Greater efficacy predicted for FGFR1/beta-klotho receptor agonists that achieve 60% or greater increases in serum adiponectin

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BACKGROUND

The FGFR1/beta-klotho receptor (FGFR1/KLB) in adipose has been demonstrated to be a promising target for treating NASH, primarily due to enhanced adiponectin secretion. Several agonists for this receptor are analogues of the endogenous hormone, FGF21. The resultant actions of increased adiponectin on the liver have been reported to lead to improvements in steatosis, NASH, and fibrosis. A quantitative systems pharmacology (QSP) model, NAFLDsym (**Fig 1**), was employed to aid in the understanding of the role that adiponectin increases play in improving NASH. Efficacy was predicted for multiple agonists of FGFR1/KLB, including pegbelfermin[2], efruxifermin[3], Bio89-100[4], and BFKB8488A[5].

METHODS

Compartmental pharmacokinetic models (**Fig 2**) were developed for each compound and combined with a mechanistic representation of the effects of the pegbelfermin, efruxifermin, Bio89-100, and BFKB8488A interactions with the FGFR1/KLB in adipose. The subsequent simulated effects to increased adiponectin were validated by comparisons with reported clinical data for each compound (**Fig 3-4**). The simulated adiponectin effects on the liver elicited a decrease in hepatic *de novo* lipogenesis and mono-acyl glycerol transferase activity and an increase in hepatic fatty acid oxidation, consistent with the activation of AMP kinase[6-9]. These effects acted in concert to reduce hepatic lipid burden and relieve lipotoxicity. The effects on liver fat, plasma ALT, NAFLD activity score (NAS), and fibrosis stage were predicted for 48 weeks of treatment with each compound in SimCohorts of F1 (n=32), F2 (n=35), F3 (n=55), or F4 (n=35) NASH patients (**Figure 4**).

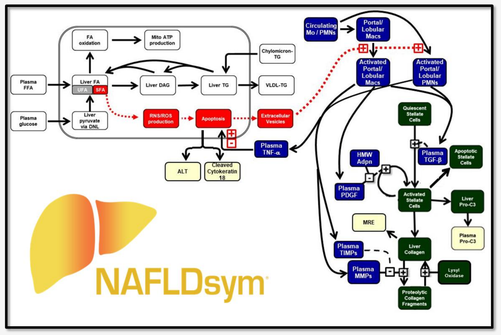

Figure 1. Diagrammatic illustration of NASH pathophysiology represented with NAFLDsym v2A.

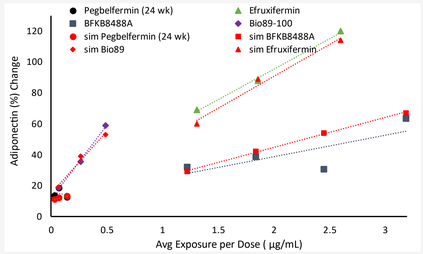

Figure 3. Potency of effects to increase adiponectin production by each compound. Relationship between average exposure per dose (at steady state) and change in adiponectin for multiple compounds, as described in references 2-5,10. Pegbelfermin data are clustered, obscuring the trendlines.

	F1	F2	F3	F4
Body Weight (kg)	114.1 ± 20.8	95.8 ± 20.4	84.7 ± 17.5	91.0 ± 12.1
Liver Fat (%)	21.2 ± 6.4	16.2 ± 8.4	13.4 ± 7.1	9.9 ± 3.5
NAS (score)	5.8 ± 1	5.3 ± 1.5	5.0 ± 1.4	4.3 ± 1.2
Fibrosis Stage	1.0 ± 0	2.0 ± 0	3.0 ± 0	4.0 ± 0
ProC3 (ng/mL)	15.3 ± 4.2	18.0 ± 6.3	22.5 ± 7.9	22.9 ± 7.6
ALT (U/L)	43.8 ±12.5	49.7 ± 16.4	55.8 ± 19.3	55.3 ± 27.2
Plasma TG (mM)	2.0 ± 0.6	1.9 ± 0.5	2.1 ± 0.6	2.2 ± 0.9
Liver Stiffness (kPa)	2.0 ± 0.5	3.5 ± 0.2	4.2 ± 0.2	5.1 ± 0.5
Total Adiponectin (mg/L)	3.9 ± 1.5	4.3 ± 1.8	4.7 ± 1.9	3.8 ± 1.8
n	32	35	55	35

Table 1. Characteristics of the SimCohorts. SimCohorts were selected with fibrosis stages 1, 2, 3, 4.

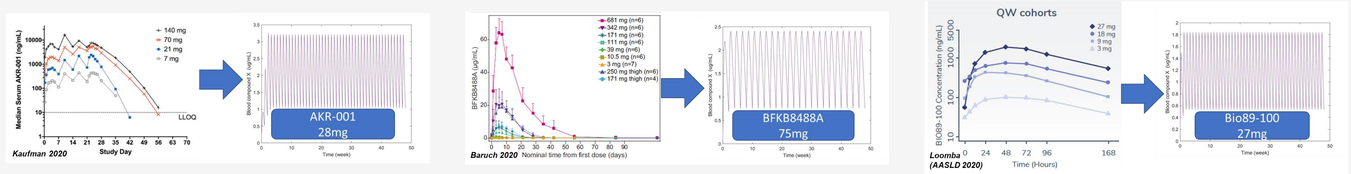

Figure 2. Predicted exposure for each compound. Measured, reported PK data for each compound was used to develop compartmental pharmacokinetic models for each compound. Exposure over time was predicted using the compartmental models and used to support the predictions of efficacy with NAFLDsym. Note that the predicted exposure of pegbelfermin is not displayed here; instead, exposure of pegbelfermin (10 mg, 20 mg, and 40 mg QW) in NASH patients was reproduced from FALCON 1 study pharmacokinetic data.

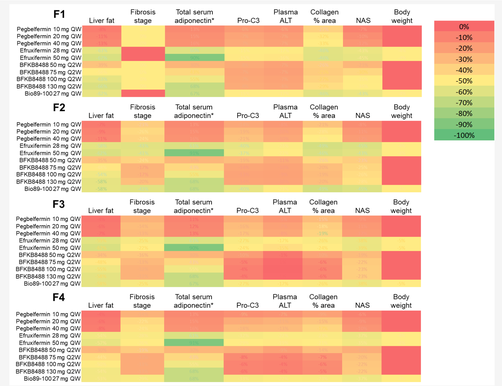

Figure 5. Heat maps comparing the relative effects of FGF21 analogues. The magnitude of effects for various doses of pegbelfermin, efruxifermin, BFKB8488A, and Bio89-100 on liver fat, fibrosis stage, serum adiponectin, Pro-C3, Plasma ALT, collagen % area, and body weight are displayed. The color (scale shown) indicates the change after 48 weeks relative to initial values. Note that changes in adiponectin are increases rather than decreases. The greatest predicted changes in fibrosis stage and NAS are associated with ≥60% increases in adiponectin.

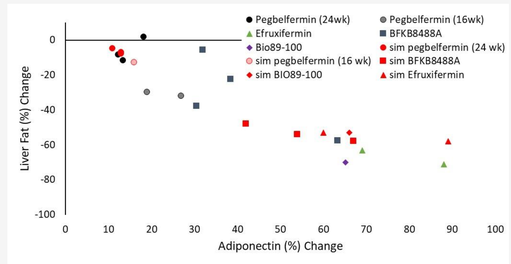

Figure 4. Relationship between change in adiponectin and liver fat. Relationship between change in adiponectin and liver fat for various doses of pegbelfermin, efruxifermin, BFKB8488A, and Bio89-100. Plot includes a comparison of the clinical data vs. the simulated responses. Note that a change with a negative value indicates a reduction while a positive value indicates an increase.

METHODS, CONT.

The simulated patients in the SimCohorts included pathophysiologic and clinical characteristics of NASH patients (**Table 1**); inter-patient variability was also included to ensure reported diversity.

RESULTS

The simulated increases in serum adiponectin and reductions of liver fat align well with reported clinical data (**Fig 4**). Of note is the trend towards greater relief of steatosis with compounds and doses that elicit higher adiponectin increases. Greater improvements in plasma ALT, NAS, and fibrosis stage were also predicted for compounds that caused the substantial increases in serum adiponectin (**Fig 5**).

CONCLUSION

Greater treatment-induced adiponectin production likely mediates enhanced simulated efficacy with FGFR1/KLB agonists. Compounds and doses that achieve ≥60% increases in serum adiponectin are predicted to have greatest benefits in clinical metrics such as fibrosis stage, collagen area, and NAS.

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