HTL'097 | GLP-1 Antagonist

EXECUTIVE SUMMARY

- Potent, selective GLP-1 antagonist for treatment of severe hypoglycaemia in rare diseases including congenital hyperinsulinism (CHI) - designed from GLP-1 and other Class B GPCR StaR® structures
- Clinically validated MoA (via exendin 9-39) – key opportunity to differentiate based on PK and PD - clear differentiation in pre-clinical models versus Exendin 9-39
- Superior efficacy and/or safety to existing products and other products in development
- Suitable for once daily sub-cut dosing in patients, with potential to develop a long-acting injectable formulation
- Rodent and primate DRFs successfully completed and API material in-hand to support GLP toxicology
- Precedented POM biomarker with direct translation from pre-clinical species to healthy volunteers to patients

Sources: [1] Globe Life Sciences

TARGET AND DISEASE INDICATION(S)

- Lead Indications – Congenital Hyperinsulinism (CHI) and Post-bariatric Surgery Hypoglycaemia (PBSH)
- Estimated peak sales – ~200M[1] (CHI) and $200-275m[1] (PBSH)

RATIONALE

- GLP-1 antagonism clinically precedented in POC demonstrated with Exendin 9,39 in CHI & PBSH
- Opportunity to differentiate from Exendin 9,39 – PK and potency (higher receptor occupancy achievable)
- No efficacious and well-tolerated therapeutic agents currently available

TARGET PRODUCT / MOLECULE PROFILE

- GLP-1 antagonist peptide suitable for once daily (preferably once weekly) subcutaneous injection for the treatment of patients with CHI and PBSH

CURRENT STATUS

- Preclinical development (rodent and primate DRFs completed)

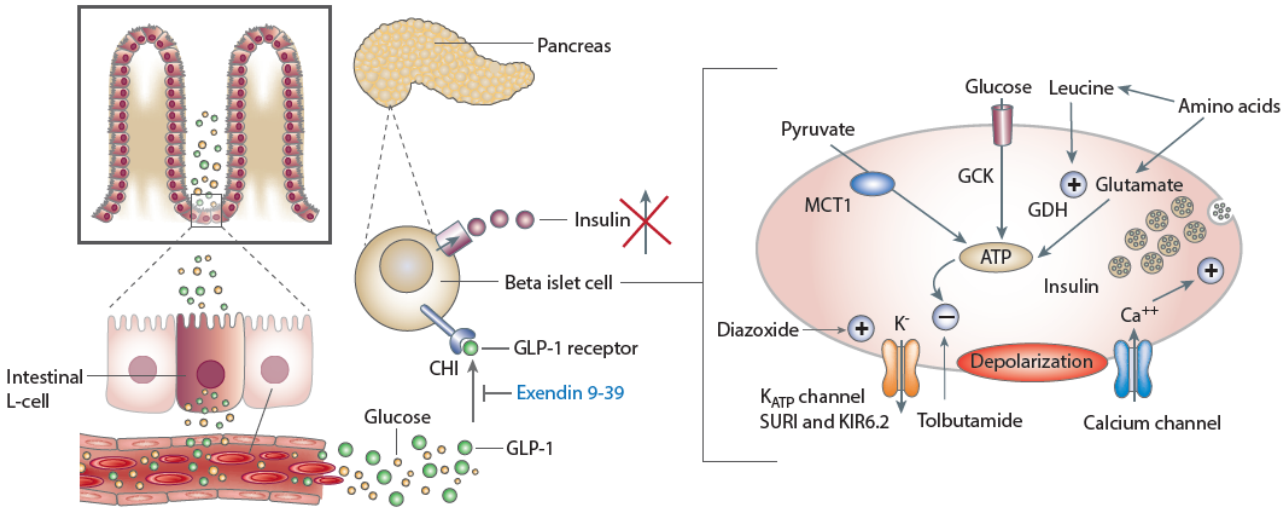
MECHANISM OF ACTION IN HYPERINSULINAEMIC HYPOGLYCAEMIA

Post-bariatric surgery hypoglycaemia (PBSH)

- PBSH is characterized by repeated episodes of symptomatic, postprandial hypoglycaemia.
- 1 – 2 % of gastric bypass patients develop moderate to severe hypoglycaemia.

Congenital hyperinsulinism (CHI)

- Results from primary defect of the pancreatic β-cell leading to inappropriately increased insulin secretion in the absence of glucose elevation.
- Associated with mutations in a number of key genes responsible for regulating insulin secretion.



HTL'097 Profile

High potency, long plasma $t_{1/2,}$ consistent with QD dosing via SC route of administration

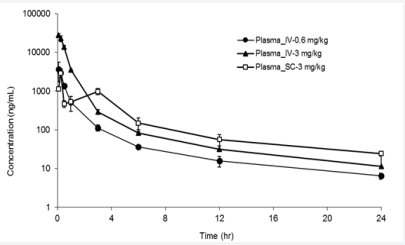
In Vitro / In Vivo Properties

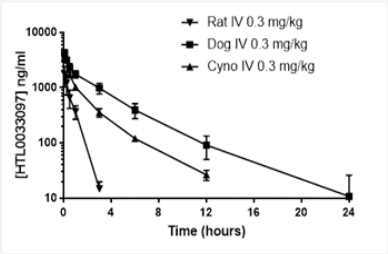
- High efficacy antagonist with consistent X-species activity

In Vitro Pharmacology	
Hum GLP1 fpKb (antagonist)	8.9 (1.3nM)
Cyno GLP1 fpKb (antagonist)	8.7 (2nM)
Mouse GLP1 fpKb (antagonist)	8.2 (6.3nM)
PK Parameters (IV mouse) and PKPD	
CL (mL/min/kg)	~2.5
Vss (L/kg)	~0.2
T1/2 (h)	~6hr
Fu (%)	~0.5%
Efficacious dose in mouse	0.6 mg/kg

Excellent PK Properties

- Mean plasma concentration-time profiles of HTL0033097 after IV dose at 0.6 mg/kg and 3 mg/kg and SC dose at 3 mg/kg in C57BL/6 mice (N=3/time point)
- Linear PK observed between 0.6 and 3 mg/kg
- Consistent exposure observed across species with long T1/2
- Allometric scaling predicts human CL 0.27 mL/min/kg and Vss 0.078 L/kg
- Supports QD dosing



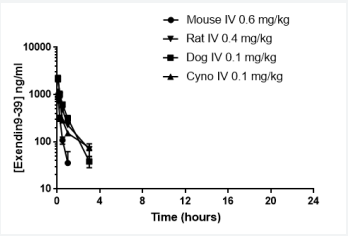


GLP-1 Antagonist: Differentiation

Exendin 9-39 (Avexitide – Eiger): Low potency, Sub-optimal PK

- Significantly weaker potency and increased clearance compared to HTL'097
- High clearance consistently observed across species
- Consistent with clinical observations

In Vitro Pharmacology	
Hum GLP1 fpKb (antagonist)	7.6 (25nM)
PK Parameters and PKPD	
CL (mL/min/kg)	~15
Vss (L/kg)	0.1
T1/2 (h)	~0.1
Fu (%)	~25%
Efficacious dose in mouse	0.4 mg/kg

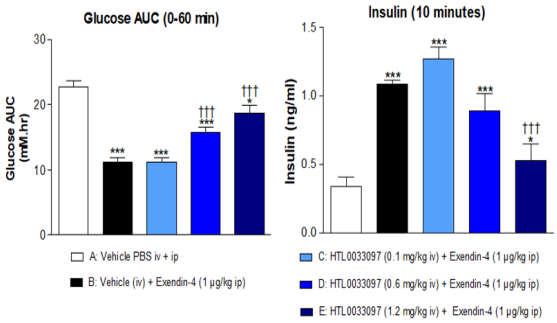


Summary of Efficacy

In Vivo Acute Efficacy Data in Mouse

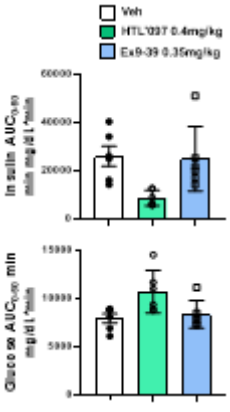
- Simple efficacy model based on reversal of GLP-1 agonist (exendin-4) stimulated insulin secretion and glucose disposal
- Pre-dosing of GLP-1 antagonist followed by GLP-1 agonist stimulated IPGTT
- HTL'097 significantly reverses GLP-1 agonist effects

Mouse Efficacy Data and PKPD



Dose dependent inhibition of insulin secretion and increased plasma glucose in NHP

- NHP IVGTT model – similar principle to mouse efficacy studies
  - Confirm potential for GLP-1 antagonist to reverse GLP-1 agonist-mediated inhibition of insulin secretion (top) and plasma glucose (bottom)
- HTL'097 dose/exposure predicted from mouse efficacy studies (latin-square IVGTT design to specifically address pancreatic effects of GLP-1 antagonist)
- Robust effects of HTL'097
- Marginal effects of Ex9-39 in same animals/study
  - Dose based on matching predicted exposures required for clinical efficacy
- NHP IVGTT model represents robust challenge model and 'stringent' test of GLP-1 antagonist efficacy
- Supports clearly differentiated effects vs. Ex9-39



Decreased plasma insulin

Increased plasma glucose

HTL'097 is promising and differentiated pre-clinical stage GLP-1 antagonist peptide available for partnering or academic collaboration, with potential for further development for the treatment of CHI and other hypoglycaemic disorders