223 A new approach to treat liver fibrosis with SERMs

Asset Overview

Product Type	Small molecule
Indication	Metabolic Diseases
Current Stage	Preclinical
Target(MoA)	Erβ agonist
Brief Description	Non-alcoholic steatohepatitis (NASH) is projected to affect over 18 million people annually by 2027 and is set to eclipse hepatitis B virus (HBV) as the leading cause of hepatocellular carcinoma. NASH is associated not only with liver cancer but also cirrhosis and multiple other chronic health complications. New selective estrogen receptor modulators (SERMs) selectively agonizing ERβ have been developed by researchers at The Ohio State University. These new compounds have the potential to meet the need for a truly effective drug in this new "epidemic" indication that has so far been nearly untreatable.
Organization	The Ohio State University

Differentiation

□ **Targeting ER-β in Non-Alcoholic SteatoHepatitis (NASH)**

- Selective ER-β agonists hold the promise of providing therapeutic efficacy with greatly reduced risks of ER-α-mediated side effects. ER-β activation could attenuate progression in multiple diseases including NASH, prostate cancer and glioblastoma
- Estrogens bound with ERb downregulate profibrotic genes, such as collagen and matrix metallopeptidases (MMPs), attenuating liver fibrosis

□ **New selective estrogen receptor modulators (SERMs) selectively agonizing ERβ**

- The high ERb selectivity: OSU'Lead compound (ERa EC50 = >30,000nM, ERb Ec50 = 44.9nM) – ERβ: ERα = >668:1
- The ERa/ERb selectivity is better than the competition (for example, LY500307)
- Reduction in liver fibrosis (approximately 42%) with ER-β agonist similar to other Phase II-III NASH agents (related to FGF21 and FXR)
- No observable toxicity at highest dose tested (300mpk in mice), No significant CYP inhibition issue was already confirmed. Good in vivo oral dose response, In vitro ADME completed, no major issues
- Non-steroidal ER-β agonists has high oral bioavailability. Novel non-steroidal pharmacophore, Strong IP position with ability to tune desired SERM activity on novel pharmacophore

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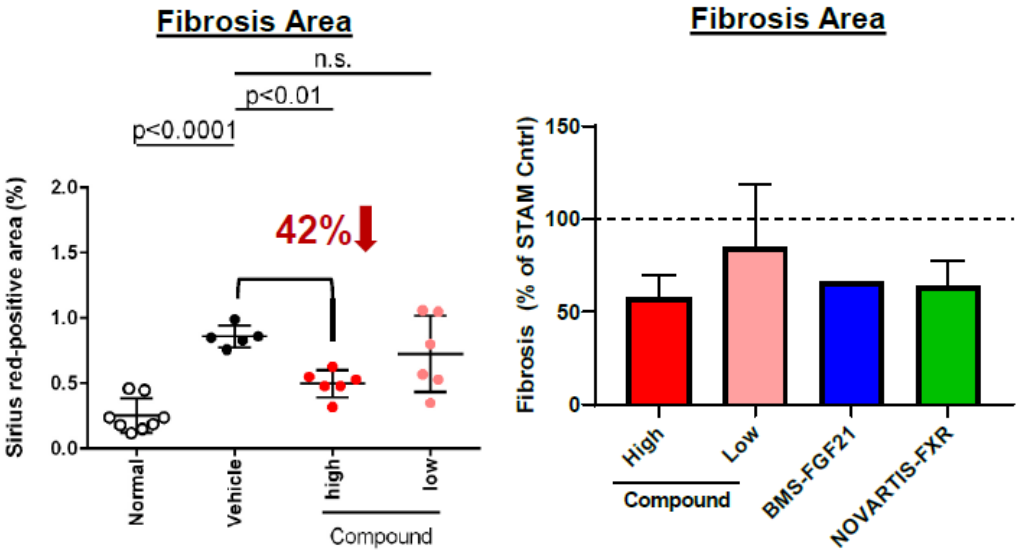
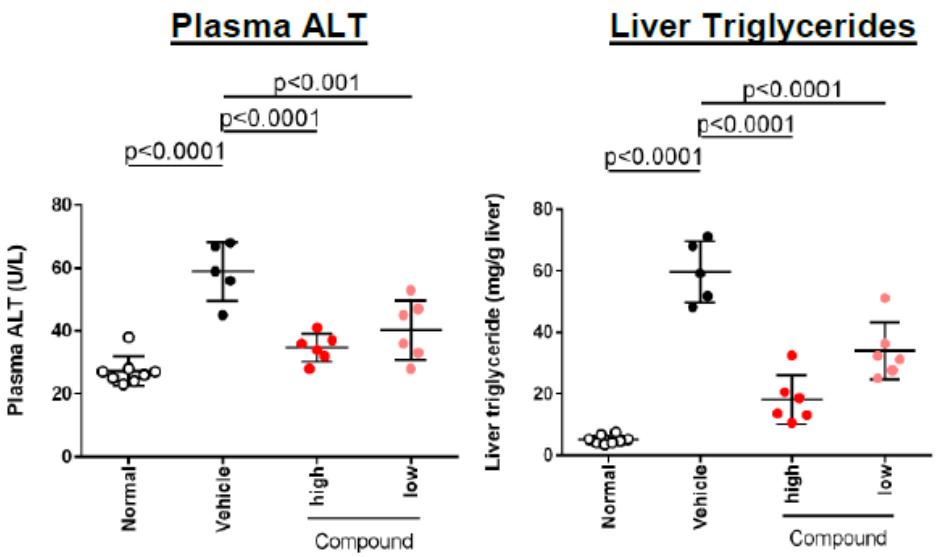
Key Data

Reduction in Fibrosis with ER-β Agonist



Reduction in fibrosis with ER-β agonist similar to other Phase II NASH agents. 42% reduction in fibrotic liver area for high dose group. High dose level significantly reduced fibrotic area with an anti-fibrotic effect similar to published STAM data for BMS-FGF21 and NOVARTIS-FXR.

Decrease in Liver Fibrosis



Following 7 Weeks of PO QD Treatment, Lead Erβ Agonist Demonstrates: Large dose dependent reductions in liver injury marker serum ALT. Large dose dependent reductions in liver triglycerides.

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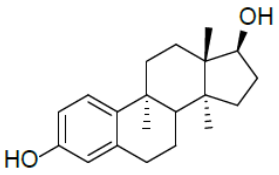
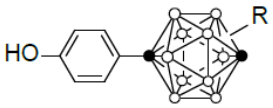
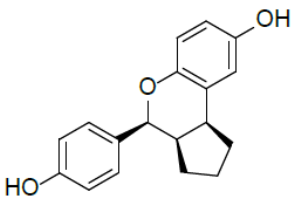
Comparison with other drug candidates



Estradiol (E2)



OSU's Lead*



LY500307

Molecule	ERα EC_{50}	ERβ EC_{50}	ERα/ERβ
E2	0.14 nM	0.075 nM	2.0
OSU's Lead	>30,000 nM	44.9 nM	>668
LY500307	346 nM	0.6 nM	577

Preclinical test

Mouse Acute Tox: No observable tox
(@ 200 mpk PO, highest dose given)

Mouse PK: (10 mg/kg, p.o.)
Plasma AUC = 122 uM-h
$T_{1/2}$ = 5.2 h, C_{max} = 22.0 uM
F = 92%, Brain / Plasma = 0.46

Dog PK: (10 mg/kg, p.o.)
Plasma AUC = 13.0 uM-h
$T_{1/2}$ = 39.8 h , C_{max} = 0.63 uM
F = 16.5%

Solubility:
Kinetic Solubility (pH 7.4) < 1 uM
Sim. Gastric Fluid (pH 1.2) < 1.56 uM
Sim. Intestinal Fluid (pH 6.8) <1.56 uM
Fed State SIF (pH 5.0 + oil) = 1770 uM
Fasted State SIF (pH 6.5) = 336 uM

hERG (Q-Patch): IC_{50} > 30 uM
Plasma Protein Binding: ≥ 99.9%
Caco-2 (Bidirectional): N/A*

Other Human Nuclear Receptors:
Following NHR's screened in agonist and antagonist mode:
AR, GR, PGR, MR, FXR, LXRα, LXRβ, ERRγ, PXR
No EC_{50} / IC_{50} < 10 uM

Microsomal Stability: Stable in human microsomes

Mouse:	$T_{1/2}$ = 47.7 min,	Cl_{int} = 29.1 uL/min/mg
Rat:	$T_{1/2}$ = 15.6 min,	Cl_{int} = 89.0 uL/min/mg
Monkey:	$T_{1/2}$ = 65.9 min,	Cl_{int} = 21.0 uL/min/mg
Human:	$T_{1/2}$ > 145 min,	Cl_{int} < 9.6 uL/min/mg
Dog:	$T_{1/2}$ > 145 min,	Cl_{int} < 9.6 uL/min/mg

CYP Inhibition: (IC_{50}) No significant issues

1A2: 53.2 uM	2B6: 6.3 uM
2B6: 16.3 uM	2C8: 48.4 uM
2C9: 68.8 uM	2C19: 13.1 uM
2D6: 63.5 uM	

3A4 (Testosterone): IC_{50} = 88.4 uM
3A4 (Midazalam): IC_{50} = 18.6 uM

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Intellectual Property

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Country	US, EP, JP, CN, AU, CA

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