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Increased adiponectin following efruxifermin treatment is associated with improvements in dyslipidemia, glucose metabolism, and liver health in a 16-week, randomized, placebo-controlled trial in NASH

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Disclosures

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Background and Aim

- **Efruxifermin (EFX)** is a long-acting Fc-FGF21 analog being developed as a therapeutic for NASH
  - EFX mimics native FGF21's balanced agonism of FGFR1c, FGFR2c, and FGFR3c, without FGFR4 activity
  - FGFR1c is expressed in adipose tissue, while FGFR2c and FGFR3c are expressed in liver
  - FGFR1c signaling in adipose tissue improves insulin sensitivity and stimulates adiponectin expression
- Serum **adiponectin** is a pharmacodynamic marker of adipose tissue **FGFR1c activation by EFX**
- In the Phase 2a, 16-week BALANCED study of EFX dosed weekly (QW) in patients with F1–F3 NASH (n=80):
  - EFX significantly reduced liver fat and improved markers of glucose and lipid metabolism, liver injury, and fibrosis
  - EFX was generally safe and well-tolerated. Most AEs were gastrointestinal, mild-to-moderate, and transient
- BALANCED results were consistent with improvements in markers of glucose metabolism observed in patients with T2D dosed QW in Phase 1b[1]
  - In contrast, in the Phase 1b study, dosing once every 2 weeks (Q2W) did not improve markers of glucose metabolism[1] indicating requirement for sustained agonism of FGF21 receptors

This analysis aimed to evaluate the association between activation of adipose tissue FGFR1c signaling, measured by serum adiponectin, and improvements in liver health and whole-body metabolism in patients with NASH

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[1] Kaufman A, et al. *Cell Rep Med* (2020) 1:100057

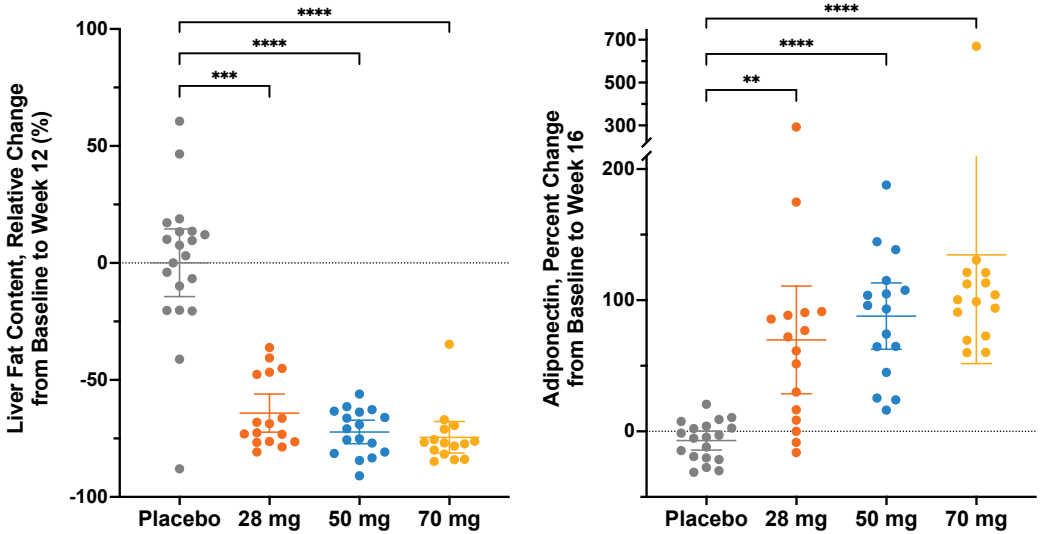
Baseline demographics

Parameter	Placebo (N=21)	EFX 28mg (N=19)	EFX 50mg (N=20)	EFX 70mg (N=20)
Age (Years)	52.4	50.4	52.6	53.0
Sex (Male/Female), n	6/15	9/10	10/10	9/11
Type 2 Diabetes, n (%)	14 (67)	7 (37)	10 (50)	10 (50)
BMI (kg/m^2)	37.6	38.8	36.7	37.2
Liver Fat Content (%)	19.3	21.4	18.3	19.4
Fibrosis Stage F2/F3, n (%)	13 (62)	12 (63)	13 (65)	13 (65)
HbA1c (%)	6.49	6.20	6.43	6.23
Urate (mg/dL)	5.7	5.9	5.6	6.2
Alanine Aminotransferase (ALT) (U/L)	50.7	62.5	53.4	56.8
Triglycerides (mg/dL)	208.3	176.3	176.5	180.0
HOMA-IR	10.5	11.9	19.6	14.1
Adiponectin (mg/L)	4.4	4.7	3.5	5.4

Demographics and characteristics are presented as means unless otherwise noted

EFX robustly reduced liver fat content and increased adiponectin, which correlates with improvements in markers of metabolic and liver health

Efruxifermin Significantly Reduced Liver Fat and Increased Adiponectin Over 16 Weeks



** p<0.01; *** p<0.001; **** p<0.0001, Kruskal-Wallis, Dunn's post-test
Each point represents an individual patient. Summary data presented as mean ± 95% confidence interval

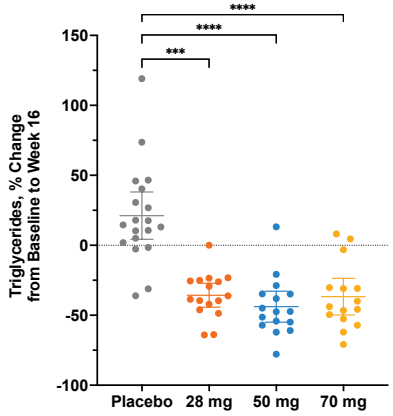
Correlation Between Percent Change in Adiponectin and Percent Change in Liver Fat Content, Body Weight and Serum Biomarkers from Baseline to Week 16

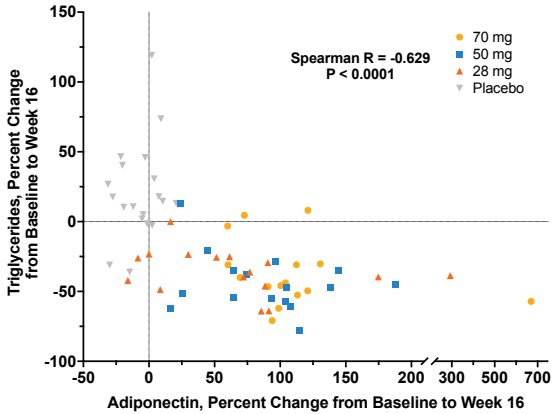
Biomarker	Spearman R	P value
Liver Fat Content [1]	-0.689	<0.0001
Body weight	-0.543	<0.0001
HDL-cholesterol	0.667	<0.0001
Triglycerides	-0.629	<0.0001
non-HDL-cholesterol	-0.140	0.260
Apolipoprotein B	-0.255	0.039
HbA1c [2]	-0.319	0.0096
C-peptide	-0.397	<0.001
Insulin	-0.384	0.001
HOMA-IR	-0.337	0.006
ALT	-0.550	<0.0001
AST	-0.554	<0.0001
GGT	-0.633	<0.0001
Uric acid	-0.528	<0.0001
Pro-C3	-0.392	0.0013
ELF [1,2]	-0.392	0.0016
FIB-4	-0.410	<0.001

[1] Week 12; [2] Absolute change

Improvements in lipid profile correlate strongly with increases in adiponectin, consistent with adipose-mediated improvement of dyslipidemia

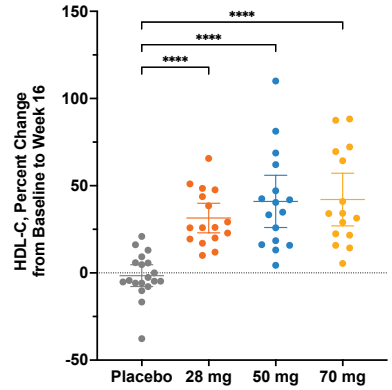
EFX significantly decreased serum triglyceride

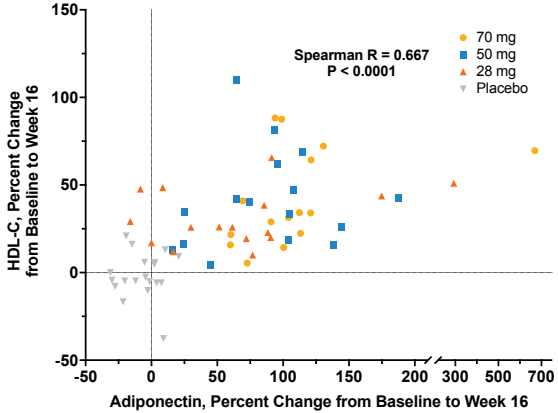




Negative adiponectin correlation with serum triglyceride

EFX significantly increased HDL-cholesterol



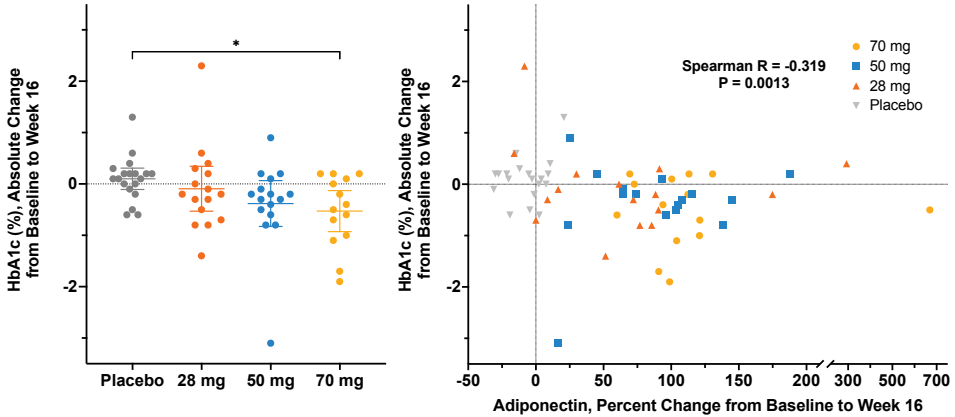


Positive adiponectin correlation with HDL-cholesterol

*** p<0.001; **** p<0.0001, Kruskal-Wallis, Dunn's post-test
Each point represents an individual patient. Summary data presented as mean ± 95% confidence interval

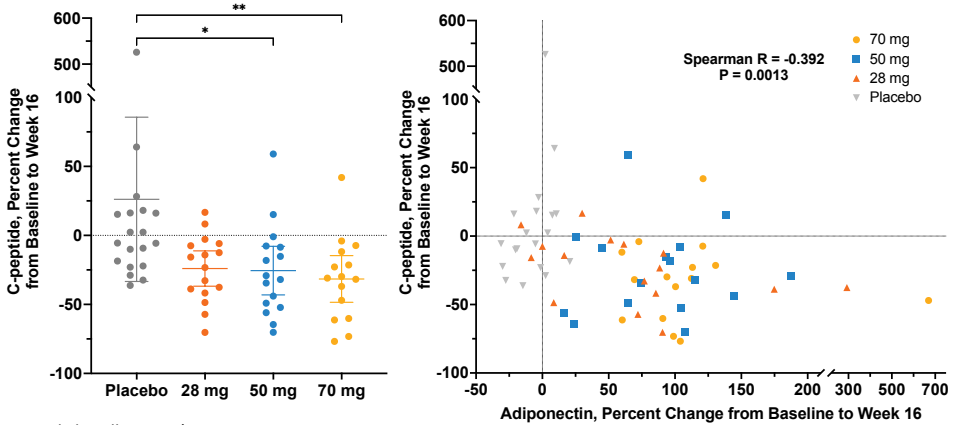
Improvements in glucose metabolism correlate with increases in adiponectin, consistent with adipose-mediated insulin sensitization

EFX decreased HbA1c



Negative adiponectin correlation with HbA1c

EFX decreased C-peptide



Negative adiponectin correlation with C-peptide

* p<0.05; ** p<0.01, Kruskal-Wallis, Dunn's post-test
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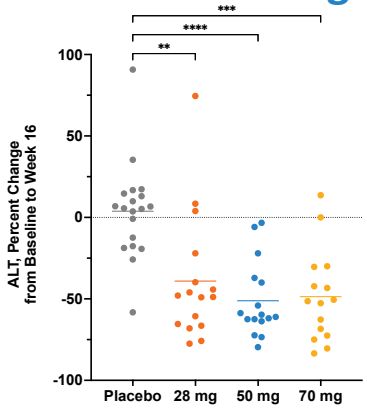
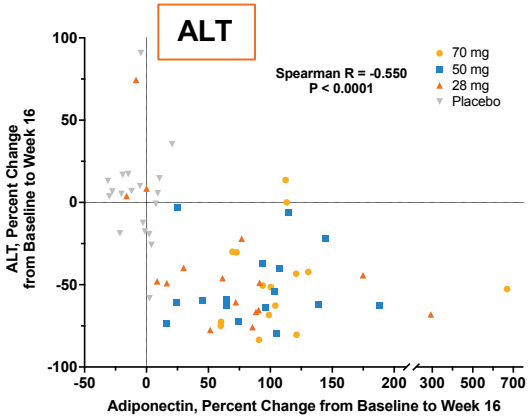
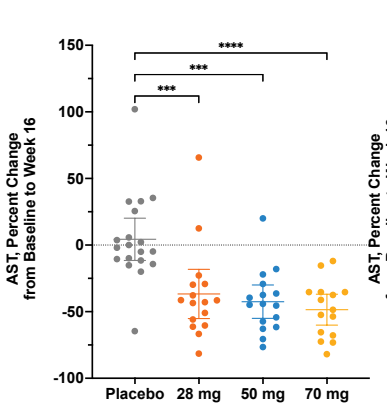
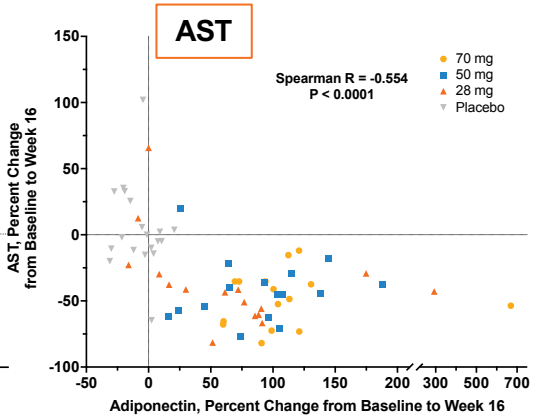
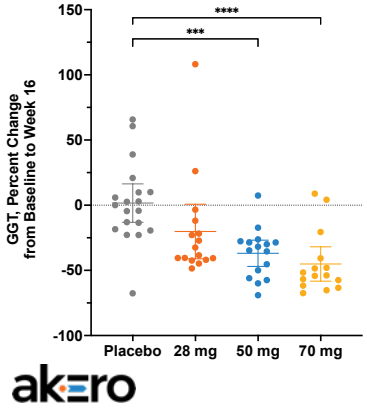
Reductions in markers of liver injury and hepatocyte stress correlate strongly with increases in adiponectin

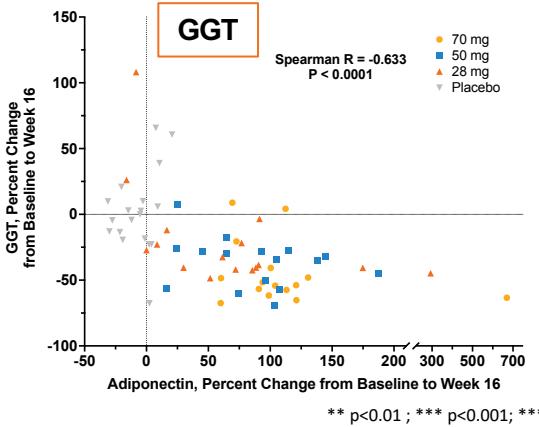


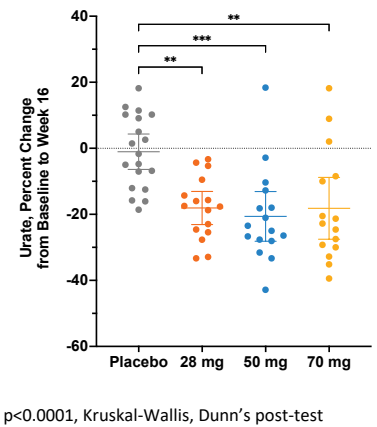


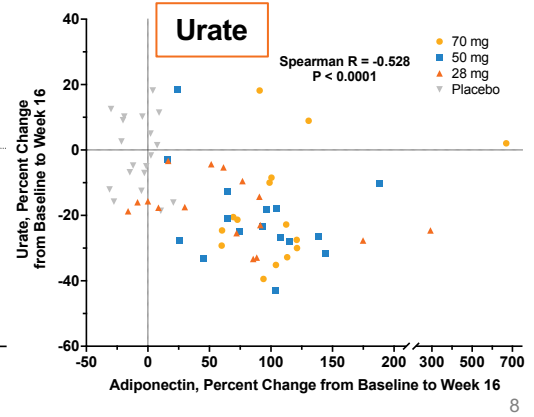












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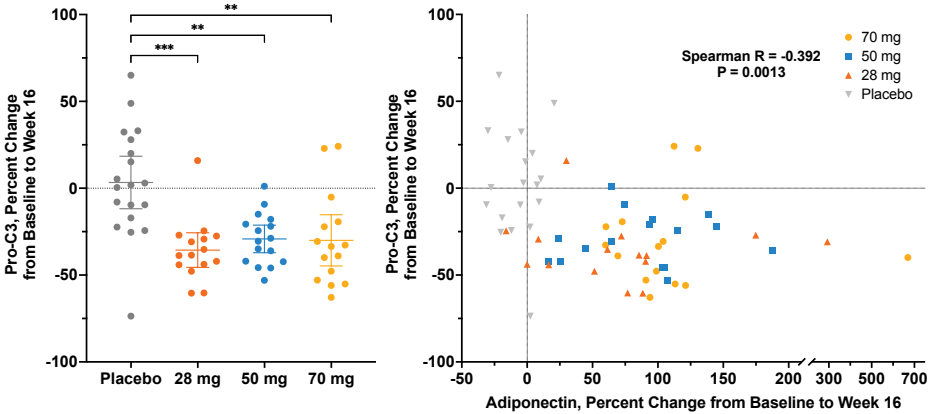
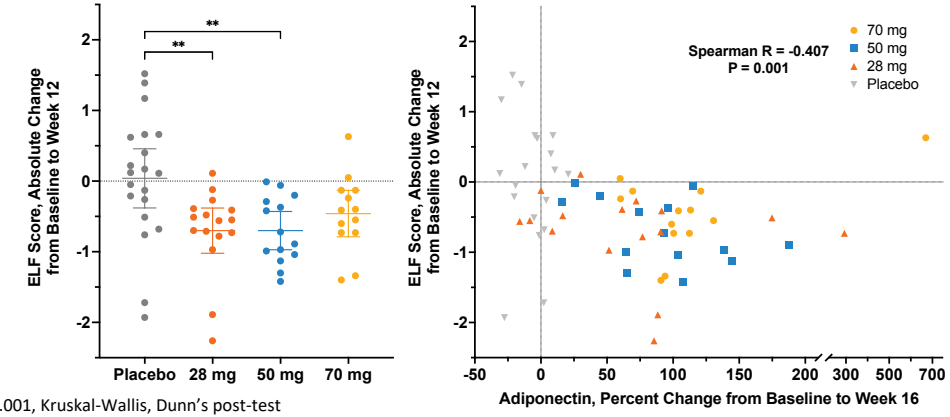
Reductions in circulating markers of liver fibrosis correlate with increased adiponectin, suggesting role of adipose tissue in resolving NASH pathology

EFX reduced Pro-C3, a marker of fibrogenesis



Negative adiponectin correlation with Pro-C3

EFX reduced ELF score, a composite, non-invasive measure of liver fibrosis



Negative adiponectin correlation with ELF score

** p<0.01; *** p<0.001, Kruskal-Wallis, Dunn's post-test
Each point represents an individual patient. Summary data presented as mean ± 95% confidence interval

Summary and Conclusions

- EFX significantly reduced liver fat and improved markers of glucose and lipid metabolism, liver injury, and fibrosis in patients with NASH
- EFX significantly and dose-dependently increased adiponectin, a pharmacodynamic marker of FGFR1c activation in adipose tissue
- Increases in adiponectin correlated strongly with:
  - Improvements in lipid and lipoprotein profile
  - Improvements in markers of insulin sensitivity and glucose metabolism
  - Reductions in biomarkers of liver injury and hepatocyte stress
  - Reductions in serum markers of liver fibrosis and fibrogenesis
- FGFR1c activation in adipose tissue by EFX correlates with, and may mediate, improvements in liver-health
- Other beneficial effects, including reduced ApoB and non-HDL-cholesterol, did not appear to correlate with adiponectin, suggesting FGFR1c-independent mechanisms also contribute to EFX's broad metabolic profile, underscoring importance of balanced agonism across FGFR1c/2c/3c without agonism of FGFR4