

Quantitative Systems Pharmacology Modeling of FGF19 Pathway Using NAFLDsym Prospectively Predicted Liver Fat and Serum Biomarker Responses to MET409 in NASH Patients



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BACKGROUND

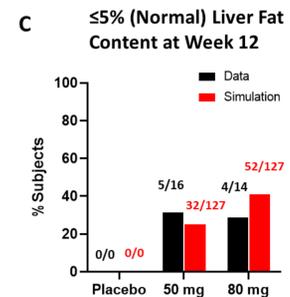
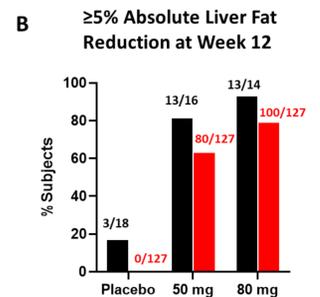
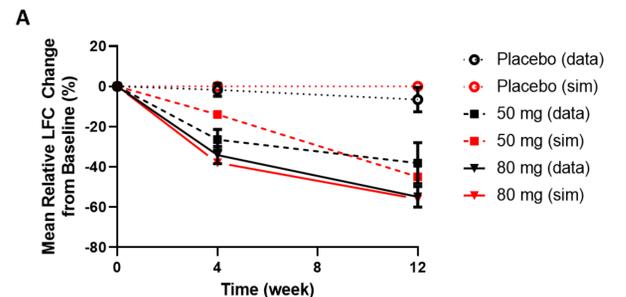
Treatment of nonalcoholic steatohepatitis (NASH) is a significant unmet medical need. In this work, therapeutic effects of MET409 via fibroblast growth factor 19 (FGF19) pathway were predicted in NASH patients using NAFLDsym, a quantitative systems pharmacology (QSP) modeling platform.

METHODS

- Representation of steatosis, lipotoxicity, inflammation, and fibrosis pathophysiology of NASH within NAFLDsym
- Representation and optimization of FGF19 PD effects within NAFLDsym using clinical data from tropifexor, cilofexor, and NGM282 studies [1]
- Prediction of liver fat and biomarker responses in NASH patients administered 50 and 80 mg QD MET409 for 12 weeks

RESULTS

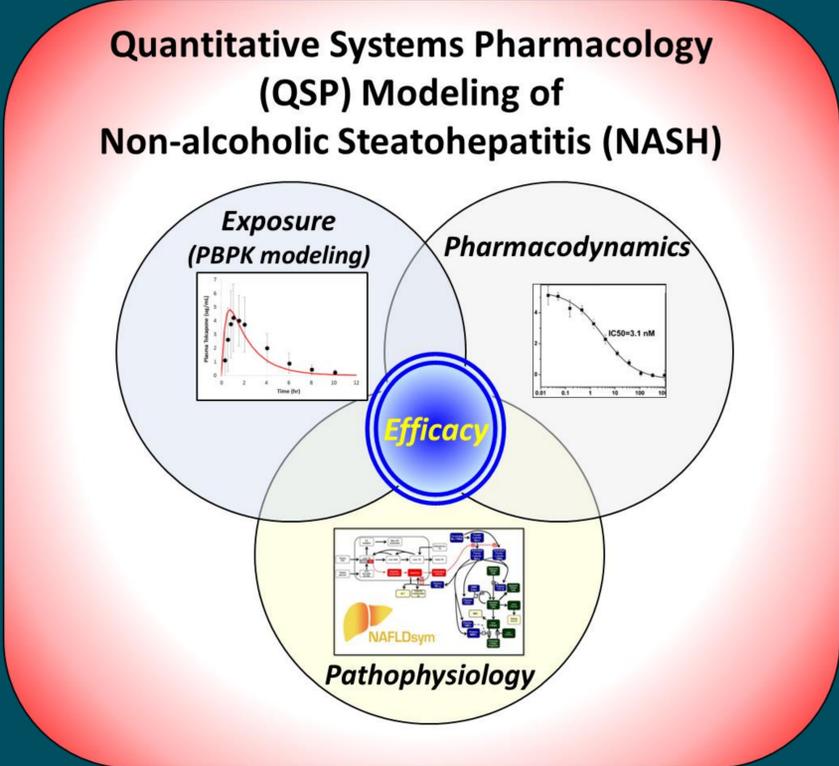
Simulations of clinical protocols of MET409 using NAFLDsym reasonably recapitulated observed liver fat and serum marker responses in NASH patients. [2]



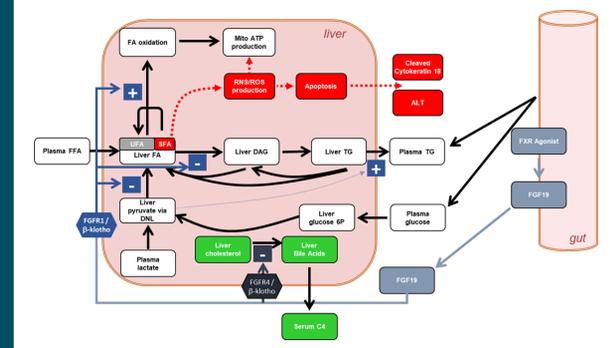
QSP modeling of MET409 leveraging known pathophysiology of NASH and FGF19-mediated PD pathways reasonably predicted efficacy outcomes in NASH patients.



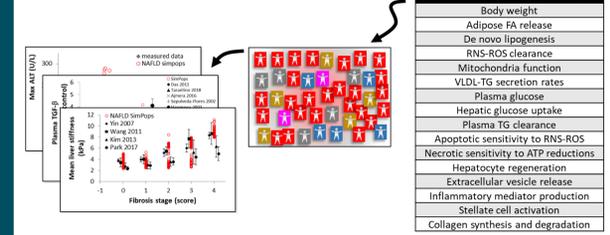
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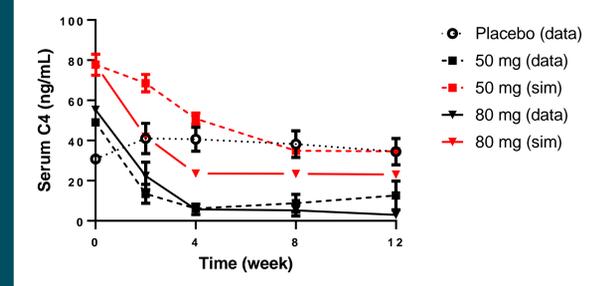
Representation of FGF19 effects in NAFLDsym.



Total 127 simulated patients (n=54 F2 patients and n=73 F3 patients) that represent variability across key areas of NASH pathophysiology were employed in simulations.



Simulations predicted serum C4 reduction by 71% and 95% at 50 mg and 80 mg MET409, respectively, generally consistent with clinical data (55% and 70%).



REFERENCES

- [1] Yang et al., AAPS PharmSci 360, 2021, Poster W7145V.
- [2] Harrison et al., J Hepatol, 2021, 75(1):25-33.

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