Quantitative Systems Pharmacology Modeling Using NAFLDsym Recapitulated Clinically Observed Histological Responses and Serum Markers to NGM282 in NASH Patients

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PURPOSE

Nonalcoholic steatohepatitis (NASH) is a growing clinical concern, but currently there is no approved medicine for treatment of NASH. Fibroblast growth factor 19 (FGF19) is an endocrine gastrointestinal hormone, which binds to hepatic FGF receptors (FGFR1 and FGFR4) and impacts multiple pathways relevant to NASH pathophysiology by altering lipid fluxes, lipotoxicity, and reducing hepatic inflammation. NGM282 is an engineered analogue of FGF19, which interacts with FGFR1 and FGFR4. In a clinical trial in patients with biopsy-confirmed NASH, administration of 1 mg or 3 mg NGM282 QD for 12 weeks significantly reduced nonalcoholic fatty liver disease score (NAS) and improved liver fibrosis stage.[1] In the current study, therapeutic effects of NGM282 were predicted using NAFLDsym®, a quantitative systems pharmacology (QSP) modeling platform that has been developed to predict efficacy for treatment modalities aimed towards treating NASH.

OBJECTIVE

- To develop mechanistic pathways representing FGF19 effects within NAFLDsym, and validate simulated pharmacological responses using NGM282 as an exemplar compound

METHODS

- Mathematical representation of numerous pathways important in the steatosis, lipotoxicity, inflammation, and fibrosis pathophysiology of NASH were previously developed within NAFLDsym v2A. [2-6]
- Mechanistic pathways representing FGF19 effects via hepatic FGFR1 and FGFR4 were added to NAFLDsym v2A (top left figure). [7-9]
- Mechanistic parameters of FGF19 effects were optimized to observed plasma FGF19 exposure-liver fat content response relationships from clinical studies of tropifexor, cilofexor, and NGM282, and then validated using clinical data from the MET409 study. [1,10-12] It was assumed that effects of FXR agonists were selective to gut FXR (induction of FGF19 synthesis), and direct liver effects via hepatic FXR was negligible (top right figure).
- To validate the simulated pharmacological effects mediated by FGF19, 12-week simulations of 1 mg and 3 mg NGM282 were performed using NAFLDsym by importing clinically observed plasma FGF19 profiles in patients administered NGM282. A simulated population (n=168) that includes variability in parameters representing NAFLD/NASH pathophysiology was employed (bottom figure).

RESULTS

- Simulated plasma FGF19 exposure-liver fat content responses reasonably recapitulated clinical data used for optimization and validation (top right figure).
- Simulations of NGM282 predicted decrease in plasma C4 (by 61% and 70% at 1 mg and 3 mg, respectively), plasma ALT (by 42% and 41%), and Pro-C3 (by 18% and 17%) at week 12, generally in agreement with clinically observed biomarker responses (decrease in plasma C4 by 76% and 93%, ALT by 67% and 60%, and Pro-C3 by 22% and 33%) (bottom figure A-C).
- Simulations generally recapitulated clinically observed NAS reduction at 12 weeks, although the magnitude of mean NAS reduction was slightly over-predicted (-3.7 and -3.4) compared to clinical data (-1.9 and -2.2) (bottom figure D).
- Simulations predicted a slight decrease in mean fibrosis stage (-0.2 and -0.3) and improvement of fibrosis in 23% and 27% of treated patients, consistent with clinical data (decrease in mean fibrosis stage by -0.1 and -0.5, fibrosis improvement in 25% and 47% of patients) (bottom figure E).
- Simulated percentages of histological responses were in agreement with clinical data (bottom figure F).

CONCLUSIONS

- Simulations of clinical protocols of NGM282 using NAFLDsym reasonably recapitulated observed serum marker and histological responses in NASH patients.
- QSP modeling leveraging known pathophysiologic characteristics of NASH, target-specific mechanistic pathways, and available preclinical and clinical data can be used to predict clinical outcomes of therapeutic agents.

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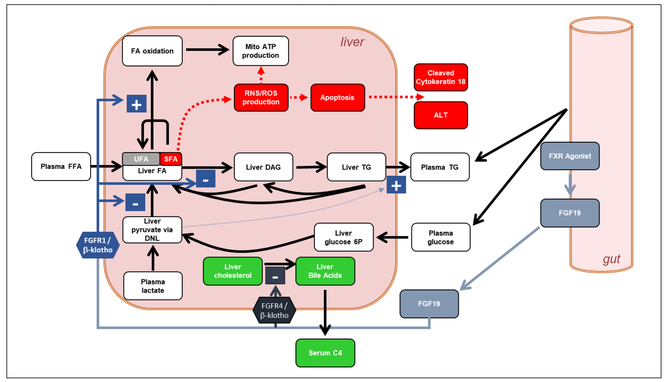
QSP modeling leveraging known pathophysiologic characteristics of NASH and FGF19 pathways recapitulated clinical responses to NGM282

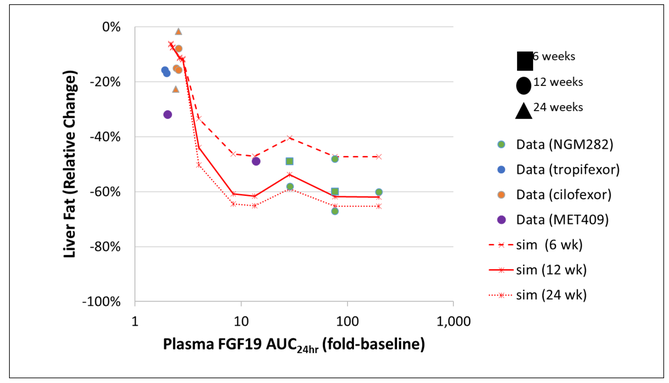
Mechanistic pathways representing FGF19 effects were added to NAFLDsym

FGF19 reduces expression and/or activity of Acetyl-CoA carboxylase, fatty acid synthase, glycerol-3-phosphate acyltransferase via FGFR1, leading to decrease in de novo lipogenesis and fatty acid esterification and increase in fatty acid oxidation and VLDL-TG secretion. FGF19 also reduces expression and/or activity of CYP7A1, a key enzyme involved in bile acid synthesis. [7-9]



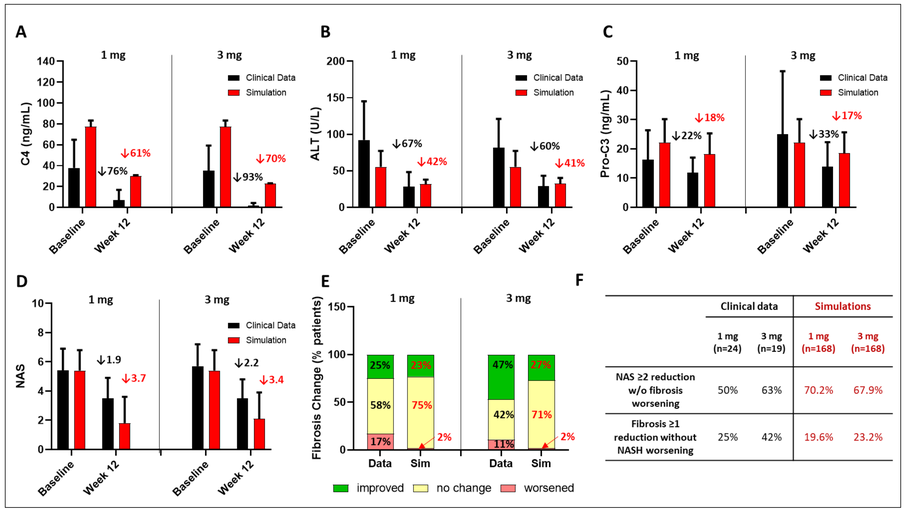
FGF19 effects on liver fat responses were optimized and validated using clinical data

Symbols represent clinical data used to optimize (NGM282, tropifexor, cilofexor) and validate (MET409) mechanistic parameters of FGF19 effects. Serum FGF19 concentration-time course and liver fat content data were obtained from published literature [1,10-12]. Lines represent simulation results in a representative NASH patient.



Simulations of NGM282 clinical protocols reasonably recapitulated observed serum marker and histological responses in NASH patients

12-week simulations of 1 mg and 3 mg NGM282 were performed using NAFLDsym by importing clinically observed plasma FGF19-time profiles in patients administered NGM282. Simulated serum markers (A-C) and histological responses (D-F) were compared to NGM282 clinical data, which were not used for optimization. A simulated population (n=168) that includes variability in parameters representing NAFLD/NASH pathophysiology was employed. Of note, simulated patients have stable disease by design and thus simulated PD endpoints in the placebo group do not change over time. Mean±SD are represented.



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