Advancing the Multi-Targeted Mechanisms of Action of a Mitochondrial Activator (AXA1125) for Treating NASH Using a Quantitative Systems Pharmacology Model

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BACKGROUND

Patients with non-alcoholic steatohepatitis (NASH) do not currently have options for pharmaceutical treatment. AXA1125 is an endogenous metabolic modulator (EMM) composition of LIVRQNac, which has shown efficacious potential when administered to patients in early clinical studies. In vitro studies and literature review have enumerated several contributing mechanisms of action (MoA's) by which AXA1125 dosing may be reducing levels of ALT, liver fat, Pro-C3, and HbA1c in patients. To further advance and quantitate the differential multi-targeted mechanisms driving improvements seen in in the clinic, a quantitative systems pharmacology (QSP) model, NAFLDsym[1], was employed to simulate AXA1125 under many combinations of candidate MoA's and further substantiate the MoA underlying the clinical benefit observed to date in patients.

METHODS

Clinical trial NCT04073368 was simulated by several software packages. Exposure of AXA1125 was modeled in Monolix® using a 1-compartment model based on data from a single 22.6 g dose (Fig 1A). This model was then used to predict the exposure of multiple doses (24 g BID) for 16 weeks using Simulx® (Fig 1B). Separately, various candidate MoA's of AXA1125 were mechanistically represented in NAFLDsym (Fig 2 & Fig 3), including the secretion of incretins (GLP-1 and GIP) and relevant downstream effects, direct reduction of oxidative stress, increased AMPK-responsive enzyme expression, inhibition of hepatic stellate cell activation and proliferation, and decreased TNFα production. Each of these MoA's has the potential to reduce the hepatic lipid burden, lipotoxicity, inflammation and/or fibrosis. NAFLDsym simulations combined the predicted exposure of 24 g BID dosing with various combinations and strengths of candidate MoA's. Simulation results were evaluated against clinical data from a Phase IIa Study[2].

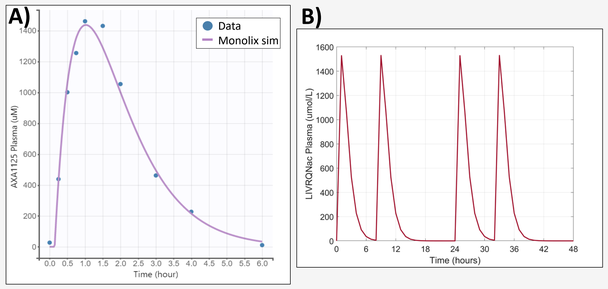

Figure 1. PK Model Results. A) Comparison of clinical data (blue dots) and 1-compartment PK model built using Monolix (purple line) of 22.6 g single dose data. B) Simulx simulation of multiple doses (24 g BID) predicts enterocyte (not shown) and plasma exposures (red line).

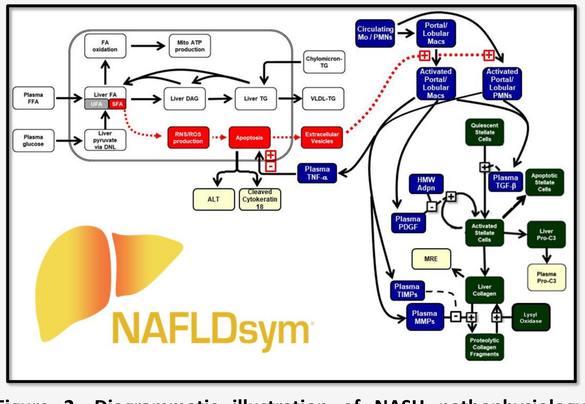

Figure 2. Diagrammatic illustration of NASH pathophysiology represented with NAFLDsym v2A. This includes steatosis, lipotoxicity, inflammation, and fibrosis.

Measure	Adult NAFLD/NASH Clinical Cohort	Adult NAFLD/NASH SimCohorts
Body mass (kg)	102.9 ± 23.82	100.2 ± 17.7
Liver fat (%)	22.4 ± 5.1	22.3 ± 4.9
Plasma ALT (U/L)	55.2 ± 26.3	51.0 ± 17.2
Plasma FFA (mM)	0.60 ± 0.24	0.71 ± 0.20
Fibrosis stage	--	2.2 ± 0.8
Type 2 Diabetes (%)	39	40
n	29	210

Table 1. Characteristics of the clinical cohort and SimCohort. Clinical cohorts represent the baseline characteristics from the Phase IIa Study[2]. Simulated patients were gathered as a SimCohort with characteristics that were consistent with the clinical cohort.

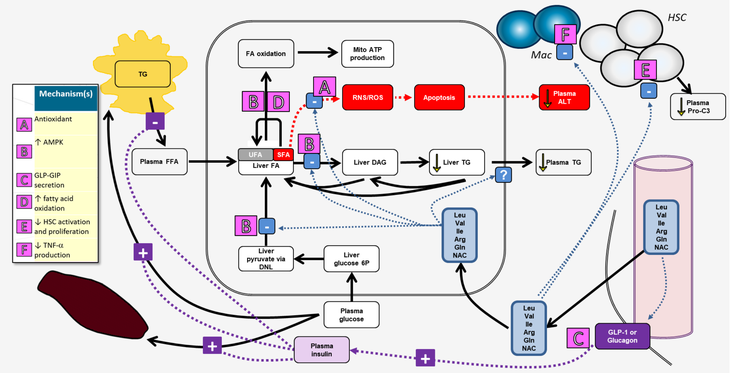

Figure 3. Diagram of AXA1125 Potential Mechanisms of Action. Six potential MoA's were identified based on published data[3]. These are listed as A – F, and their impacts are shown relative to pathophysiological processes. A) Nac-driven antioxidant activity; B) AMPK activation leads to changes in lipid metabolism and mitochondrial fatty acid uptake; C) calories consumed leads to secretion of incretins by enterocytes; D) increased fatty acid oxidation; E) decreased activation and proliferation of hepatic stellate cells; F) decreased TNF-α production.

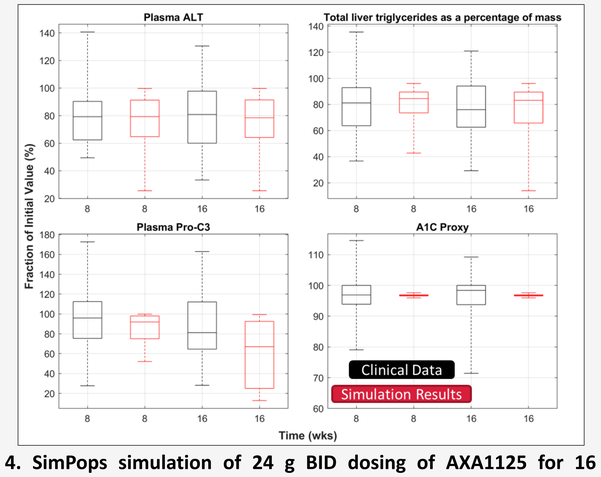

Figure 4. SimPops simulation of 24 g BID dosing of AXA1125 for 16 weeks compared to clinical observations[2]. In this simulation, the active MoA's included the incretin secretion, and increased AMPK-responsive enzyme expressions (i.e. increased free fatty acid oxidation, decreased *de novo* lipogenesis, and increased MGAT-driven lipogenesis via esterification). Clinical observations are shown as black box-and-whisker plots, and simulated patients are shown as red box-and-whisker plots. Simulated results show decreases in plasma ALT, liver fat, plasma Pro-C3 and A1C levels. This combination of MoA's meets the acceptance criteria across all clinical metrics and timepoints. Simulations of three other combinations of MoA's and parameterization also predicted outcomes similar to clinical[2] outcomes. Note because HbA1c is not explicitly modeled in NAFLDsym, an approximation, "A1C Proxy", was calculated as a 3-week average of simulated plasma glucose levels.

RESULTS

Simulations with NAFLDsym implicate multiple mechanisms that may be playing a role in the efficacy of AXA1125. The clinical data[2] were recapitulated in simulations invoking combinations of incretin secretion, and increased AMPK-responsive enzyme expressions (Figure 3). Additional simulations which further invoked direct antioxidant activity, or antioxidant activity and decreased TNFα production, increased fatty acid oxidation, also recapitulated clinical observations.

CONCLUSION

NAFLDsym, a QSP model of NAFLD/NASH, was used to investigate the combination of mechanisms playing a role in AXA1125, a NASH therapeutic candidate. NAFLDsym simulations support the following mechanisms contributing to the clinical response of AXA1125: incretin effects, AMPK-responsive enzyme expression, antioxidant-mediated reduction of lipotoxicity, and inhibition of TNFα production. This work independently recapitulates previously published MoA findings, including AXA1125 as a mitochondrial activator, and predicts novel contributions which require additional work to be validated and expanded upon.

REFERENCES

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2. A 16-Week, Single-Blind Randomized, Placebo- Controlled Food Study of the Safety and Tolerability of AXA1125 and AXA1957 in Subjects With Non-Alcoholic Fatty Liver Disease (NAFLD) – Clinical Trials ID: NCT04073368, AXA1125-003
3. Daou, N., Viader, A., Cokol, M., Nitzel, A., Chakravarthy, M. v., Afeyan, R., Tramontin, T., Marukian, S., & Hamill, M. J. (2021). A novel, multitargeted endogenous metabolic modulator composition impacts metabolism, inflammation, and fibrosis in nonalcoholic steatohepatitis-relevant primary human cell models. Scientific Reports, 11(1), 11861.

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