METACRINE®

MET409: Optimized FXR Agonist with Best-in-Class Potential for NASH

3rd Global NASH Congress 2020

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FXR Pathway as a Compelling NASH Target

Clinical Studies with Liver Biopsy Results

Only mechanism to date showing both significant fibrosis improvement & NASH resolution in large-scale liver biopsy studies

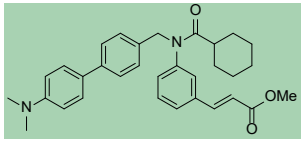
Target	Company	Fibrosis Improvement	NASH Resolution	Tolerability	Oral
FXR	Intercept	+	+	+/–	+
THR-beta	Madrigal	–	+	+	+
PPARα/δ	Genfit	–	+	+	+
PPARγ	Academia	–	+	+/–	+
ASK1	Gilead	–	–	+	+
ACC	Gilead	–	–	+/–	+
CCR2/5	Allergan	–	–	+	+
Caspase	Conatus	–	–	+	+
SCD1	Galmed	–	+	+	+
Galectin	Galectin	–	–	+	–
FGF19	NGM	+	–	+/–	–
LOXL2	Gilead	–	–	+	–

Source: Company websites and press releases, abstracts and peer reviewed publications

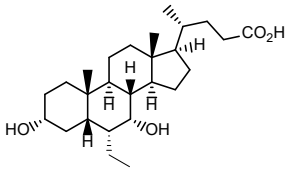
Metacrine FXR Program: >2,500 Purposefully Designed Candidates with Best-in-Class Potential

Unique, non-bile acid structure

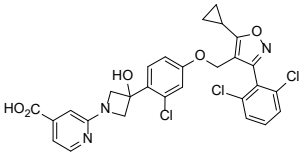
Metacrine's Unique Scaffold



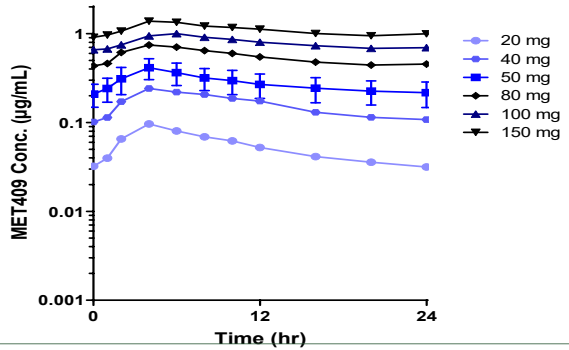
Bile Acid Derivatives (OCA, EDP-305)

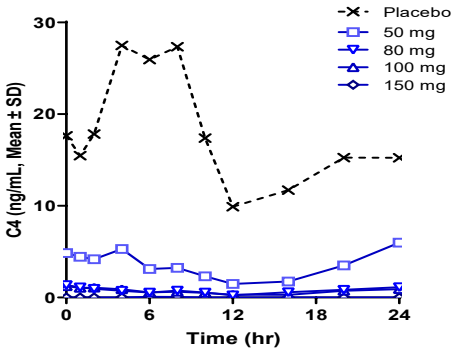


GW-4064 Derivatives (tropifexor, cilofexor)



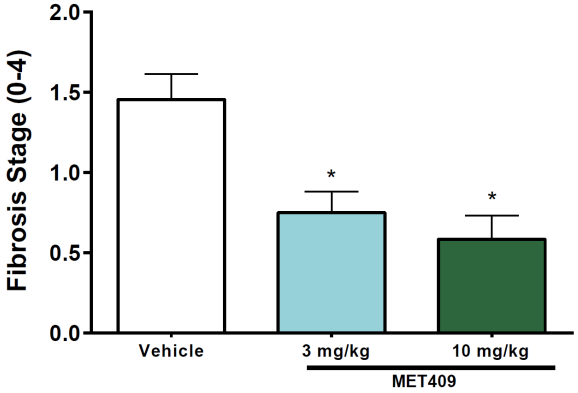
Sustained PK and PD profiles



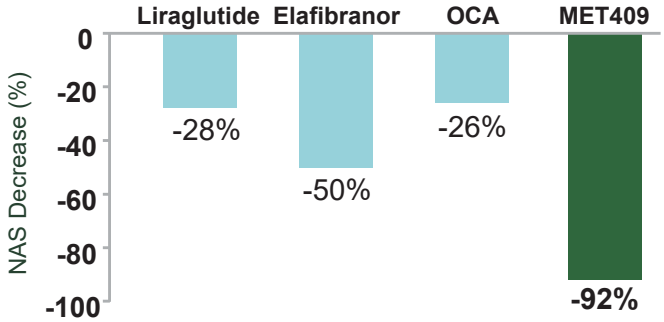


Metacrine FXR Program: Robust Preclinical Efficacy Results with MET409

Fibrosis improved in NASH model with Metacrine FXR agonist (MET409)



NASH resolution superior in NASH model with MET409 compared to other drugs



Sources: PS-105 EASL 2018 abstract,, Tølbøl KS et al. World J Gastroenterol. 2018 Jan 14;24(2):179-194;
*Studies were not conducted head-to-head with MET409 but performed by same contract research organization under the same protocol

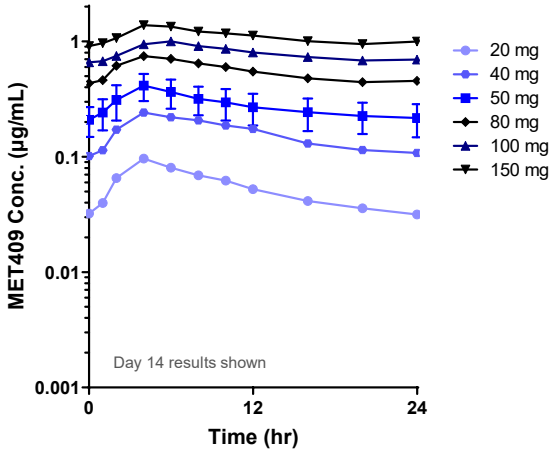
MET409 Phase 1 Study Results in Healthy Subjects

Sustained PK/PD and Tolerability Profiles Project a Wider Therapeutic Index

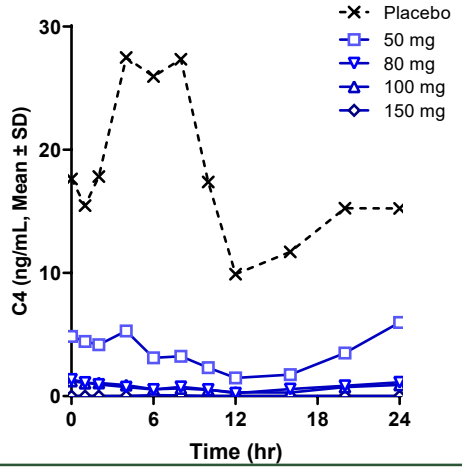
Sustained Drug Properties

- Evaluated in over 100 healthy subjects
- Oral daily dosing for 14 days (20→150mg)
- Sustained PK and target engagement over 24 hrs

Pharmacokinetics



Pharmacodynamics (C4)



Safety/Tolerability

- Well tolerated
- Pruritus
  - None through 80 mg
  - Mild pruritus at 100 mg and 150 mg; no interventions required
- Serum Cholesterol
  - On-target HDL cholesterol reductions
  - No material changes in LDL cholesterol

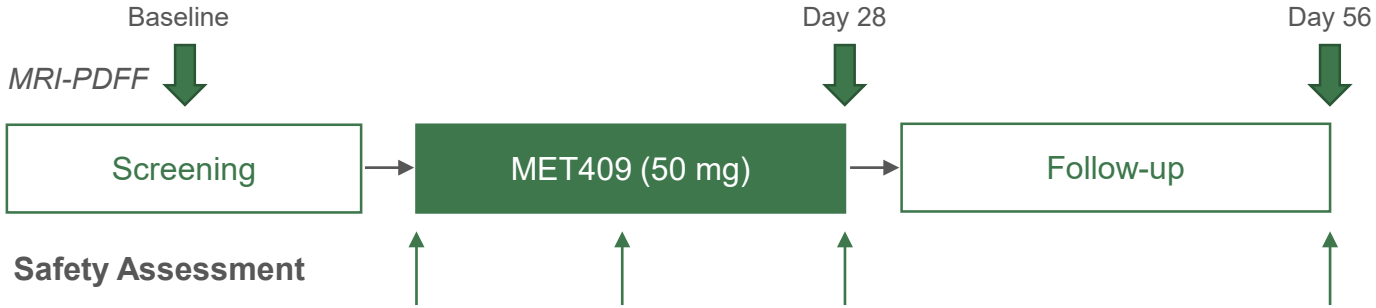
MET409 Proof-of-Concept Study in NASH Patients

Two-part evaluation of MET409 in NASH patients (biopsy-confirmed or liver stiffness ≥8.5 kPa on transient elastography) and liver fat content ≥ 10%

	Pilot	Main
Dose	50 mg	Placebo, 50 & 80 mg
Subjects	10	58
Design	Open-label, single-center	Randomized, multi-center, placebo-controlled
Treatment duration	4 weeks	12 weeks
Evaluation	Short-term safety/tolerability, liver fat content, liver enzymes	Longer-term safety/tolerability, liver fat content, liver enzymes
Status	Completed 2Q19	Completed 1Q20

MET409 Four-Week Pilot Study in NASH Patients

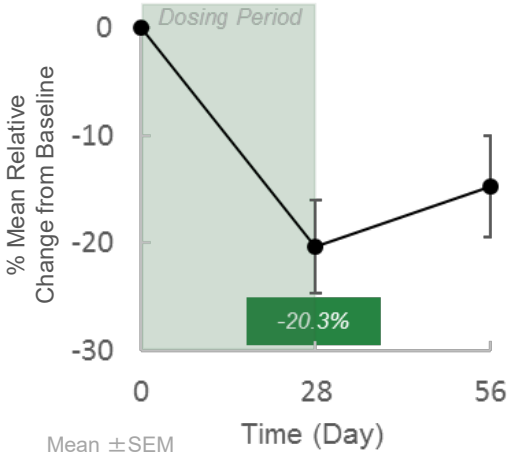
Open-label, single-center, 28-day treatment duration
10 patients evaluated with NASH (biopsy or imaging) and liver fat content ≥ 10%



- **No serious or severe adverse events**
- **No treatment-related adverse events above mild grade**
- **No pruritus reported after 4 weeks**

MET409 Pilot Study: Encouraging Magnitude of Relative Liver Fat Reduction after Only 4 Weeks of Treatment

Liver Fat Reduction after 28 Days of Dosing



Magnitude of Reduction Relative to Other FXR Agonists

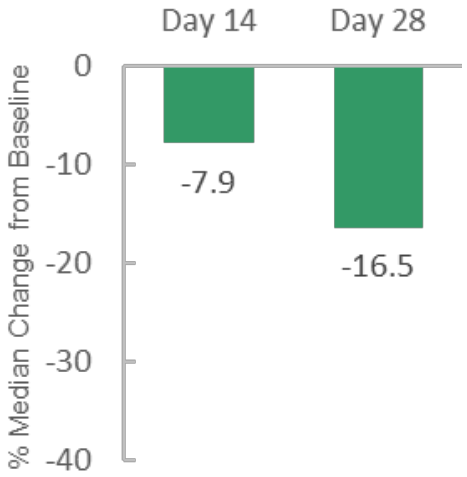
Candidate	Profile/ Structure	Treatment Duration	Relative Liver Fat Reduction
MET409 (Metacrine)	Sustained/ Non-bile acid	4 wks	20%
Obeticholic Acid (Intercept)	Sustained/ Bile acid	72 wks	17%*
Cilofexor (Gilead)	Transient, Non-bile acid	12 wks	8% (low dose) 16% (high dose)
Tropifexor (Novartis)	Transient, Non-bile acid	12 wks	7% (low dose) 17% (high dose)

*OCA is placebo subtracted

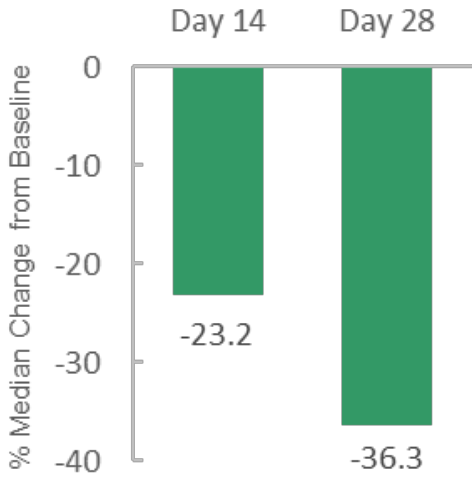
Source: AASLD 2018 abstracts, EASL 2019 abstracts, FLINT publications

MET409 Pilot Study: Time-Dependent Improvements in Liver Enzymes Consistent with Therapeutic Benefits

Alanine Aminotransferase (ALT)



Gamma-Glutamyl Transferase (GGT)



Positive MET409 Results from a 12-Week, Placebo-Controlled, Randomized Trial in NASH Patients

METACRINE

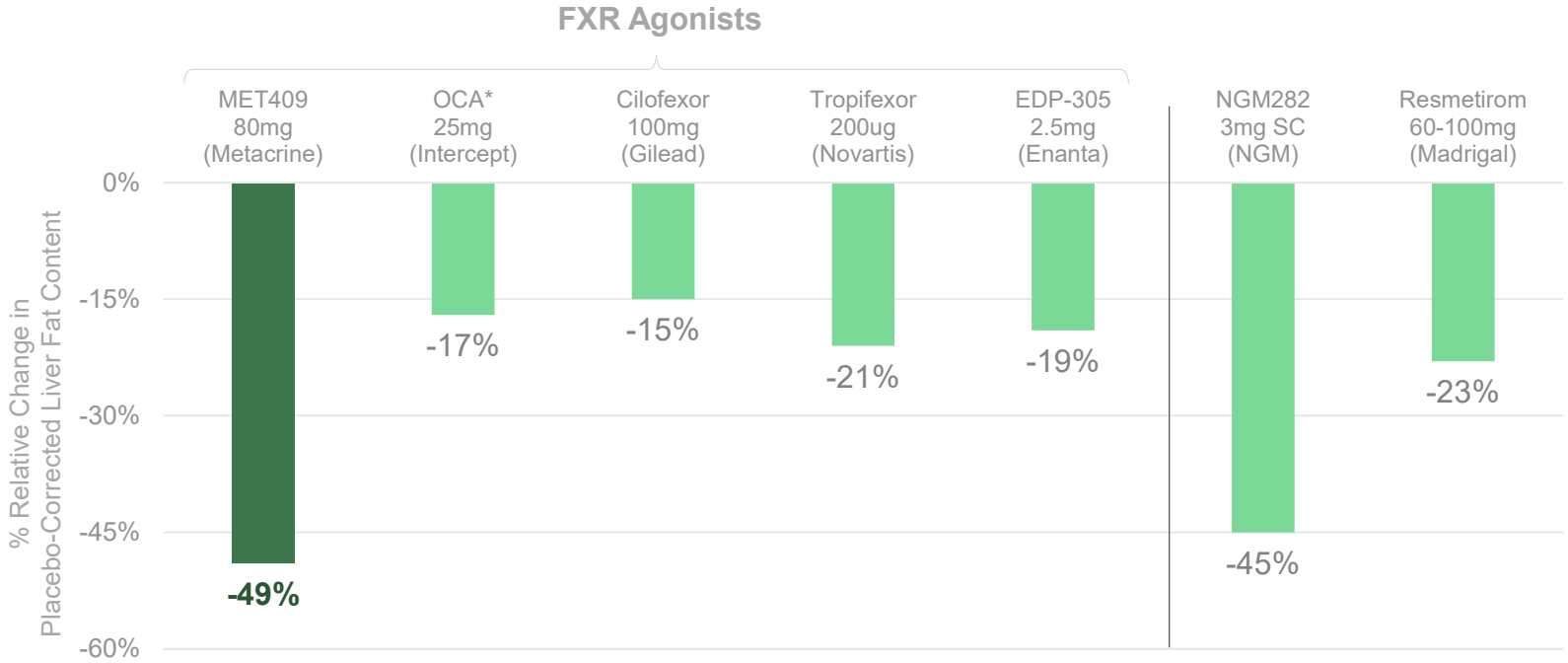
FOR IMMEDIATE RELEASE

Metacrine Demonstrates Best-in-Class FXR Drug Program with Positive Clinical Results in NASH Patients

- *Randomized, placebo-controlled 12-week study showed mean liver fat reduction of up to 55% with MET409*
- *93% of patients showed liver fat reduction of at least 30% from baseline*

SAN DIEGO, January 22, 2020 – Metacrine, Inc., a clinical-stage biotechnology company focused on building an innovative pipeline of best-in-class drugs to treat liver and gastrointestinal (GI) diseases, announced topline results from a 12-week, randomized, placebo-controlled study of MET409 in patients with non-alcoholic steatohepatitis (NASH). MET409 is a purposefully-designed farnesoid X receptor (FXR) agonist with two key features: non-bile acid chemical scaffold and sustained FXR activation.

Comparison of Placebo-Corrected Relative Liver Fat Reduction: Superior Efficacy of MET409 after 12 Weeks of Treatment



*Data at 72 weeks based on FLINT study

References: OCA (AASLD 2017, poster 2123), Cilofexor (AASLD 2018, poster 736), Tropifexor (AASLD 2019, late breaking oral 04), EDP-305 (Enanta Sept 25, 2019 presentation), NGM282 (SA Harrison et al. Lancet 2018 Mar 24), Resmetirom (SA Harrison et al. Lancet 2019 Nov 30)

MET409 Clinical Data: Favorable Efficacy and Tolerability Comparisons vs Other FXR Candidates

	MET409 50 mg	**MET409 80 mg**	**Intercept** OCA 25 mg	**Enanta** EDP-305 2.5 mg	**Gilead** Cilofexor 100 mg	**Novartis** Tropifexor 200 µg
Mean relative liver fat reduction	**38%**	**55%**	n/a	31%	15%	31%
Placebo-corrected mean liver fat reduction	**32%**	**49%**	17%* *(72wks)*	19%	15%	21%
Pruritus	**5% moderate** *(10% overall)*	**10% moderate** *(35% overall)*	20% ≥moderate *(30% overall)*	20% ≥moderate *(50% overall)*	15% ≥moderate *(n/a overall)*	20% ≥moderate *(53% overall)*

*Data at 72 weeks based on FLINT study

References: OCA (AASLD 2017, poster 2123; Lancet 2019), Cilofexor (AASLD 2018, poster 736), Tropifexor (AASLD 2019, late breaking oral 04), EDP-305 (Enanta Sept 25, 2019 presentation)