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Evaluation of the safety and pharmacokinetic effects of the oral, acetyl-CoA carboxylase-2 (ACC2) inhibitor TLC-3595 in healthy volunteers

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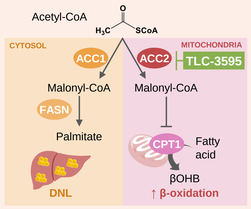
Introduction

ACC2 Inhibition to Increase Fatty Acid Oxidation

- ACC catalyzes the conversion of acetyl-CoA to malonyl-CoA[1]
- ACC1 is cytoplasmic and promotes DNL[1]
- ACC2 is mitochondrial and impacts FAO by regulating entry of fatty acids into mitochondria via CPT1[1]
  - ACC2 KO mice have increased FAO and energy expenditure, reduced ectopic lipid deposition in muscle and liver, and improved insulin sensitivity[2,3]



ACC, acetyl-CoA carboxylase; βOHB, β-hydroxybutyrate; CPT1, carnitine palmitoyltransferase 1; DNL, *de novo* lipogenesis; FAO, fatty acid oxidation; FASN, fatty acid synthase.

TLC-3595 is a Potent, Selective, Allosteric Inhibitor of ACC2

- TLC-3595 is 76-fold selective for ACC2 vs ACC1
  - Liabilities of ACC1 inhibition (e.g., thrombocytopenia, hypertriglyceridemia)[4,5] have not been observed with TLC-3595
- TLC-3595 increases FAO, reduces ectopic lipid in muscle and liver, and improves insulin sensitivity in dysmetabolic rodents[6]
- TLC-3595 is being evaluated for the treatment of type 2 diabetes and other disorders characterized by impaired FAO

ACC Inhibitor	IC_{50} (nM)		Selectivity ACC2 vs ACC1
	ACC1	ACC2	
Firsocostat (Gilead)[7]	2.1	6.1	0.3x
Clesacostat (Pfizer)[8]	13	9	1.4x
TLC-3595 (OrsoBio)[6]	**1039**	**13.7**	**76x**

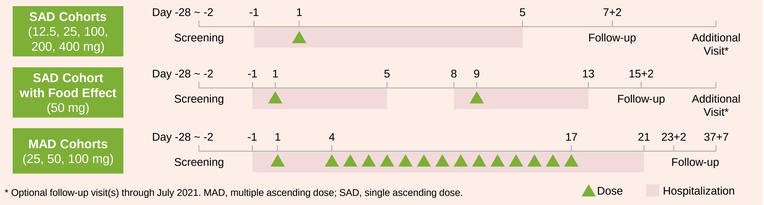
IC_{50}, half-maximal inhibitory concentration.

Objectives

- **Primary:** to evaluate the safety and tolerability of single and multiple ascending doses of TLC-3595 in healthy subjects
- **Secondary:** to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of TLC-3595 in healthy subjects following single and multiple ascending doses

Methods

Study Design



* Optional follow-up visit(s) through July 2021. MAD, multiple ascending dose; SAD, single ascending dose.

- Double-blind, placebo-controlled, SAD and MAD study in healthy, male, Japanese subjects
  - Age 20–55 years; body mass index (BMI) 18.5–30 kg/m^2
  - No significant medical conditions by history, physical examination, or laboratory evaluation
- For each cohort, 6–8 subjects were randomized to receive TLC-3595 and 2 to receive placebo
  - Single doses of 12.5, 25, 50, 100, 200, and 400 mg administered fasted were evaluated in SAD cohorts
  - Once daily doses of 25, 50, and 100 mg for 14 days were evaluated in MAD cohorts
  - The effect of food on TLC-3595 exposure was evaluated in the 50 mg SAD cohort dosed with TLC-3595 or placebo in the fed state (high-fat, high-calorie meal) in a crossover design
- Safety and tolerability assessments, including adverse event (AE) monitoring, clinical laboratory tests, physical examination, and electrocardiographic evaluations were performed throughout the study
- Intensive PK sampling over 72 h postdose on Day 1 (SAD and MAD) and Day 17 (Day 14 of dosing in MAD)
  - TLC-3595 plasma concentrations determined using validated liquid chromatography-tandem mass spectrometry assay
  - PK parameters estimated via noncompartmental methods using Phenix® WinNonlin® 6.2.1 and 8.3.4 (Certara, LP, Princeton, NJ) and summarized using descriptive statistics

Results

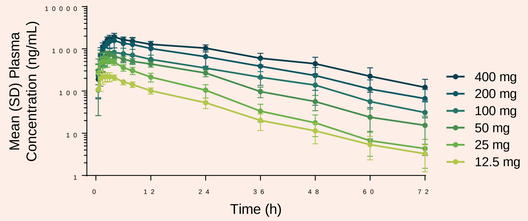
SAD Cohorts

Subject Enrollment and Demographics

	12.5 mg: n=6	25 mg: n=6	50 mg: n=8	100 mg: n=6	200 mg: n=6	400 mg: n=6	Placebo: n=12
Age, y	23.5 (21, 34)	25 (23, 36)	23 (20, 36)	25 (21, 37)	27.5 (20, 42)	29.5 (22, 39)	25 (21, 38)
Weight, kg	62.8 (51.2, 75.0)	57.2 (53.0, 72.8)	66.0 (55.2, 84.8)	60.9 (56.4, 75.6)	61.5 (51.9, 72.5)	66.7 (57.0, 72.2)	63.6 (53.5, 75.2)
BMI, kg/m^2	22.7 (18.5, 24.8)	20.1 (18.8, 24.0)	22.2 (18.8, 26.6)	21.3 (19.4, 26.4)	20.6 (20.0, 24.2)	22.7 (20.3, 27.7)	21.6 (19.1, 24.8)

Data are median (min, max).

Plasma Concentration Time Profiles on Day 1



PK Parameters

Parameter	12.5 mg: n=6	25 mg: n=6	50 mg: n=8	50 mg fed: n=6	100 mg: n=6	200 mg: n=6	400 mg: n=6
AUC_∞, h·ng/mL	3544 (21.0)	7240 (24.9)	14,380 (13.6)	15,730 (14.6)	20,320 (17.7)	35,170 (47.0)	54,300 (19.5)
C_{max}, ng/mL	257 (23.9)	553 (16.4)	771 (17.7)	811 (19.7)	805 (32.1)	1530 (32.0)	1950 (16.9)
T_{max}, h	2.0 (0.5, 4.0)	2.0 (1.0, 3.0)	2.5 (1.0, 4.0)	3.5 (2.0, 6.0)	5.0 (2.0, 6.0)	4.0 (2.5, 4.0)	4.0 (4.0, 6.0)
$t_{1/2}$, h	10.8 (17.7)	9.5 (12.8)	11.7 (20.2)	10.9 (13.2)	10.5 (23.5)	12.3 (28.4)	13.3 (20.5)

Unless indicated, TLC-3595 was administered in the fasted state. Data are geometric mean (CV% geometric mean), except for time to C_{max} (T_{max}), which is presented as median (min, max). AUC_∞, area under the concentration-time curve from time 0 to infinity; C_{max}, maximum concentration; $t_{1/2}$, half-life.

- TLC-3595 was rapidly absorbed, with median T_{max} occurring 2 to 5 h postdose
- Mean TLC-3595 $t_{1/2}$ ranged from 9.5 to 13.3 h
- Dose-dependent increase in TLC-3595 exposure up to 400 mg, with less than dose-proportional increases above 50 mg
- Administration of TLC-3595 50 mg with food did not affect TLC-3595 exposures
  - Geometric least squares mean ratios for AUC_∞ 1.10 (90% CI 1.06, 1.14) and C_{max} 1.04 (90% CI 0.92, 1.18)

MAD Cohorts

Subject Enrollment and Demographics

	25 mg: n=8	50 mg: n=8	100 mg: n=8	Placebo: n=12*
Age, y	31.5 (23, 39)	33.5 (20, 39)	26.5 (21, 34)	23 (22, 38)
Weight, kg	59.9 (51.3, 65.0)	62.6 (54.5, 80.1)	63.4 (53.1, 84.6)	66.1 (53.8, 82.8)
BMI, kg/m^2	20.7 (19.4, 23.3)	21.2 (18.7, 26.1)	23.0 (18.8, 24.4)	21.9 (20.0, 24.1)

Data are median (min, max).

Safety

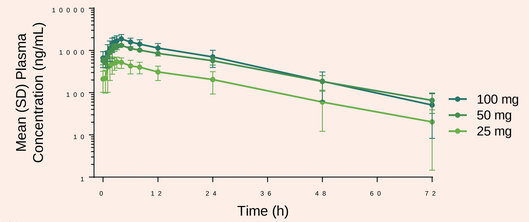
	25 mg: n=8	50 mg: n=8	100 mg: n=8	Placebo: n=12*
Any TEAE	2 (25)	3 (38)	3 (38)	4 (33)
Mild	2 (25)	3 (38)	3 (38)	3 (25)
Moderate or severe	0	0	0	1 (8)
Related TEAEs	2 (25)	0	2 (25)	3 (25)
Serious TEAEs	0	0	0	0
Treatment discontinuation due to TEAE	0	0	0	0

Data are n (%). TEAE, treatment-emergent AEs. *Placebo group includes 3 subjects from a separate drug-drug interaction cohort.

- TLC-3595 25, 50, and 100 mg for 14 d were well tolerated
- All TEAEs in the TLC-3595 cohorts were non-serious and mild in severity
- TEAE of increased ALT was reported in 25% in the placebo group (n=3), and 25% (n=2), 38% (n=3), and 0% in the TLC-3595 25, 50, and 100 mg cohorts, respectively
  - No symptoms or changes in bilirubin
- No other clinically significant laboratory abnormalities

MAD Cohorts

Plasma Concentration Time Profiles on Day 17



PK Parameters

Parameter	25 mg: n=8	50 mg: n=8	100 mg: n=8
AUC_{tau}, h·ng/mL	7547 (36.8)	20,430 (14.2)	26,690 (28.2)
AUC_{tau} accumulation ratio	1.45 (1.30, 1.61)	1.65 (1.48, 1.83)	1.56 (1.44, 1.69)
C_{max}, ng/mL	565 (31.7)	1330 (9.9)	1850 (23.1)
C_{max} accumulation ratio	1.36 (1.16, 1.59)	1.45 (1.34, 1.56)	1.46 (1.27, 1.67)
T_{max}, h	3.0 (1.0, 4.0)	3.5 (2.5, 4.0)	4.0 (3.0, 6.0)
$t_{1/2}$, h	14.2 (25.9)	17.4 (15.4)	13.8 (7.5)

Data are geometric mean (CV% geometric mean), except for T_{max}, which is presented as median (min, max), and accumulation ratios, which are presented as geometric mean ratios (90% CIs) comparing exposures on Day 17 and Day 1.

- TLC-3595 showed less than dose-proportional increase in exposure above 50 mg
- Mean TLC-3595 $t_{1/2}$ at steady-state ranged from 14 to 17 h
- In agreement with the $t_{1/2}$ and once-daily dosing, TLC-3595 exhibited modest accumulation of AUC_{tau} and C_{max}, ranging from 1.36 to 1.65-fold

Changes in Lipids and Platelets

Parameter	Time Point	25 mg: n=8	50 mg: n=8	100 mg: n=8	Placebo: n=9
Total cholesterol, mg/dL	Baseline	178.6 (31.1)	174.5 (26.4)	166.4 (30.4)	172.3 (35.5)
	End of treatment	151.0 (14.9)	151.1 (20.3)	138.4 (23.2)	169.4 (39.7)
	Change from baseline	-27.6 (31.4)	-23.4 (19.2)	-28.0 (11.5)	-2.9 (17.4)
	Relative (%) change from baseline	-13.2 (18.6)	-12.6 (10.6)	-16.4 (5.0)*	-1.8 (11.0)
LDL-C, mg/dL	Baseline	110.1 (25.5)	102.6 (25.5)	101.9 (20.5)	93.9 (29.1)
	End of treatment	83.5 (11.5)	80.5 (21.6)	77.0 (15.1)	94.9 (39.9)
	Change from baseline	-26.6 (15.9)	-22.1 (20.0)	-24.9 (7.9)	1.0 (15.7)
	Relative (%) change from baseline	-22.4 (10.7)*	-20.1 (18.4)	-24.1 (4.9)*	-2.3 (21.4)
Triglycerides, mg/dL	Baseline	77.1 (29.3)	119.0 (62.8)	108.6 (44.3)	73.9 (26.5)
	End of treatment	131.4 (107.3)	156.5 (79.2)	123.6 (41.7)	99.9 (36.1)
	Change from baseline	54.3 (99.7)	37.5 (49.3)	15.0 (28.5)	26.0 (28.9)
	Relative (%) change from baseline	67.9 (108.3)	44.4 (43.8)	18.8 (31.4)	42.3 (55.6)
Platelets, $10^3/\mu L$	Baseline	244.1 (34.3)	224.0 (35.0)	234.4 (40.8)	234.3 (36.5)
	End of treatment	247.1 (47.2)	226.1 (33.7)	219.4 (38.4)	244.6 (37.9)
	Change from baseline	3.0 (15.6)	2.1 (13.4)	-15.0 (12.8)	10.2 (16.1)
	Relative (%) change from baseline	0.7 (5.9)	1.2 (6.2)	-6.2 (6.2)*	4.6 (6.9)

Data are mean (SD). MAD dosing between Days 4 and 17; end of treatment laboratory values on Day 18. * p <0.05 vs. placebo based on t-test.

- Non-dose dependent reductions in plasma total and LDL cholesterol with TLC-3595 vs placebo
- No substantial differences in plasma triglycerides or platelets to suggest clinically relevant ACC1 inhibition

Conclusions

- Single and multiple daily doses of the selective ACC2 inhibitor TLC-3595 up to 100 mg/d for 14 days were safe and well tolerated in healthy subjects
- Selectivity of TLC-3595 for ACC2 over ACC1 supported by absence of significant changes in triglycerides or platelets
- The tolerability, PK profile, and biological activity of TLC-3595 support its further evaluation in patients with diabetes and other disorders characterized by impaired FAO

References: 1. Abu-Elheiga L, et al. PNAS 1995; 2. Choi SC, et al. PNAS 2007; 3. Takagi H, et al. Endocrinology 2018; 4. Kim CW, et al. Cell Metab 2017; 5. Huard K, et al. J Med Chem 2020; 6. Shionogi (data on file); 7. Harriman G, et al. PNAS 2016; 8. Ross TT, et al. Cell Mol Gastroenterol Hepatol 2020.

Disclosures: RS Huss, E Murakami, GM Subramanian, RP Myers: OrsoBio; T Ishibashi, H Tanioka, T Sonoyama: Shionogi.

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