

ASC35, a Once-Monthly Next-Generation GLP-1R/GIPR Dual Agonist Peptide, Demonstrated 14-day Average Observed Half-life, 6-fold Longer than Tirzepatide, in NHP Model and 71% More Relative Weight Loss than Tirzepatide in DIO Mouse Model

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Introduction

ASC35, a potent GLP-1R and GIPR dual peptide agonist, was discovered and developed in-house utilizing Ascletis' Artificial Intelligence-Assisted Structure-Based Drug Discovery (AISBDD) and Ultra-Long-Acting Platform (ULAP) technologies. ASC35 is engineered for a longer observed half-life (as measured by time to 50% C_{max}) and higher bioavailability per milligram of peptide, compared to once-weekly administered tirzepatide, to support once-monthly SQ dosing, with injection volume of one milliliter or less. These engineered properties also allow for scalability advantages in manufacturing.

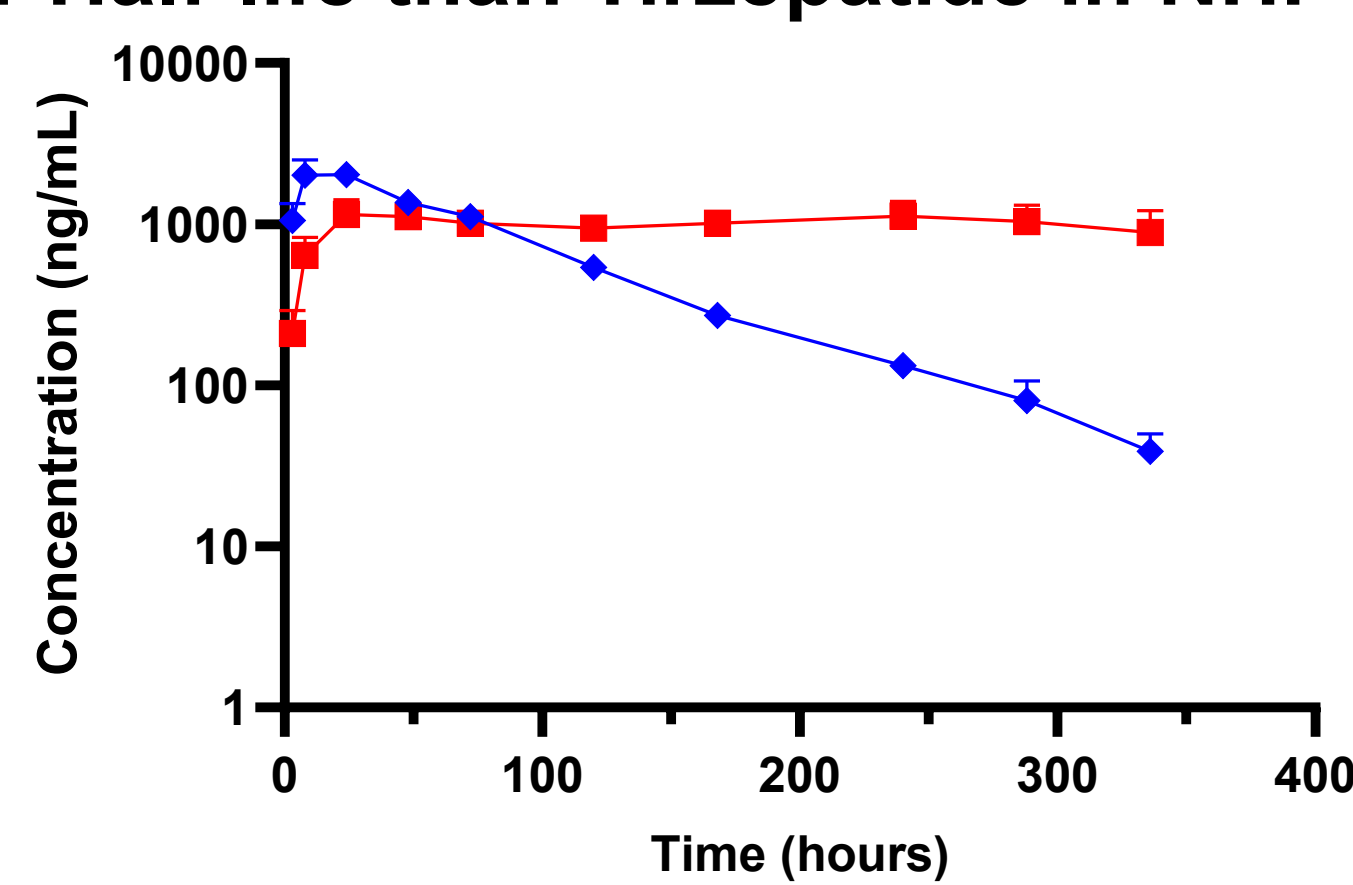
Methods

Pharmacokinetic profile of ASC35 in proprietary formulations developed Ascletis' ULAP technology was evaluated in non-human primates. cAMP production was evaluated to determine ASC35's agonist activity on human GLP-1R and GIPR. *In vivo* efficacy of ASC35 was evaluated in DIO mouse model.

Results

PK Studies in Non-human Primate (NHP)

Study 1: ASC35 Slow-release SQ Depot Formulations Had Longer Half-life than Tirzepatide in NHP



◆ TZP solution197, SQ, 0.2 mg/kg, 0.2 mL/kg, 1 mg/mL
 ◆ ASC35 solution257, SQ, 0.5 mg/kg, 0.2 mL/kg, 2.5 mg/mL

Group	Monkey	ROA	dose (mg/kg)	$T_{1/2}$ (h)
Tirzepatide in buffer-based formulation	n=3	SQ	0.2	57.1
ASC35 in slow-release SQ depot formulation	n=3	SQ	0.5	328 (13.6 days)

- In head-to-head non-human primate (NHP) studies, ASC35 slow-release SQ depot formulations had an average observed half-life of approximately 14 days, 6-fold longer than tirzepatide in its FDA-authorized SQ formulation

Study 2: In the same formulations, ASC35 I.V. and SQ Administration Had Greater Drug Exposure than Tirzepatide in NHP

Group	Monkey	ROA	dose (mg/kg)	$AUC_{(0-inf)}$ (h*ng/mL)	Ratio
Tirzepatide	n=3	IV	0.1	99,103	100%
ASC35	n=3	IV	0.1	182,000	183.60%

Group	Monkey	ROA	dose (mg/kg)	$AUC_{(0-288h)}$ (h*ng/mL)	Ratio
Tirzepatide	n=3	SQ	1	288,000	100%
ASC35	n=3	SQ	1	511,000	177.40%

- In head-to-head NHP studies, drug exposures of ASC35 I.V. and SQ administration were approximately 80% and 70% greater than tirzepatide (TZP) I.V. and SQ administration, respectively.

Study3: ASC35 SQ Injection half-life Prediction

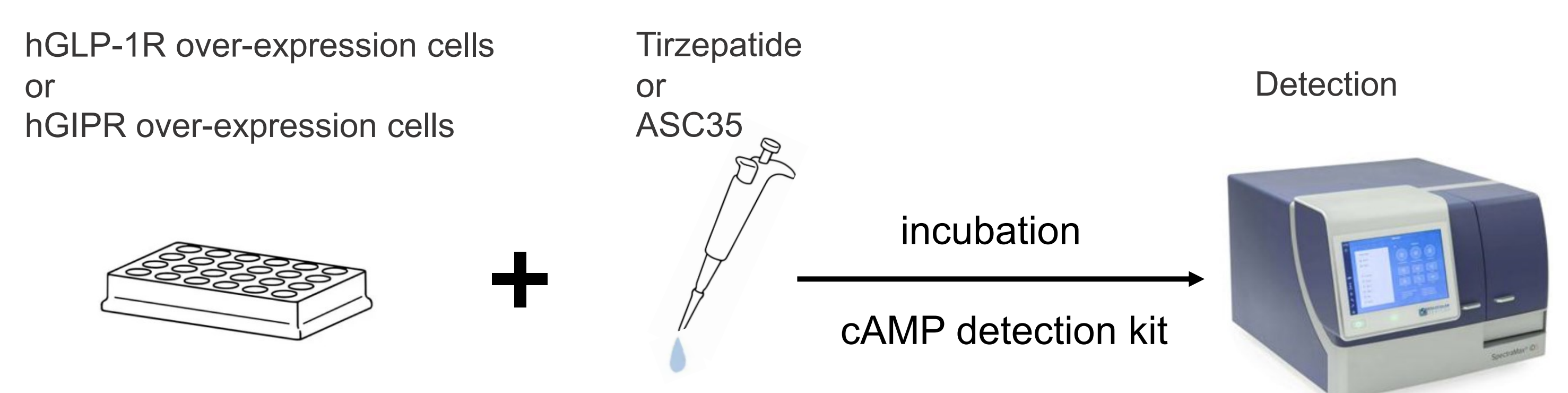
	Tirzepatide GLP-1R/GIPR (actual)		Semaglutide GLP-1R (actual)		ASC35 GLP-1R/GIPR	
	NHP	Human	NHP	Human	NHP (actual)	Human (predicted)
Half-life (SQ injected)	56 h (2.3 days)	128 h (5.3 days)	54 h (2.3 days)	149 h (6.2 days)	14 days	32 days
Human to animal ratio	-	2.3 fold	-	2.8 fold	-	2.3 fold

- ASC35 have 6-fold longer $T_{1/2}$ than tirzepatide.

Conclusions

ASC35's longer observed half-life, better SQ bioavailability and greater weight loss compared to tirzepatide demonstrate its potential as a best-in-class treatment for obesity.

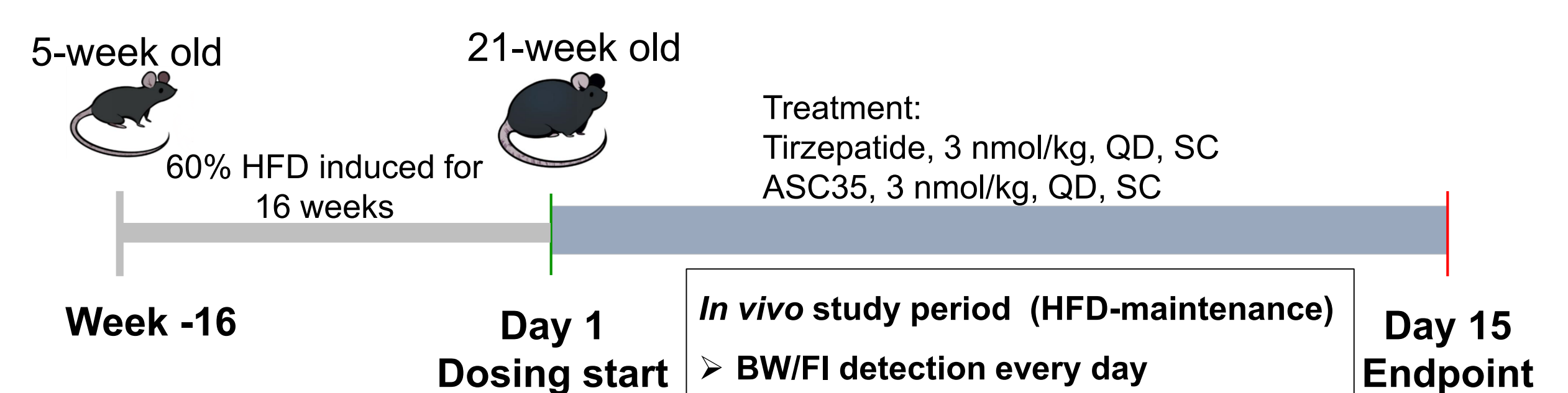
In vitro cAMP Production Assay



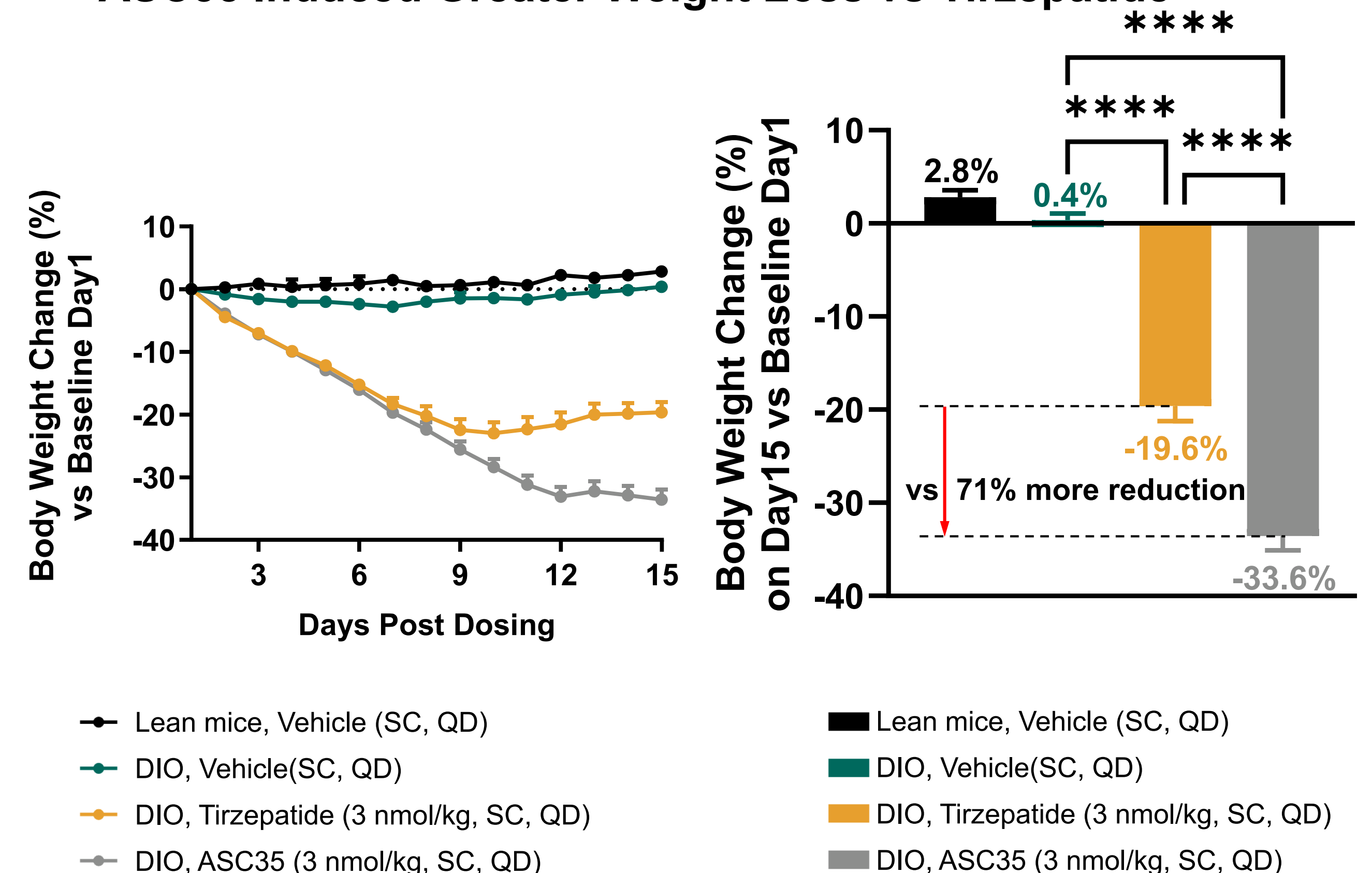
- ASC35 was approximately 4-fold more potent than tirzepatide for both GLP-1R and GIPR *in vitro*.

In vivo Efficacy Study

Study Illustration



ASC35 Induced Greater Weight Loss vs Tirzepatide



- ASC35 reduced body weight by 33.6%, compared to 19.6% for tirzepatide, a relative increase in efficacy of 71%.

ASC35 Produced More Potent Food Intake Suppression than Tirzepatide.

