Mo3209

Preliminary safety, pharmacokinetics, and lipid lowering effects of the liver-targeted liver X receptor (LXR) inverse agonist TLC-2716 in healthy volunteers

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Introduction

Liver X Receptor (LXR) Pathway

- LXR, a nuclear hormone receptor, regulates *de novo* lipogenesis (DNL) and maintains cholesterol homeostasis by regulating absorption, uptake, synthesis, metabolism, excretion, and reverse transport[1-4]
- Systemic LXR agonism (eg, with BMS-852927) enhanced reverse cholesterol transport (RCT) but increased hepatic and plasma triglycerides (TG), LDL-C, apolipoprotein B (apoB), and CETP, and reduced neutrophils[5]
- LXR inhibition in liver and intestine has potential to reduce hepatic steatosis and plasma TG and LDL-C via multiple mechanisms,[6] including inhibition of DNL, enhanced clearance of TG and cholesterol-rich lipoproteins (via ANGPTL3, apoC3),[7] and reduced intestinal lipid absorption[8-10]

TLC-2716 is a Potent, Liver-Targeted, LXR Inverse Agonist

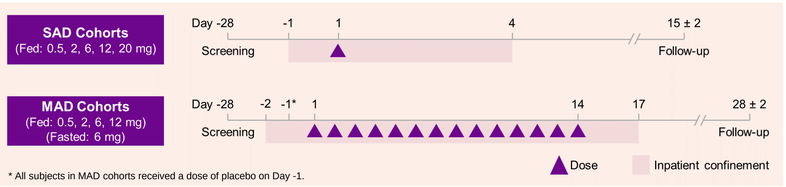
- TLC-2716 is a potent inhibitor of both LXRα and LXRβ (EC_{50} = 7 to 15 nM)[7]
- High hepatic extraction mediated by OATP and NTCP transporters leads to liver targeting and reduces maximal plasma concentrations preventing inhibition of peripheral RCT[7]
- In preclinical models, TLC-2716 caused marked reductions in liver and plasma TG and plasma cholesterol[7]
- TLC-2716 is in development for the treatment of severe hypertriglyceridemia (SHTG) and nonalcoholic steatohepatitis (NASH)

Objectives

- To evaluate the safety, tolerability, and pharmacokinetics (PK) of single and multiple ascending doses of TLC-2716 in healthy subjects
- To evaluate the pharmacodynamic effects of LXR inhibition with TLC-2716, including changes in lipid parameters and impact on peripheral RCT
- To evaluate the effects of fasted vs. fed dosing on the PK profile of TLC-2716

Methods

Study Design



* All subjects in MAD cohorts received a dose of placebo on Day -1.

- Double-blind, placebo-controlled, SAD and MAD study in healthy subjects (NCT05483998)
  - Age 18–55 years; body mass index (BMI) 19–35 kg/m^2; no significant medical conditions
  - Within each MAD cohort, attempts made to enrich for ≥3 subjects with elevated TG and/or LDL-C
- For each cohort, 8 subjects were randomized to receive TLC-2716 and 2 to receive placebo
  - Single doses of 0.5, 2, 6, 12, and 20 mg administered fed were evaluated in SAD cohorts
  - Once-daily doses of 0.5, 2, 6, and 12 mg (all fed) and 6 mg (fasted) for 14 days were evaluated in MAD cohorts
- Safety and tolerability assessments, including adverse event (AE) monitoring, laboratory tests, physical examinations, and ECG evaluations were performed throughout the study
- Intensive PK sampling over 72 h postdose on Day 1 (SAD and MAD) and Day 14 (MAD)
  - TLC-2716 plasma concentrations determined using validated liquid chromatography-tandem mass spectrometry assay
  - PK parameters estimated via noncompartmental methods using Pheonix® WinNonlin® 6.2.1 and 8.3.4 (Certara, LP, Princeton, NJ)
- Lipid parameters, including apoB, evaluated by NMR LipoProfile® (Labcorp, Burlington, NC)
- Plasma apoC3 and ANGPTL3 evaluated by ELISA (360biolabs, Melbourne, Australia)
- Peripheral RCT evaluated by assessing changes in expression of *ABCA1*/*ABCG1* in PBMCs, predose and 4 hours postdose on Day 14 (Gnomix, Bedford Park, Australia)

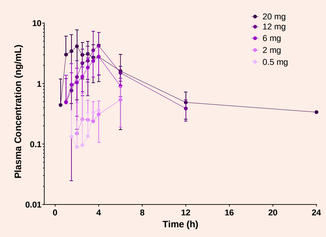
Results

SAD Subject Enrollment and Demographics

	0.5 mg: n=8	2 mg: n=8	6 mg: n=8	12 mg: n=8	20 mg: n=8	Placebo: n=10
Age, y	38 (18, 48)	30 (18, 48)	33 (24, 47)	33 (21, 48)	31 (20, 53)	40 (21, 50)
Male	3 (38)	1 (13)	3 (38)	2 (25)	4 (50)	4 (40)
BMI, kg/m^2	25.1 (19.5, 32.2)	24.7 (21.5, 28.3)	28.0 (20.2, 34.0)	30.2 (22.4, 34.5)	24.8 (19.9, 32.2)	25.8 (21.7, 35.0)

Data are median (min, max) or n (%).

SAD Concentration Time Profiles on Day 1



	0.5 mg: n=8	2 mg: n=8	6 mg: n=8	12 mg: n=8	20 mg: n=8
AUC_{inf} (h·ng/mL)	1.2 (n=1)	8.5 (107.5) (n=3)	10.0 (17.5) (n=8)	17.1 (32.5) (n=8)	20.6 (40.7) (n=8)
C_{max} (ng/mL)	0.37 (7.7) (n=3)	0.54 (56.4) (n=8)	3.33 (28.5) (n=8)	4.69 (76.5) (n=8)	6.79 (42.8) (n=8)
T_{max} (h)	3.5 (1.5, 4.0) (n=3)	3.75 (2.5, 6.0) (n=8)	4.0 (1.5, 4.1) (n=8)	3.0 (1.0, 4.0) (n=8)	2.5 (1.0, 6.0) (n=8)
$t_{1/2}$ (h)	2.10 (n=1)	4.96 (1.38, 30.49) (n=3)	1.37 (0.74, 2.76) (n=8)	2.02 (1.45, 4.18) (n=8)	2.36 (1.09, 6.55) (n=8)

PK parameters presented as mean (%CV) except $t_{1/2}$ and T_{max}, which are presented as median (min, max). Number of subjects with calculable PK parameter indicated in parentheses. Blank cells indicate parameter could not be calculated due to low systemic exposures of TLC-2716.

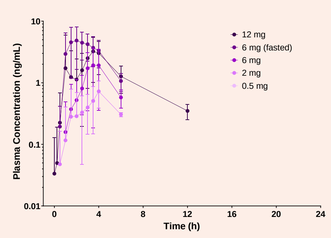
- TLC-2716 was rapidly absorbed, with T_{max} occurring ~3 to 4 hours postdose
- Short $t_{1/2}$ (~2 to 3 hours) and low maximal plasma concentrations consistent with rapid hepatic uptake
- Less than dose-proportional increases in plasma exposure

MAD Subject Enrollment and Demographics

	0.5 mg: n=8	2 mg: n=8	6 mg: n=8	6 mg (fasted): n=8	12 mg: n=8	Placebo: n=10
Age, y	28 (21, 36)	26 (19, 30)	33 (26, 54)	28 (20, 53)	29 (19, 49)	26 (20, 43)
Male	4 (50)	6 (75)	7 (88)	8 (100)	6 (75)	8 (80)
BMI, kg/m^2	25.4 (19.2, 34.5)	23.7 (19.9, 26.6)	24.2 (19.5, 31.4)	21.9 (19.8, 25.8)	23.2 (20.3, 34.6)	24.5 (19.8, 30.1)
TG, mmol/L	0.8 (0.5, 1.2)	1.05 (0.5, 3.0)	1.45 (0.6, 2.3)	0.95 (0.8, 1.5)	0.85 (0.5, 1.3)	1.1 (0.5, 1.8)
Total cholesterol, mmol/L	4.35 (2.7, 5.2)	4.65 (3.7, 5.4)	4.8 (3.4, 5.9)	4.55 (3.3, 5.5)	4.05 (3.3, 5.1)	4.5 (3.2, 5.7)
LDL-C, mmol/L	2.4 (1.2, 3.4)	2.8 (2.1, 3.7)	2.75 (1.8, 4.2)	2.45 (1.5, 3.9)	2.2 (1.6, 3.3)	2.75 (1.6, 4.0)
HDL-C, mmol/L	1.32 (0.79, 2.16)	1.30 (0.83, 1.54)	1.29 (0.79, 1.57)	1.63 (0.97, 2.17)	1.44 (0.88, 2.00)	1.30 (0.93, 1.95)

Data are median (min, max) or n (%). Lipid parameters measured by routine chemistry predose on Day 1.

MAD Plasma Concentration Time Profiles on Day 14



	0.5 mg: n=8	2 mg: n=8	6 mg: n=8	6 mg (fasted): n=8	12 mg: n=8
AUC_{tau} (h·ng/mL)	--	2.7 (8.56) (n=4)	6.05 (43.15) (n=8)	19.0 (34.78) (n=7)	14.6 (28.01) (n=8)
C_{max} (ng/mL)	--	0.95 (20.6) (n=6)	2.16 (75.0) (n=8)	6.37 (44.3) (n=7)	4.85 (72.6) (n=8)
T_{max} (h)	--	4.0 (1.0, 4.1) (n=6)	3.5 (1.5, 4.0) (n=8)	2.0 (1.0, 3.5) (n=7)	3.5 (1.0, 6.0) (n=8)
$t_{1/2}$ (h)	--	1.43 (1.06, 4.04) (n=4)	1.51 (0.52, 1.83) (n=8)	1.46 (1.09, 2.86) (n=7)	1.74 (0.92, 5.25) (n=8)

Unless indicated, study drug was administered in fed state. PK parameters presented as mean (%CV) except $t_{1/2}$ and T_{max}, which are presented as median (min, max). Number of subjects with calculable PK parameter indicated in parentheses.

- Mean TLC-2716 steady-state $t_{1/2}$ ranged from 1.4 to 2.6 hours
- TLC-2716 exposures increased less than dose proportionally and were 25-50% lower on Day 14 vs Day 1
- With fasted dosing, exposures were similar on Day 1 and 14 and ~3-fold higher than with fed dosing

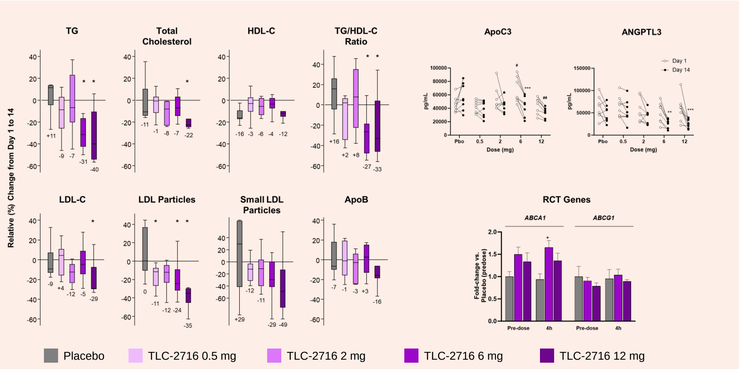
Safety and Tolerability

	0.5 mg: n=8	2 mg: n=8	6 mg: n=8	6 mg (fasted): n=8	12 mg: n=8	Placebo: n=10
Any TEAE	7 (88)	3 (38)	5 (63)	1 (13)	3 (38)	4 (40)
Diarrhea	2 (25)	0 (0)	1 (13)	0 (0)	2 (25)	1 (10)
Headache	1 (13)	0 (0)	1 (13)	0 (0)	2 (25)	2 (20)
Abdominal pain	1 (13)	0 (0)	1 (13)	1 (13)	1 (13)	0 (0)
Back pain	0 (0)	0 (0)	2 (25)	0 (0)	0 (0)	1 (10)
Pruritus	4 (50)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Grade ≥2 TEAE	0 (0)	1 (13)*	0 (0)	0 (0)	0 (0)	0 (0)
Treatment-related TEAE	0 (0)	0 (0)	1 (13)	0 (0)	2 (25)	1 (10)
TEAE leading to study drug discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Serious TEAE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Unless indicated, all doses were administered in fed state. TEAE, treatment-emergent AE. TEAEs reported by at least 3 subjects overall are listed by MedDRA Preferred Term.
* Grade 2 thrombophlebitis considered unrelated to study treatment.

- TLC-2716 0.5, 2, 6, and 12 mg for 14 days were well tolerated
- All TEAEs in the TLC-2716 cohorts were non-serious, and all but one were mild in severity
- Treatment-related TEAEs, all mild in severity and gastrointestinal in nature, occurred in 3 subjects treated with TLC-2716 (abdominal discomfort and diarrhea [6 mg fed; n=1]; abdominal pain and/or diarrhea [12 mg; n=2]) and 1 subject with placebo (nausea)
- No clinically significant changes in laboratory or ECG parameters or vital signs

TLC-2716 Causes Dose-Dependent Improvements in Lipids, ApoC3 and ANGPTL3, but Does Not Suppress Peripheral RCT



Figures above indicate median relative change in NMR LipoProfile® parameter from Day 1 to Day 14.
* p<0.05 for comparison of change from Day 1 vs. placebo by Mann-Whitney test. TLC-2716 6 mg fed and fasted groups combined (N=16); TLC-2716 0.5, 2, and 12 mg groups (N=8 each); pooled placebo group (N=10).

ApoC3 and ANGPTL3 measured 12h postdose. RCT assessed predose and 4h postdose on Day 14. * p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001 vs. Day 1; # p<0.05; ## p<0.01 vs. placebo on Day 1 or 14 by two-way ANOVA.

Conclusions

- Single and multiple daily doses of the liver-targeted LXR inverse agonist TLC-2716 for 14 days were safe and well tolerated in healthy subjects
- Liver-targeted pharmacology of TLC-2716 supported by its short half-life (~1.5-2.5 h), low systemic exposures, and lack of effect on expression of genes involved in peripheral RCT (ie, *ABCA1*, *ABCG1*)
- TLC-2716 caused significant, dose-dependent improvements in atherogenic lipids, including TG, total and LDL-C, LDL particles, and apoB, particularly in subjects with higher baseline values
- The tolerability, PK profile, and lipid lowering benefits of TLC-2716 support its further evaluation in patients with SHTG and NASH

References: 1. Janowski BA, et al. Nature 1996; 2. Janowski BA, et al. Proc Natl Acad Sci USA 1999; 3. Korach-André M, et al. BioMol Concepts 2015; 4. Yang CJG, et al. J Biol Chem 2006; 5. Kirchgessner TG, et al. Cell Metab 2016; 6. Griffett K, et al. Front Med 2023; 7. Vijayakumar A, et al. AASLD 2022 (Abstract #2352); 8. Hambruch E, et al. EASL 2017; 9. Hambruch E, et al. EASL 2018; 10. Griffett K, et al. ACS Chem Biol 2017.

Acknowledgements: We extend our thanks to all study subjects and participating investigators. This study was funded by OrsoBio, Inc.

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Presented at AHA's Scientific Sessions 2023, November 11-13, 2023, Philadelphia, PA