HTL'310 | SSTR5 Selective Somatostatin Agonist

EXECUTIVE SUMMARY

- Clinical stage SSTR5 selective somatostatin agonist – highly potent agent with > 100-fold selectivity vs SSTR2.
- Novel profile clearly differentiated from first generation (SSTR2 selective) agonists Octreotide and Lanreotide, and the second generation (non-selective agonist) Pasireotide.
- Phase 1 single ascending dose study completed. Confirms potential of HTL'310 to meet Target Product Profile.
- Complete package of non-clinical GLP safety studies available with confirmed good safety margin vs predicted clinical efficacious dose.
- CHI & PBSH are rare diseases with high unmet medical needs for agents with superior efficacy and/or toleration to current SoC.
- Additional therapeutic indications for HTL'310 include Gastro-Entero-Pancreatic-Neuroendocrine Tumours (GEP-NETs).

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)
- Global market for somatostatin analogues expected to reach $3.1B by 2024[2]

RATIONALE

- Prevention of hypoglycaemia via inhibition of insulin release from pancreas and incretin release from small intestine

TARGET PRODUCT / MOLECULE PROFILE

- SSTR5 Selective Somatostatin Agonist
- Potential for o.d. dosing (s.c.)
- Provides more effective treatment of CHI & PBSH than current standard of care
- Safe and well-tolerated

CURRENT STATUS

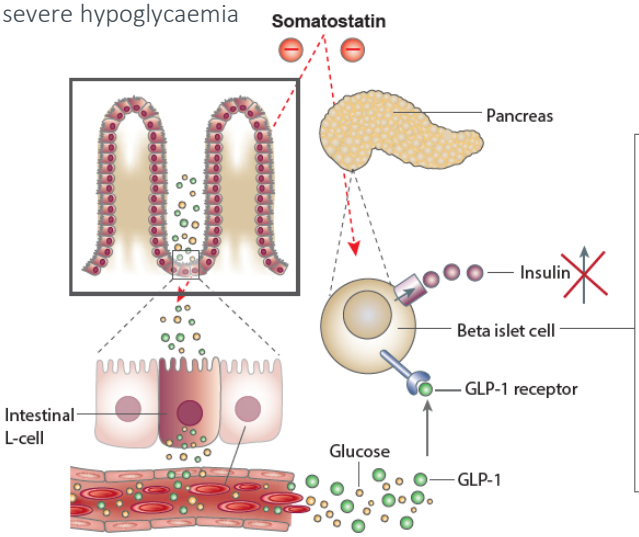
- Phase 1 SAD completed

Sources: [1] Globe Life Sciences; [2] Evaluate Pharma

MECHANISM OF ACTION IN HYPERINSULINAEMIC HYPOGLYCAEMIA

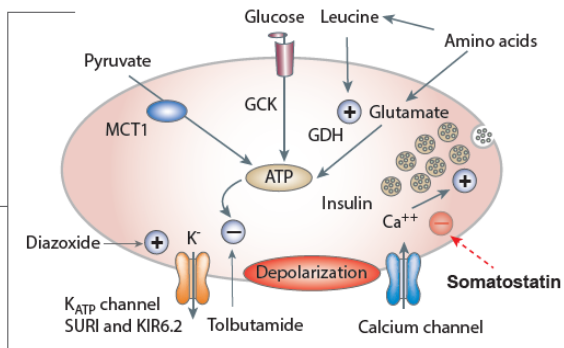
Post-bariatric surgery hypoglycaemia (PBSH)

- 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.
- Results from mutations in key genes responsible for regulating insulin secretion.

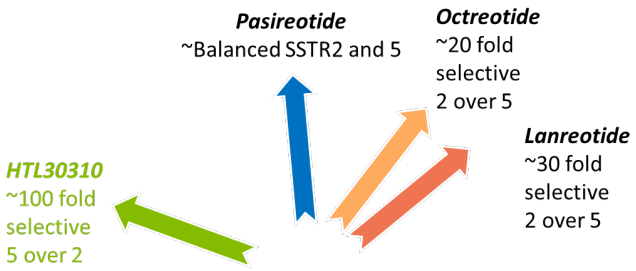


- Endogenous somatostatin plays a key role in the control of glucose homeostasis
- SSTR5 stimulation in pancreatic beta cells inhibits insulin release independently of the stimulus
- Dual action to inhibit insulin release and reduce GLP-1 secretion from L-cells is the basis for efficacy in PBSH.

HTL '310 Pharmacology

pEC_{50} SSTR5 = 9.3, SSTR2 = 6.4
~1000-fold functionally selective

Binding profile: pKi SSTR1 = 7.9, SSTR2 = 7.6, SSTR3 = 9.2, SSTR4 = 6.5, SSTR5 = 9.7



HTL30310 is the First SSTR agonist showing a significant selectivity for SSTR5 over 2 to be studied in the clinic

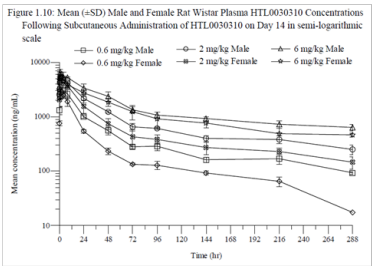
Data is binding affinity in house and literature

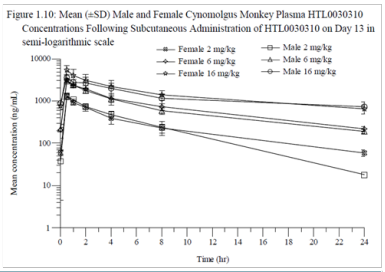
HTL '310 ADME Profile

Bioavailability	• SC: 50-100%; • Oral: <1%
Distribution	• High Plasma protein binding (> 98%) • Low CSF penetration (< 1%)
Metabolism	• Low clearance (≤ 13% of liver blood flow) • Likely no CYP-mediated metabolism ; no putative metabolites detected
Excretion	• Elimination of unchanged HTL0030310 in urine and faeces low (< 5%) except in bile duct cannulated rat (45% in bile and 1.3% in urine) • Good to moderate T1/2 across species
DDI Potential	• Reversible CYP3A4 inhibitor (IC50: 8 µM)

Source: Investigator's Brochure, Version 1.0, dated 29 October 2018

Multiple Dose (14 Day) TK by SC Injection in Rat and NHP





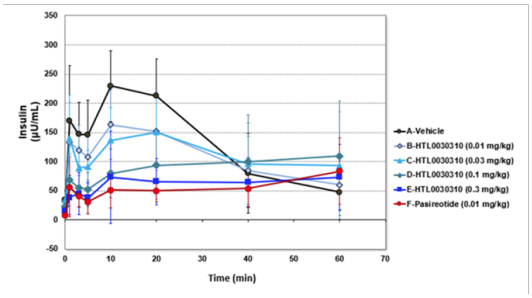
DAY 14 - RAT		Dose Level (mg/kg/day)					
Parameters		0.6 Male	0.6 Female	2.0 Male	2.0 Female	6.0 Male	6.0 Female
t½	h	141	139	163	145	250	154

DAY 14 - NHP		Dose Level (mg/kg/day)					
Parameters		2 Male	2 Female	6 Male	6 Female	16 Male	16 Female
t½ (to 24h)	h	4.91	7.69	8.14	8.87	n/c	8.70
t½ (24–144h)	h	n/d	n/d	n/d	n/d	72.5	55.9

HTL '310 Preclinical Efficacy

Monkey IVGTT

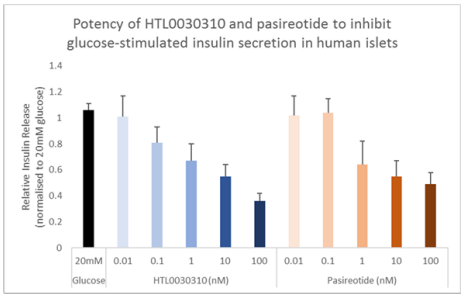
Mean Insulin Concentration Profile following IVGTT



Predicted Receptor Occupancy (%) at Cmax

PASIREOTIDE	SSTR5	SSTR2	SSTR3
0.01 mg / kg	95	90	94
HTL0030310	**SSTR5**	**SSTR2**	**SSTR3**
0.01 mg / kg	95	3	51
0.03 mg / kg	98	10	78
0.1 mg / kg	100	31	94
0.3 mg/ kg	100	51	97

Human isolated pancreas islets



- Control of glucose homeostasis has been demonstrated to be affected by HTL'310 in vitro and in vivo acting predominantly via the SST5 receptor
- These and other data supported initiation of a First Time in Human study designed to explore effects on glucose, insulin and counter-regulatory hormones

HTL '310 Phase 1 Study

- First in Human study to assess the safety, tolerability, PK and PD of HTL0030310 has completed (NCT03847207)
- Study concluded early with clear evidence of elevation of glucose at low and well tolerated doses