CVI-2742, a liver-directed and potent THR-β selective agonist, demonstrates strong efficacies in reducing plasma cholesterol and hepatic lipids with desirable tissue distribution

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PREMISE

- Selective activation of thyroid hormone receptor-beta (THR-β) in liver tissue ameliorates NASH symptoms without causing cardiac abnormalities mediated by THR-α activation.
- A liver-targeted selective THR-β agonist with low exposures in non-hepatic tissues will further reduce side effects and improve safety in patients.
- Applying a two-step new screening method that combines THR mediated reporter activation assay and active membrane transporter assay we have discovered a series of novel compounds including the preclinical candidate compound CVI-2742 that are liver-directed and potent THR-β selective agonists with EC_{50} in low nmol concentrations.
- Here we demonstrate the potency and liver-selectivity of CVI-2742 in biochemical assays and its in vivo efficacy and tissue distribution in hyperlipidemic mouse model and rat model.

METHODS

- Potency and selectivity of CVI-2742 in activation of THR were assessed biochemically using THR-β or THR-α/RXR heterodimeric assays (reference 1).
- TRE-Luc reporter gene assay (reference 2) was performed in the presence of control plasmid (empty vector, CON) or plasmid SLC encoding a human liver transporter.
- Quantitative RT-PCR was performed to measure mRNA levels of ANGPTL4 and ABCD2 in human liver cell line Huh7 treated with different doses of CVI-2742 or MGL-3196 for 24 hours.
- Male rats (3 animals/time point) were dosed with 9 mg/kg CVI-2742 via oral gavage. Plasma and tissues were collected at the indicated time points and CVI-2742 levels were quantified via LC-MS/MS method.
- Male mice (3 animals/time point) were dosed with 5 mg/kg of CVI-2742 or MGL-3196 via oral gavage. Plasma and liver tissue were collected at the indicated time points. CVI-2742 and MGL-3196 levels were quantified via LC-MS/MS method.
- C57BL/6 mice fed a diet containing high fat and high cholesterol for 4 weeks received vehicle (n=5), MGL-3196 (5 mg/kg, n=5) or CVI-2742 (0.5 mg/kg and 5 mg/kg, 6/dose) for 10 days via oral gavage once a day. Serum TC and LDL-C were measured at baseline and Day 11. Terminal liver and heart samples were collected for gene expression analysis by quantitative RT-PCR.
- Thirty-six SD rats (18 rats/sex) were randomly divided into 6 dose groups (3 rats/sex/group) of 0 mg/kg (blank control group), 0 mg/kg (vehicle control group), and 2.5 mg/kg (low dose group), 5 mg/kg (medium dose group), 10 mg/kg (high dose group) and 15 mg/kg (very high dose group) of CVI-2742. Each group of animals was orally administered with a volume of 10 mL/kg once a day for 14 consecutive days for a preliminary toxicity study.

REFERENCES

1. Kelly M. J. et al. J. Med. Chem. 2014,57, 3912-3923.
2. EASL-ILC2023-Poster FRI-505

CONTACT INFORMATION

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In Vitro Receptor Activation Study Results

Figure 1. CVI-2742 potency and selectivity assay with MGL-3196 and T3 as reference compounds.

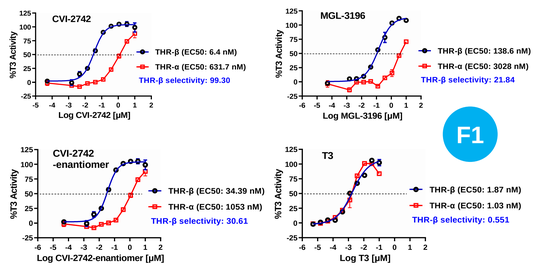
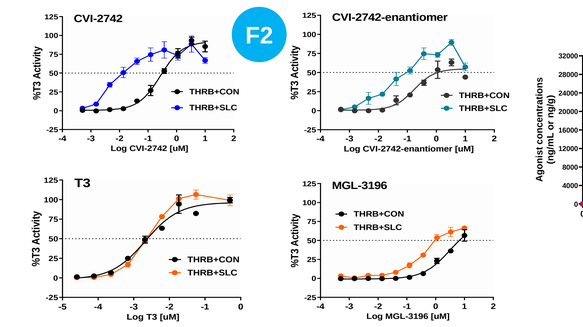


Table 1	THR-β EC_{50} (nM) mean ± SEM (n=3)	THR-α EC_{50} (nM) mean ± SEM (n=3)	THR-β-selectivity mean ± SEM (n=3)	Relative THR-β potency (fold of MGL-3196)
CVI-2742	8.4 ± 1.0	507.3 ± 79.8	64.5 ± 17.9	19.8
CVI-2742-enantiomer	41.1 ± 4.5	1290.0 ± 133	31.3 ± 0.86	4.0
MGL-3196	166.1 ± 15.1	3449.7 ± 270.5	21.0 ± 1.7	1.0

Data in Table 1 are derived from three independent assays.

CVI-2742 is a highly selective & extremely potent THR-β full agonist

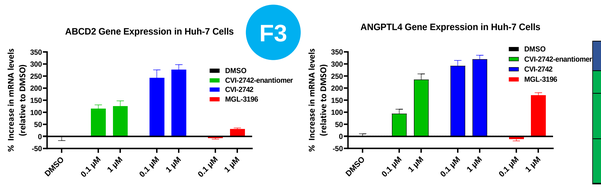
Figure 2. Stimulation of THR-β mediated reporter gene expression by agonists is differently enhanced by liver transporter.



HEK293 TRE-Luc reporter	THR-β + SLC EC_{50} (nM)	THR-β + CON EC_{50} (nM)	Activity enhancement (EC_{50} CON/EC_{50} SLC)
CVI-2742	48.2	507.7	10.5
CVI-2742-enantiomer	87.6	705.3	8.1
T3	7.4	5.6	0.8
MGL-3196	612.5	3665	6

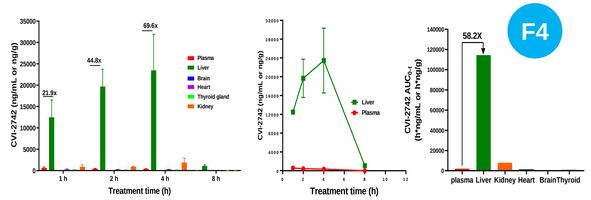
CVI-2742 is a liver-directed & potent THR-β full agonist

Figure 3. Strong induction of THR-β target gene expression in human liver cells by CVI-2742.



CVI-2742 Tissue Partition Study Results

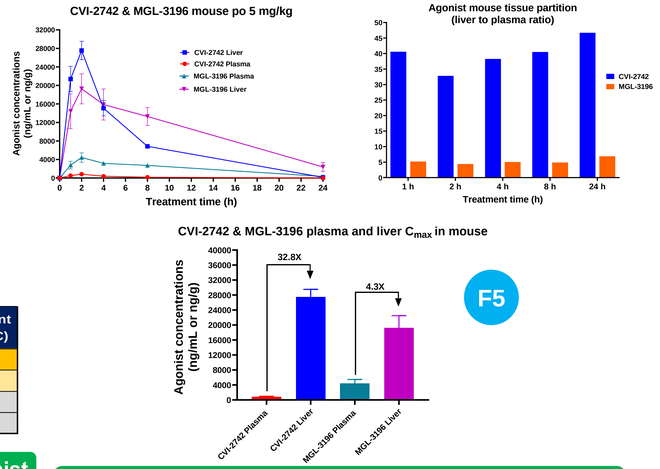
Figure 4. CVI-2742 tissue partition in rat model.



Samples	CVI-2742 tissue to plasma ratio				
	C_{max}	1 h	2 h	4 h	8 h
Plasma	1.00	1.00	1.00	1.00	1.00
Brain	0.04	0.04	0.03	0.02	0.39
Heart	0.44	0.44	0.55	0.69	0.79
Kidney	3.26	1.57	2.02	5.52	2.23
Liver	41.09	21.88	44.80	69.58	43.59

CVI-2742 is rapidly localized in the liver after oral administration with neglectable levels in other tissues

Figure 5. Tissue partition properties of CVI-2742 and MGL-3196 were examined in mouse model.
CVI-2742 (5 mg/kg) and MGL-3196 (5 mg/kg) were orally administered to ICR mice and samples of plasma and liver tissue were collected at the indicated time points (3 animals/time point). Data are mean ± SEM.



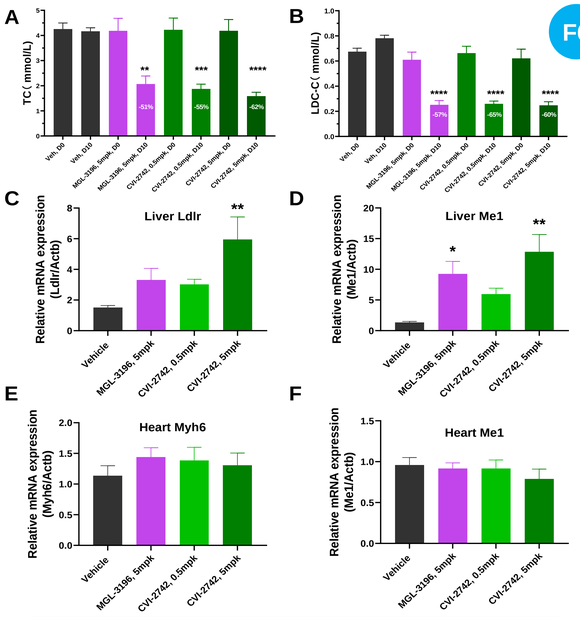
CVI-2742 is superior in liver targeting than MGL-3196 in mouse model

Table 2. CVI-2742 demonstrated consistent high liver penetration properties in preclinical animal models.

CVI-2742 Liver to Plasma Ratio							
Species	Samples	C_{max}	1 h	2 h	4 h	8 h	24 h
Rat	Plasma	1.00	1.00	1.00	1.00	1.00	NA
	Liver	41.09	21.88	44.80	69.58	43.59	NA
Mouse	Plasma	1.00	1.00	1.00	1.00	1.00	1.00
	Liver	40.63	40.63	32.78	38.19	40.45	46.66

CVI-2742 Efficacy and Safety Study Results

Figure 6. Reduction of plasma TC and LDL-C (A, B) and upregulation of THR-β target genes in the liver (C, D) without affecting cardiac THR-α regulated genes (E, F) in hyperlipidemic mouse model by CVI-2742 and MGL-3196. Data shown are mean ± SEM. *p < 0.05, **p<0.01, ***p<0.001, ****p < 0.0001 vs Vehicle control; statistics determined by one-way ANOVA.



CVI-2742 minimal effective dose (MED) is 0.5 mg/kg in the mouse PD model

Table 3. CVI-2742 demonstrated a wide safety window of over 60-fold of efficacy MED dose in rat toxicity study. (–), not different from vehicle; MED, minimal effective dose in mouse PD study.

Items	Placebo	Vehicle	Low dose 2.5 mg/kg 10x MED	Medium dose 5 mg/kg 20x MED	High dose 10 mg/kg 40x MED	Very high dose 15 mg/kg 60x MED
Blood Biochemical						
ALT	–	–	–	–	–	–
AST	–	–	–	–	–	–
ALP	–	–	–	–	–	–
Glucose	–	–	–	–	–	–
TSH	–	–	–	–	–	–
Weight						
Body weight gain	–	–	–	–	–	–
Brain index	–	–	–	–	–	–
Heart index	–	–	–	–	–	–
Liver index	–	–	–	–	–	–
Kidney index	–	–	–	–	–	–
Food intake	–	–	–	–	–	–

Conclusions

- **CVI-2742 is a liver-directed and highly selective THR-β new generation agonist with a broad safety window and high potency.**
- **CVI-2742 is currently undergoing IND enabling studies and planed for human Phase 1 clinical studies in 2024-H2.**

Disclosures: authors are employees in CVI Pharmaceuticals Limited.