Poster No. 767-P

TERN-601, a Novel Oral GLP-1R Agonist, Suppresses Food Intake and Improves Glucose Tolerance in Transgenic Mice Expressing Human GLP-1 Receptor

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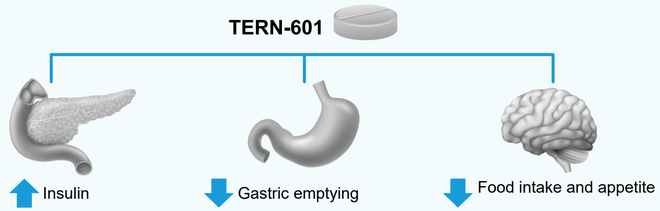
1 INTRODUCTION

- Glucagon-like peptide-1 receptor (GLP-1R) agonists emulate the natural ligand GLP-1, a transient peptide hormone that: 1) triggers the release of pancreatic insulin after meals to decrease blood glucose levels, 2) slows down gastric emptying, and 3) promotes a feeling of fullness, resulting in reduced food consumption and potential body weight loss



- TERN-601 is a novel, potent, oral small molecule GLP-1R agonist in preclinical development
- Humanized GLP-1R (hGLP-1R) mice were used to assess the *in vivo* pharmacodynamics of TERN-601 due to the inactivity of small molecule GLP-1R agonists on non-primate receptors[1]

2 METHODS

- Intracellular cAMP accumulation was assessed in CHO-K1 cells expressing human GLP-1R and measured by TR-FRET. Activity on mouse GLP-1R was determined in a U2OS mouse GLP-1R cell line using the HitHunter cAMP assay detection kit
- Glucose-stimulated insulin secretion (GSIS) was evaluated in 3D InSight™ human Islet microtissues treated with TERN-601, danuglipron, or DMSO in the presence of 16.7 nM glucose. Insulin levels were measured by ELISA and normalized for intracellular ATP content
- In an intraperitoneal glucose tolerance test (IPGTT), fasted mice received TERN-601 (0.3, 1, 3 mg/kg, PO) or liraglutide (0.3 mg/kg, SQ) before glucose challenge (2 g/kg IP) and blood glucose was monitored for 120 minutes
- Food intake was recorded for 24 hours in fasted mice treated with TERN-601 (10, 30, 60 mg/kg, PO) or liraglutide (0.3 mg/kg, SQ), with food available *ad libitum* 15 minutes post dose
- Gastric emptying was assessed using acetaminophen pharmacokinetics as a marker in fasted mice given TERN-601 (30 mg/kg, PO) or semaglutide (10 nmole/kg, SQ), followed by acetaminophen (APAP, 100 mg/kg) and glucose (2 g/kg). Acetaminophen levels in plasma were measured at various time points by LC-MS/MS

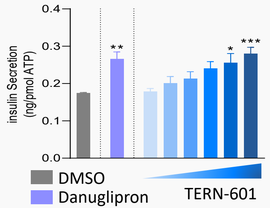
3 RESULTS

In vitro potency on GLP-1R (cAMP assay)

TERN-601

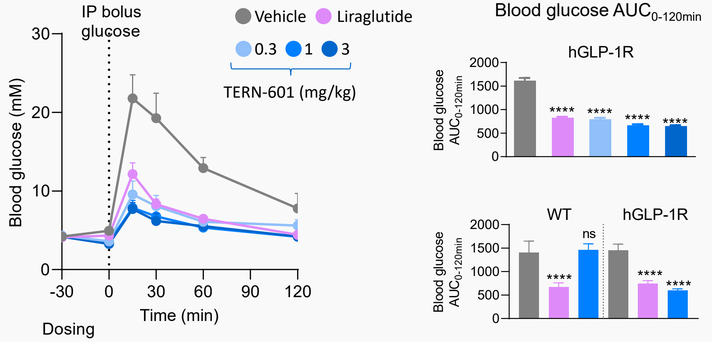
Species	EC_{50}, nM	E_{max}, %	N
Human	2.92 (0.81)	98 (2)	22
Mouse	>10,000	3 (3)	3

Human islet microtissues (GSIS assay)



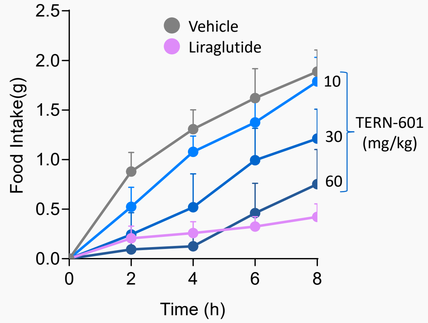
- TERN-601 showed potent activity in cells expressing human but not mouse GLP-1R using intracellular cAMP generation as a readout. Data presented as mean ±SD
- TERN-601 enhanced insulin secretion from human pancreatic islet microtissues in a glucose stimulated insulin secretion (GSIS) assay. Data presented as mean ±SD insulin levels normalized to ATP content (9-10 replicates per condition). *p<0.05, **p<0.01, ***p<0.001 vs. DMSO control

Intraperitoneal glucose tolerance test (IPGTT) in hGLP-1R mice

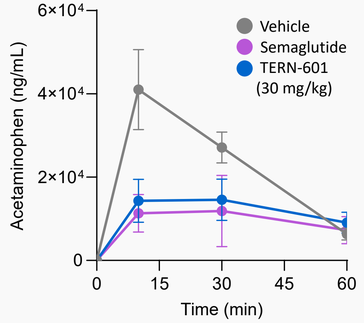


- TERN-601 (0.3, 1, and 3 mg/kg, PO) reduced blood glucose in hGLP-1R mice during glucose challenge. Data presented as mean ±SD (n = 7/group)
- Blood glucose $AUC_{0\text{-}120min}$ values decreased at all TERN-601 doses in hGLP-1R mice (Top, right), but not in wild type (WT) mice (Bottom, right), reflecting differences in the binding pocket of the mouse receptor (Griffith 2022). Data presented as mean ±SD (n = 5/group). ns= not significant; ****p<0.0001 vs. Vehicle

Cumulative food-intake



Gastric emptying



- TERN-601 (10, 30, and 60 mg/kg, PO) reduced *ad libitum* food-intake in fasted hGLP-1R mice (left). Data presented as mean ±SD (n = 10/group)
- Acetaminophen (APAP) plasma levels were reduced in fasted hGLP-1R mice administered TERN-601 (30 mg/kg, PO) 4 hours prior to oral ingestion of APAP-glucose solution, indicating slowed gastric emptying. Data presented as mean ±SD APAP plasma concentration (n = 5/group)

4 CONCLUSIONS

- TERN-601 is a novel, potent, oral small molecule agonist of human GLP-1R
- TERN-601 enhanced glucose-stimulated insulin secretion in human pancreatic islet microtissues
- Oral doses of TERN-601 significantly improved glucose tolerance, suppressed food-intake, and slowed gastric emptying in C57BL/J6 mice expressing human GLP-1R
- These results support the continued development of TERN-601 for the treatment of metabolic disease including obesity
- The Phase 1 first-in-human (FIH) of TERN-601 is expected to initiate in 2H23 in participants with elevated body mass index

5 REFERENCES

1. Griffith D. et al. A Small-Molecule Oral Agonist of the Human Glucagon-like Peptide-1 Receptor. J Med Chem (2022), 65(12): 8208-8226