Poster number: 750-P

ASC30, an Oral GLP-1R Biased Small Molecule Agonist in Participants with Obesity—A First-in-Human Single Ascending Dose Study

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① Introduction

ASC30 is a fully biased oral GLP-1R small-molecule agonist that does not recruit β-arrestin and is more potent than orforglipron (Table 1.). It is designed as one small molecule for both once-daily oral and once-monthly subcutaneous administration to treat obesity and related metabolic disorders.

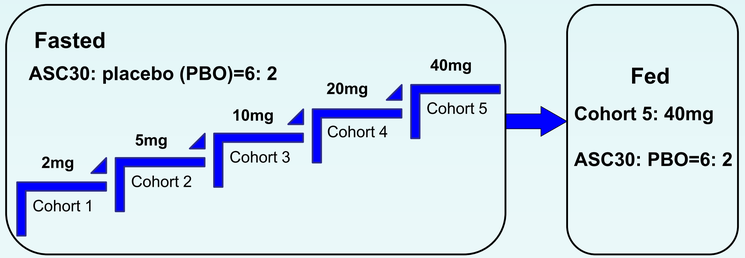
Table 1. cAMP activation in Flp-In-293-GLP1R cells expressing human GLP-1R (Head-to-head study)

Compound	cAMP activation EC_{50}, nM (mean±SD)	β-arrestin 2 EC_{50}, nM (mean±SD)
Orforglipron	0.0180 ± 0.0043	>30,000
ASC30	0.0088 ± 0.0017	>30,000

② Methods

This was a randomized, double-blind, placebo-controlled single ascending dose FIH study of ASC30 tablet (NCT06680440, Figure 1.).

Figure 1. FIH SAD Study Design



③ Results

Key findings in ASC30 tablet SAD PK

- Mean half-lives (T1/2) support once-daily oral dosing (Table 2.).
- ASC30 pharmacokinetics show dose proportional across the range of 2 mg to 40 mg tested. (Table 2. and Figure 2.). No statistically significant difference between fasted and fed cohorts.

Table 2. ASC30 tablet SAD PK profile in humans

	Cohort 1 OB (n=6)	Cohort 2 OB (n=6)	Cohort 3 OB (n=6)	Cohort 4 OB (n=6)	Cohort 5 OB (n=6)
Fasted Condition	Fasted	Fasted	Fasted	Fasted	Fasted
Dose level (mg)	2	5	10	20	40
$T_{1/2}$ (hr)	11.1±1.1	56.4±36.1	43.7±4.5	33.9±9.3	39.3±15.5
T_{max} (hr) Median (Min, Max)	7.0 (4.0,8.0)	5.0(4.0,6.0)	5.0(4.0,6.0)	6.0(4.0,8.0)	6.0(6.0,8.0)
C_{max} (ng/mL)	8.5±2.3	48.8±20.5	73.4±27.3	209.3±56.1	409.0±161.9
AUC_{0-24} (hr*ng/mL)	88.2±20.4	450.0±142.6	746.9±360.9	2,250.9±648.8	4,251.7±1,246.5
AUC_{last}* (hr*ng/mL)	109.0±24.1	691.1±319.4	1,110.5±561.9	3,058.3±787.8	6,776.5±1,969.0
AUC_{inf} (hr*ng/mL)	131.3±24.8	889.6±674.7	1,175.9±742.8	3,098.6±891.1	7,283.9±2,874.9

Note: *AUC_{last}: Cohort 1: calculated from 0 to 36 or 48 hours; Cohort 2: calculated from 0 to 96 or 120 hours; Cohort 3-5: calculated from 0 to 120 hours. OB = obesity.

Figure 2. ASC30 oral daily tablet PK curves

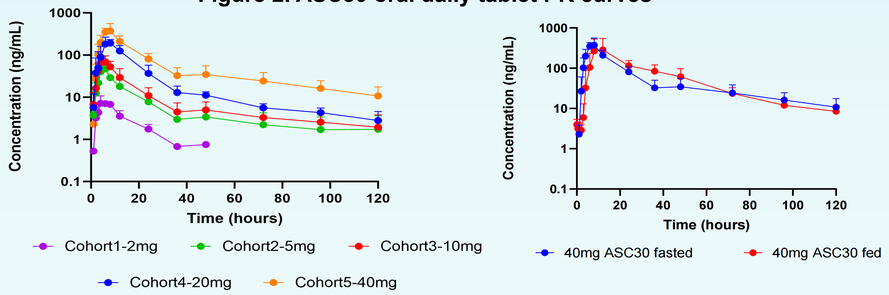
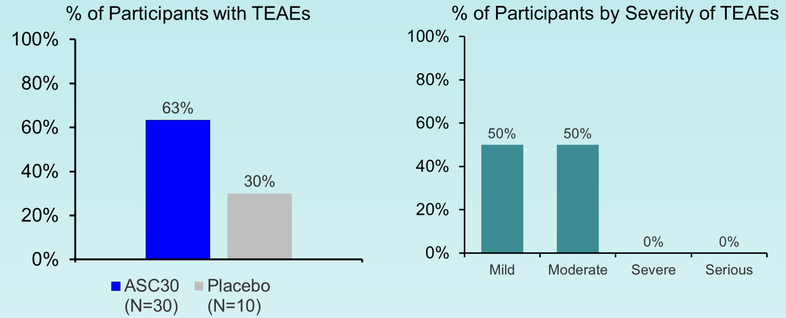


Figure 3. ASC30 tablet SAD Safety Profile



Key findings in safety profile

- TEAEs were higher than placebo, with all mild/moderate in severity (Figure 3.).
- No SAEs, deaths, or discontinuations.
- No liver enzyme elevations, QTc prolongation, or other clinically significant ECG/lab changes.
- GI TEAEs were mild or moderate, consistent with other incretin therapies. No vomiting at 2 mg and 5 mg doses.

④ Conclusions

- ASC30 tablet was well tolerated, with low GI TEAEs and no vomiting at 2 or 5 mg.
- ASC30 demonstrated high potency and a superior, dose-proportional PK profile supporting once-daily oral dosing.
- In MAD study, ASC30 tablet achieved up to 6.3% weight loss in 4 weeks in participants with obesity*.
- In participants with obesity, ASC30 SQ injection exhibited a half-life of 36 days, supporting once-monthly dosing*.

* Detailed results will be presented at future conferences.

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