Attenuations in adiponectin production over time restrict simulated efficacy for pegbelfermin in F3 NASH patients

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BACKGROUND

Patients with non-alcoholic steatohepatitis (NASH) and fibrosis do not currently have options for pharmaceutical treatment. Numerous compounds have been in development including pegbelfermin, a polyethylene glycol-conjugated recombinant analogue of the metabolic hormone FGF21[1]. The recent completion of the FALCON 1 study[2] showed modest clinical benefit for NASH or fibrosis improvement in patients with fibrosis stage 3. A quantitative systems pharmacology (QSP) model, NAFLDsym[3] (Figure 1), was subsequently employed to simulate and better understand the mechanistic underpinnings contributing to the observed top-line clinical responses.

METHODS

Exposure of pegbelfermin in NASH patients was reproduced from FALCON 1 pharmacokinetic data and combined with a mechanistic representation of the actions of the pegbelfermin on adipose. The subsequent simulated effects of increased adiponectin on the liver elicited a decrease in *de novo* lipogenesis and mono-acyl glycerol transferase activity along with an increase in hepatic fatty acid oxidation[5-8] (Figure 2). All are consistent with AMP kinase activation. These effects act to reduce hepatic lipid burden and relieve lipotoxicity. Phase IIa clinical data were used to help validate these quantitative effects[1]. Subcutaneous administration of 10 mg QW, 20 mg QW, and 40 mg QW over 24 weeks was simulated in a cohort of F3 NASH patients (n=55) with similar clinical characteristics as the clinical cohorts (Table 1). Changes in liver fat, plasma ALT, NAFLD activity score, and fibrosis stage were simulated and compared with clinical data for each dose. Some parameter adjustments were made to provide better alignment with clinical data.

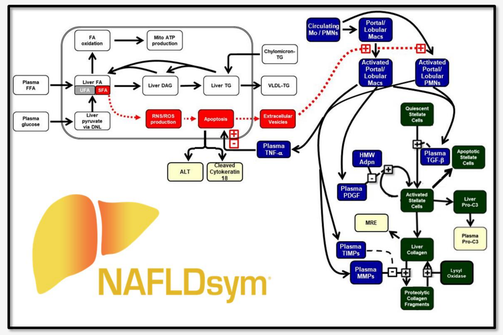

Figure 1. Diagrammatic illustration of NASH pathophysiology represented with NAFLDsym v2A. This includes steatosis, lipotoxicity, inflammation, and fibrosis.

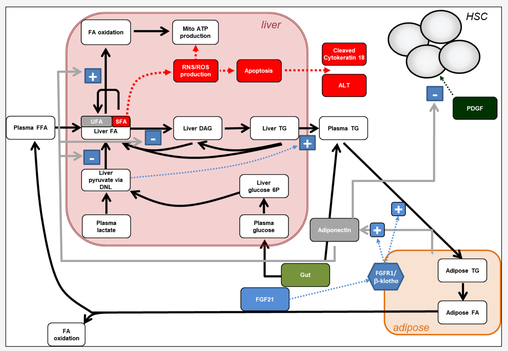

Figure 2. Representation of pegbelfermin pharmacodynamic and downstream effects that contribute to the overall mechanisms of action. This figure illustrates the effects of pegbelfermin to increase adipose adiponectin production in addition to adiponectin's effects on specific liver metabolic pathways. These pathways are all responsive to changes in AMPK (which is stimulated via the adiponectin receptor). This diagram also shows how adiponectin interacts with hepatic stellate cells (HSC) to antagonize the effects of PDGF.

	Clinical Cohorts				SimCohort
	Placebo	10 mg QW	20 mg QW	40 mg QW	All doses
Liver fat (%)	12.5±5.9	13.9±6.3	13.5±6.3	13.0±5.2	13.4±7.1
Fibrosis stage (score)	3.0±0	3.0±0	3.0±0	3.0±0	3.0±0
ProC3 (ng/mL)	19.0±9.2	19.1±8.4	20.1±11.9	19.7±8.6	22.5±7.9
ALT (U/L)	53.5±33.1	59.8±38.4	50.1±30.1	52.3±34.7	55.8±19.3
Plasma TG (mM)	2.3±2.6	1.6±0.5	1.8±0.7	2.1±1.2	2.1±0.6
Total adiponectin (mg/L)	4.1±2.1	4.4±2.6	3.6±1.9	4.2±3.2	4.7±1.9
n	49	49	50	49	55

Table 1. Characteristics of the clinical cohorts and SimCohorts. Clinical cohorts represent the baseline characteristics from Falcon 1[2]. Simulated patients were selected into SimCohorts that had characteristics that were consistent with the clinical cohorts.

		Fibrosis Improvement	Fibrosis improvement with no worsening of NASH	NASH improvement with no worsening of fibrosis	Fibrosis improvement with no worsening of NASH OR NASH improvement with no worsening of fibrosis
No treatment	Clinical data	8%	8%	10%	16%
	Simulation results	0%	0%	0%	0%
10 mg QW	Clinical data	16%	16%	22%	33%
	Simulation results	20%	20%	7%	22%
20 mg QW	Clinical data	14%	14%	14%	27%
	Simulation results	24%	24%	11%	29%
40 mg QW	Clinical data	20%	16%	16%	29%
	Simulation results	24%	24%	11%	29%

Table 2. Comparison of fibrosis and NASH improvement from FALCON 1 clinical cohorts and SimCohorts. The predicted responses to pegbelfermin treatment were generally consistent with the clinical responses. Modest efficacy was shown across all outcomes. However, NAFLDsym was unable to predict the improvements observed in the placebo clinical cohort due to lack of identifiable mechanistic contributors.

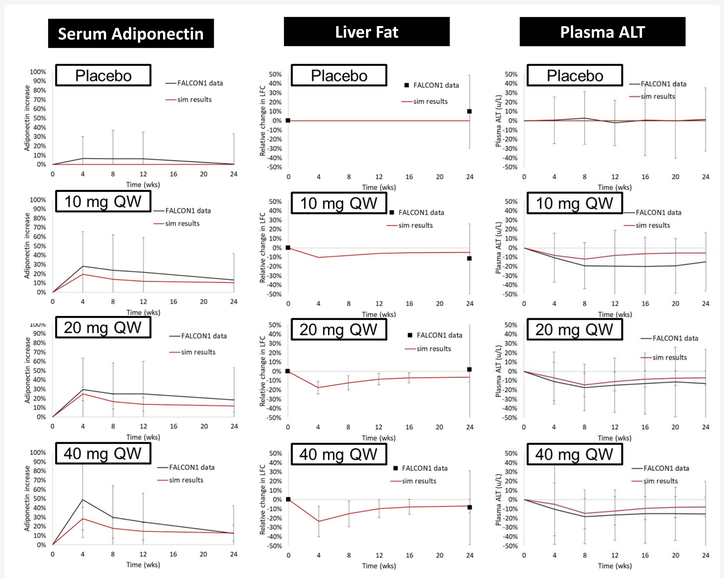

Figure 3. Comparison of adiponectin, liver fat, and ALT from FALCON 1 clinical cohorts and SimCohorts.
The predicted responses to 10 mg QW, 20 mg QW, and 40 mg QW were in general agreement with the measured changes to serum adiponectin, liver fat, and plasma ALT over 24 weeks. Note the attenuation in simulated and measured pegbelferimin-stimulated adiponectin over time. Similarly, the predicted liver fat and plasma ALT showed attenuations in improvement over time while also retaining consistency with the measured clinical data for each.

RESULTS

NAFLDsym recapitulated the observed modest efficacy in NASH patients with F3 fibrosis scores treated with pegbelfermin over 24 weeks (FALCON 1). Of note was an attenuation in the adiponectin increase over time (Figure 3). Liver fat and plasma ALT were reduced 5-20% for all doses, and the simulated change for each attenuated over time (Figure 3). The fraction of patients predicted to show improvement in both fibrosis and NASH ranged from 8-33% across the doses (Table 2); the simulation results in the treatment groups were generally in agreement with the clinical data. Note that NAFLDsym was unable to predict improvements in simulated patients treated with placebo.

CONCLUSION

Simulations in NAFLDsym helped substantiate the hypothesis that pegbelfermin-driven increases in adiponectin mediate the observed effects on liver outputs in NASH patients. However, the attenuated increase in adiponectin over time may be associated with loss of durability over time.

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