Project Plan : **TGR5 agonist program**

Product Profile: **hypoglycemic (*% effect to be defined*)** **ameliorate lipid profile (*lower TG, % effect to be defined*)** **reduced body weight gain (*% effect to be defined*)** **once daily oral dosing**		
Lead optimization	**1.1 Stable CHO-TGR5** activity at 10µM >50% LCA	**LISP**
	1.2 TTA h/m TGR5 EC50 <500nM; > 50% LCA **TTA h/m Gal4 FXR** EC50 > 10 µM	**BSP (with help of LISP)**
	1.3 Solubility Fassif > 10 µM **Log D Chi** Log D Chi 2>x< 5 **Microsomal stability** >10min/mg	**Chembridge & LISP**
	1.4 Cytotoxicity MTT/ATP HepG2, CaCo-2 No cytoxicity at 10 µM	**LISP**
	CYP450 inhibition CYP3A4, CYP2D6, CYP2C9 @ 10 µM < 20%	**Subcontract**
	1.5 In vitro efficacy assay(s) : **GLP1 secretion (STC1 intestinal cells)** **0_2 consumption Seahorse (C2C12 muscle cells)** **Mitochondrial enzyme (C2C12 muscle cells)**	**LISP**
In vivo validation (1)	**2.1 Simplified mouse pK :** p.o. 10, 50 mpk Cmax > 2 µM	
	2.2 HFD mouse 2 weeks treatment, Gene expression, plasma levels	**LISP & CPG**
	2.3 HFD (or ob/ob ?) 8-10 weeks, dose response curve (3 doses) Plasma levels Gene expression Body composition (qNMR) Metabolic performances OGTT	**LISP & CPG**
	Project team decision point : 4 lead candidates to be selected	
Development candidate selection	**2.4 Rat pK p.o. & i.v. 10, 50 mpk** T1/2 > 1.5 h Cmax > 2 µM; Cl < 0.5 hepatic blood flow; F% > 20	**Subcontract**
	2.5 Plasma protein binding	**Subcontract**
	2.6 non-GLP AMES **non-GLP mouse lymphoma** **non-GLP hERG** **CYP inhibition hu. Microsomes** <20 at 10µM **NovaScreen Receptogram**	**Subcontract**
	2.7 Dog pK p.o. i.v. 10, 50 mpk T1/2 > 1.5 h Cmax > 2 µM; Cl < 0.5 hepatic blood flow; F% > 20	**Subcontract**
	2.8 Rat 7 day toxicology No adverse effect(s) at 20x pharmacological dose	**Subcontract**