breakfast (800–1000 calories with at least 50% of the caloric content derived from fat) consumed within 30 minutes with 7 days washout in between treatment periods (**Figure 1**).
- ECC5004 was administered within 30 minutes of the start of the meal in the fed condition.
- Serial plasma concentrations of ECC5004 were measured for 120 hours following a single dose of ECC5004 50 mg and PK parameters were derived and compared for each condition.
- Safety and tolerability were assessed as secondary endpoints.

Figure 1. Study design



BMI, body mass index.

Results

Disposition and baseline characteristics

- 23 participants were screened, 14 randomized, 1 discontinued due to investigator decision and 13 (92.9%) completed the study.
- All participants were healthy volunteers and were predominantly male (71.4%) and White (85.7%).
- Participants had a mean age of 46.7 years (SD 12.5) and a mean body mass index of 27.1 kg/m² (SD 3.2).

Pharmacokinetics

- The PK characteristics were comparable to those observed in the FIH study[6] (**Figure 2** and **Table 1**).
- The estimated half-life ($t_{1/2}$) in the fasted state was 21.2 hours, which is comparable to the $t_{1/2}$ in the fed state (20.7 hours), supporting once-daily dosing (**Table 1**).

Figure 2. Individual concentration–time pharmacokinetic profiles

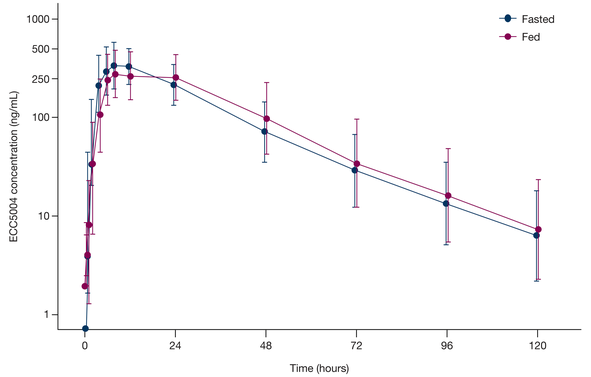


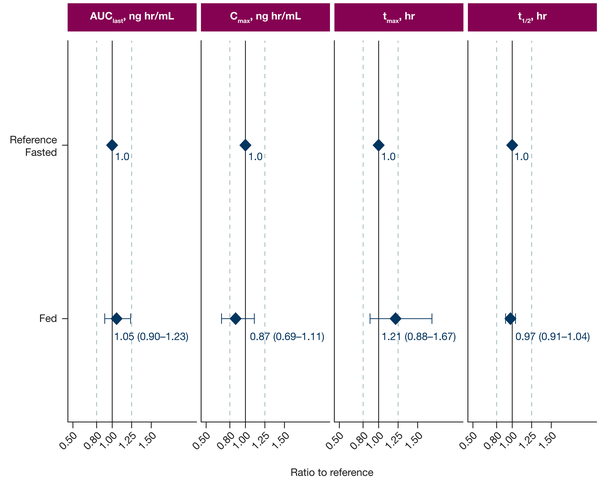
Table 1. Pharmacokinetic parameters

Arms	AUC_{last}, ng hr/mL GM (CV%)	C_{max}, ng/mL GM (CV%)	t_{max}, hr GM (CV%)	$t_{1/2}$, hr GM (CV%)
50 mg fasted (n = 14)	11443.21 (56.22)	374.5 (53.6)	8.8 (42.2)	21.2 (19.1)
50 mg fed (n = 14)	12054.39 (65.48)	326.9 (51.1)	10.7 (54.3)	20.7 (14.7)

CV, coefficient of variation; C_{max}, maximum concentration; GM, geometric mean; $t_{1/2}$, elimination half-life time; t_{max}, time to maximum concentration.

- There were no statistically significant differences under fed or fasted conditions for AUC_{last} (geometric mean ratio [RoGM] 1.05; 90% confidence interval [CI]: [0.9, 1.23], with fasted state as reference), elimination half-life ($t_{1/2}$) (0.97; [0.94, 1.04]), time to maximum concentration (t_{max}) (1.21; [0.88, 1.67]) and maximum concentration (C_{max}) (0.87; [0.69, 1.11]) (**Figure 3**).

Figure 3. Food effect analysis



Safety and tolerability

- There were no serious adverse events, deaths or discontinuations due to treatment-emergent AEs (**Table 2**).
- The overall frequency of adverse events (AEs) was 64.3% in the fed state and 50% in the fasted state.
- The most common AEs were nausea, dyspepsia, abdominal discomfort, and vomiting.
- There were no clinically relevant treatment-emergent abnormalities on laboratory assessments or ECGs.

Table 2. Treatment-emergent adverse events

Variables, n (%)	ECC5004 50 mg	
	Fasted n = 14	Fed n = 14
TEAEs		
Overall	7 (50)	9 (64.3)
Leading to study discontinuation		
TEAEs	0 (0)	0 (0)
Investigator decision	1 (7.1)	0 (0)
SAEs	0 (0)	0 (0)
Gastrointestinal (GI) TEAEs		
Overall GI	6 (42.9)	9 (64.3)
Nausea	5 (35.7)	5 (35.7)
Constipation	2 (14.3)	0 (0)
Dyspepsia	1 (7.1)	3 (21.4)
Abdominal discomfort	0 (0)	4 (28.6)
Abdominal distension	1 (7.1)	0 (0)
Vomiting	3 (21.4)	1 (7.1)
Abdominal pain upper	1 (7.1)	0 (0)
Dry mouth	1 (7.1)	0 (0)
Diarrhea	0 (0)	0 (0)

SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Conclusions

- ECC5004 exhibited a PK profile supportive of once daily dosing that was not significantly different between fed and fasted states.
- ECC5004 may therefore be administered under fed or fasted conditions and has the potential to be a more convenient therapy for patients.
- Safety and tolerability were in accordance with previous studies[6,7] and there was no difference in GI tolerability observed between fed and fasted states.
- Phase 2b studies in overweight/obesity (VISTA, **NCT06579092**) and T2D (SOLSTICE, **NCT06579105**) are ongoing.

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Disclosures

AH has no conflicts of interest. LB, XS, XP, HL, WC, JX, JZ and JX are employees and equity holders of Eccogene. AJ, HY, AK, and VP are employees and stockholders of AstraZeneca.

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