HTL'023 | DUAL GLP-2/GLP-1 Agonist

EXECUTIVE SUMMARY

- HTL'023 is a highly potent (Sub nM), dual GLP-2/GLP-1 candidate molecule with excellent preclinical PK profile – well-tolerated in rodent and NHP DRF tox. studies
- Novel multifunctional peptide: expected to provide superior efficacy to current SoC in SBS
  - Current SoC pharmacotherapy is Teduglutide (Gattex ®; Revestive ®) - selective GLP-2 agonist
  - HTL'023 has a superior PK profile to teduglutide (> 24 hour cover on single dose)
  - Combination of GLP-2 and GLP-1 agonist activity expected to provide superior efficacy to GLP-2 agonism alone – greater reduction in parenteral nutrition and improved QoL
  - Differentiation from SoC (teduglutide) demonstrated in pre-clinical efficacy model
- Opportunity for HTL'023 as a novel treatment for NASH
  - Clinical benefit of GLP-1 agonism in NASH is precedented (liraglutide/semaglutide)
  - GLP-2 agonism postulated to reduce hepatic inflammation via reduced endotoxin absorption from G.I. tract
  - HTL'023 demonstrated efficacy in pre-clinical models of metabolic disease

TARGET AND DISEASE INDICATION(S)

- Short bowel syndrome (SBS) / Intestinal Failure (IF) – Estimated peak sales – ~$500M[1]
- Non-alcoholic steatohepatitis (NASH) – Market size to reach $27bn by 2029[2]

RATIONALE

- Provides superior efficacy to current SOC in SBS - GLP-2 agonist, via added benefit of GLP-1 agonism
- Provides superior efficacy to GLP-1 agonist in NASH by reducing hepatic inflammation via GLP-2 agonist activity

TARGET PRODUCT / MOLECULE PROFILE

- Highly potent and selective, dual GLP-2/GLP-1 agonist peptide suitable for once daily (preferably once weekly) subcutaneous injection

CURRENT STATUS

- Preclinical development (rodent and primate DRFs completed)

Sources: [1] Globe Life Sciences; [2] ResearchAndMarkets.com

In vitro properties

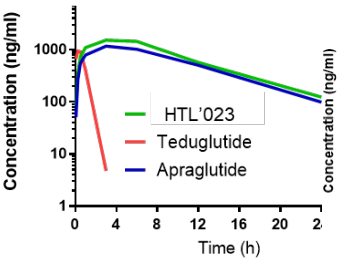
In Vitro Pharmacology	
GLP2R cAMP pEC50	10.9
GLP1R cAMP pEC50	10.5
Selectivity ratio GLP-2R: GLP-1R	3*
Pharmacokinetic parameters	
Hu blood/plasma stability	No degradation
In Vivo Rat CL	0.015 L/hr/kg
In Vivo Rat Vss	0.07 L/kg

* Clear pharmacological differentiation from other GLP-2 agonists in development (reduced GLP-1R selectivity)

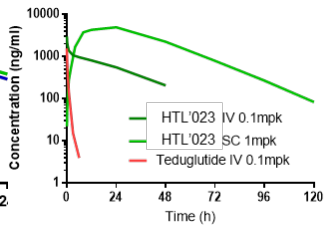
- Teduglutide & apraglutide: >10,000
- Glepaglutide ~30

Excellent PK profiles in rodent and non-rodent species

Mouse SC PK (0.4mg/kg)



Cyno IV/SC PK



- Clear PK differentiation from Teduglutide
- Supports low dosing frequency in clinical use, likely once weekly dosing

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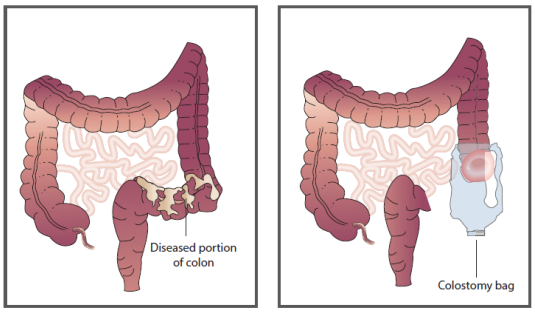
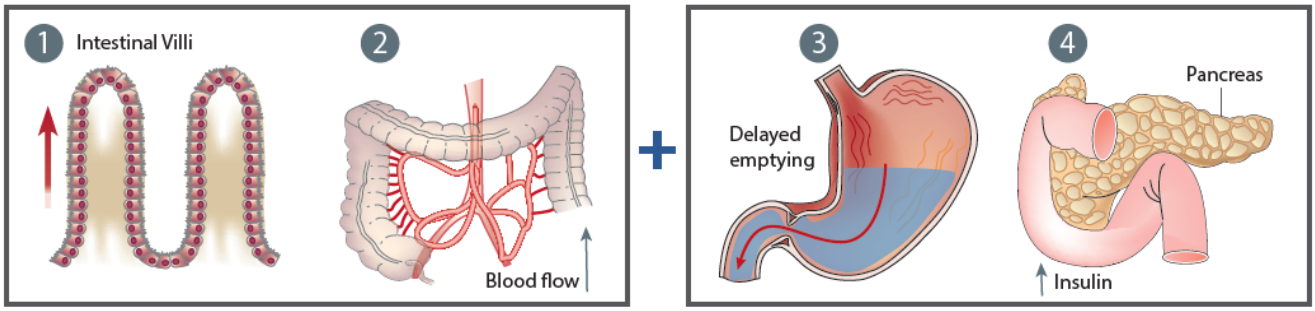
PROPOSED MECHANISTIC HYPOTHESIS FOR SUPERIOR TREATMENT OF SBS/IF*

Before | Colostomy



1. **Promotes mucosal growth and healing** – GLP-2 is a trophic factor: through enhanced crypt cell proliferation and intestinal villi length, GLP-2 enhances the nutrient absorptive capacity in the remnant bowel following intestinal resection.
2. **Enhances intestinal blood flow** – GLP-2 stimulates mesenteric blood flow and may facilitate nutrient absorption.
3. **Reduced GI transit** – GLP-1 slows gastric emptying and intestinal transit. This allows more time for water and nutrient absorption resulting in reduced ostomy output and diarrhoea.
4. **Improved glucose homeostasis** –GLP-1 agonists improve glucose handling and minimise risk of complications associated with higher blood glucose levels in patients on long term parenteral nutrition (PN) therapy.

GLP-2 | GLP-1



* Clinical Proof of Principle demonstrated in SBS patients - infusion of GLP-1 and GLP-2 native peptides provides additive effects on intestinal absorption compared to either peptide given alone (Madsen et al (2013) Regul Pept. 184: 30-39)

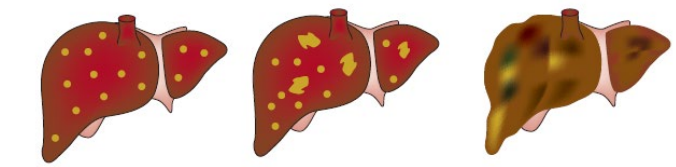
PROPOSED MECHANISTIC HYPOTHESIS IN NASH

TREATMENT OBJECTIVE

- Reduce excessive fatty accumulation in the liver and inflammation, decrease hepatocyte ballooning and fibrosis

STAGES OF NON-ALCOHOLIC FATTY LIVER DISEASE

Fatty Liver | NASH | Cirrhosis



Fatty liver

Fatty liver plus inflammation and scarring

Scared liver cells

PROPOSED BENEFITS OF GLP-2/GLP-1 AG PEPTIDE

1. **Reduced hepatic inflammation**
   GLP-2 agonists decrease the permeability of the intestinal epithelial barrier by enhancing tight junction integrity, leading to reduced translocation of bacterial endotoxins.
2. **Weight loss/hepatic benefits**
   GLP-1 agonists reduce body weight in NASH patients resulting in reduced de novo lipogenesis, decreased adipose tissue lipolysis, decreased hepatic lipid accumulation and oxidative stress.
3. **Improved metabolic function**
   GLP-1 agonists enhance glucose-stimulated insulin secretion and reduce glucagon secretion, resulting in improved glycaemic control and lowered HbA1c.

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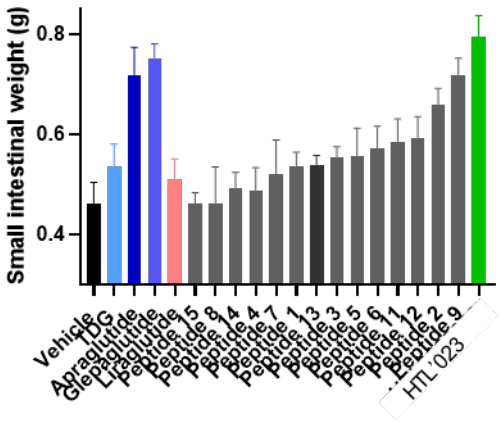
DATA SUMMARY

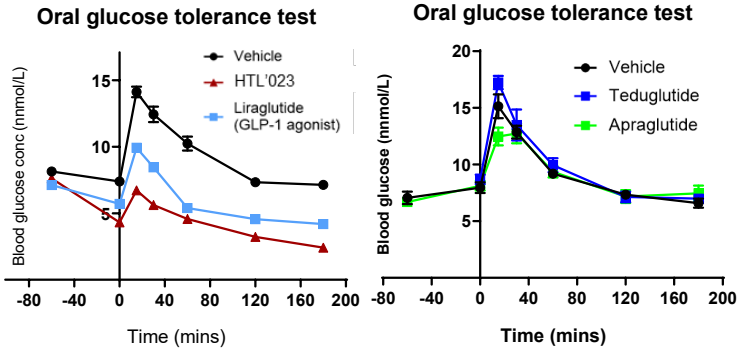
TARGET AND DISEASE INDICATION(S) – SBS

In vivo phenotypic screen in intestinal mass assay



- Screening of novel peptides in the mouse intestinal mass assay led to the identification of HTL'023 which demonstrates superior efficacy compared to teduglutide.
- Daily dosing of HTL'023 promotes lengthening of intestinal villi and crypt depth. HTL'023 may offer promise in improving intestinal absorption and nutrient handling in SBS patients.

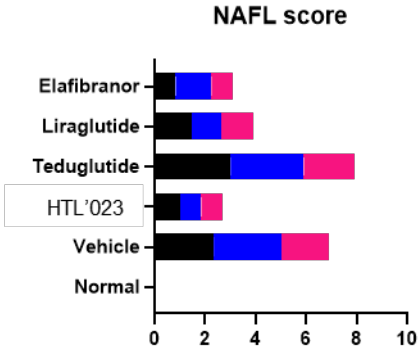
HTL'023 shows differentiated profile to GLP-2 selective peptides



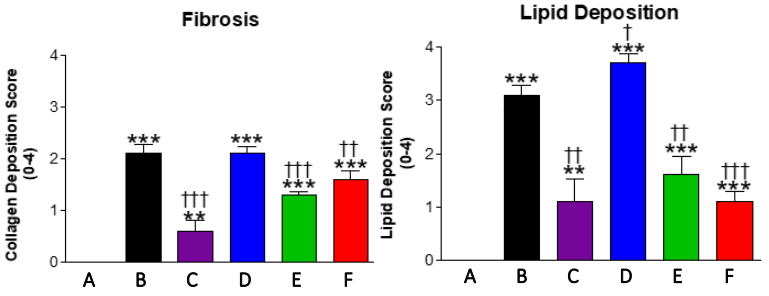
- HTL'023 shows robust efficacy in mouse oral glucose tolerance test, comparable to the clinical GLP-1 agent, liraglutide.
- Neither teduglutide nor apraglutide demonstrated benefits in the OGTT assay.
- Confirms benefit of GLP-1 activity via improving glucose homeostasis and delaying GI transit to allow more time for fluid and nutrient absorption.

TARGET AND DISEASE INDICATION(S) – NASH

HTL'023 reduces NAFL score in mice on choline deficient diet



HTL'023 shows differentiated profile to GLP-2 selective peptides



- Animals maintained on choline deficient diet for 6w develop changes in liver pathology and increase in non-alcoholic fatty liver disease activity score (NAS) consistent with the development of NASH.
- HTL'023 demonstrates benefits on liver lipid metabolism and improves histological signs of fibrosis.
- Data from mouse diet induced obesity (DIO) model also available. Clear benefits demonstrated on glucose handling and weight loss / body fat mass endpoints.

A: Normal vehicle
B: Choline deficient diet: Vehicle
C: Choline deficient diet: HTL'023
D: Choline deficient diet: Teduglutide
E: Choline deficient diet: Liraglutide
F: Choline deficient diet: Elafibranor