Oral Small Molecule GIPR Agonist ASC48 for Obesity: *in Vitro* and *in Vivo* Studies

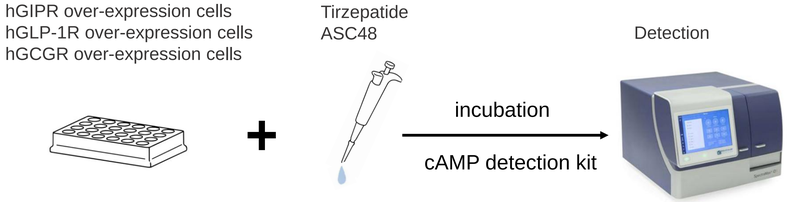
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Background: ASC48 is a potential first-in-class oral small-molecule GIPR agonist, discovered and developed in-house at Ascletis. ASC30 is a GLP-1R-fully biased oral small molecule agonist without β-arrestin recruitment. The GLP-1R/GIPR dual-targeted oral small molecule ASC30_48 fixed-dose combination (FDC) represents a promising first-in-class one-pill, once-daily oral treatment for obesity and other metabolic diseases.

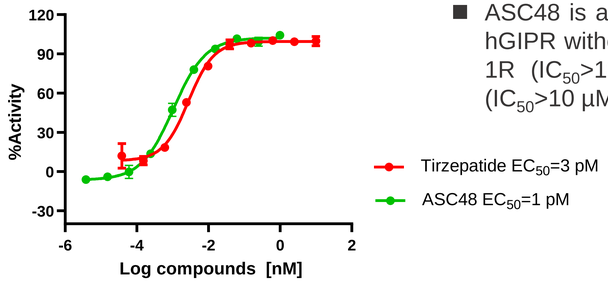
Methods: Human GIPR-mediated cAMP activation induced by ASC48 and tirzepatide was compared. Fifteen male cynomolgus monkeys underwent a 14-day acclimation phase before random allocation into three groups (n=5 per group). Animals received daily oral gavage for 8 consecutive days: Group 1 received 2 mg/kg ASC30, Group 2 received 5 mg/kg ASC48, and Group 3 received ASC30_48 FDC (2 mg/kg ASC30 and 5 mg/kg ASC48). Body weight measurement was performed at a fixed time point each day throughout the study.

Results

In vitro cAMP Activation Assay



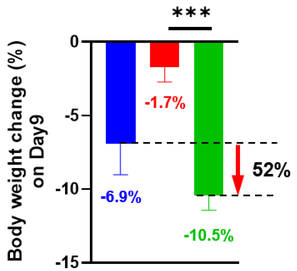
hGIPR Agonist cAMP Assay



- ASC48 is a selective agonist for hGIPR without activity for hGLP-1R (IC_{50}>10 μM) and hGCGR (IC_{50}>10 μM).

In vivo Efficacy Study in Non-human Primate (NHP)

Treatment	N	Dose, mg/kg	ROA	Frequency
ASC30	5	2	PO	QD*8 days
ASC48	5	5	PO	QD*8 days
ASC30_48 FDC	5	ASC30: 2 ASC48: 5	PO	QD*8 days

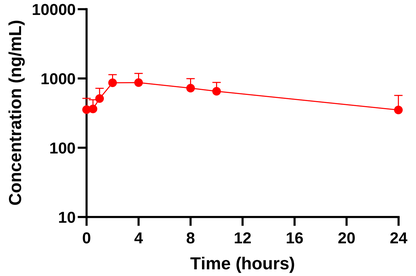


ASC30 (2 mg/kg, PO, QD)
ASC48 (5 mg/kg, PO, QD)
ASC30_48 FDC (2 mg/kg / 5 mg/kg, PO, QD)

- ASC30_48 FDC demonstrated approximately **52%** greater relative body weight reduction compared to ASC30 monotherapy.

PK Studies in Non-human Primate (NHP)

Mean Plasma Concentration-Time Profile of ASC48 in Cynomolgus Monkeys after 8 Repeated i.g. Doses of 5 mg/kg



Species	Compound	Dose, mg/kg	$T_{1/2}$, h	AUC_{0-24h}, h*ng/mL
Cynomolgus Monkeys	ASC48	5	16.2	14,500

- ASC48 demonstrated robust oral bioavailability and drug exposure in NHP.

Conclusions: ASC48 demonstrated potent and selective activity for hGIPR. ASC30_48 FDC is a potential first-in-class once-daily oral fixed-dose combination treatment for obesity, targeting both GLP-1R and GIPR. ASC30_48 FDC demonstrated approximately 52% greater relative body weight reduction compared to ASC30 monotherapy in a head-to-head NHP study. Both *in vitro* and *in vivo* data warrant ASC30_48 FDC to advance into clinical development.

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Disclosure:
Jinzi Jason Wu: Employee of Ascletis Pharma (China) Co., Limited;
Chengfei Wu: Employee of an affiliate of Ascletis Pharma (China) Co., Limited

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