

FGF-21 analogues for treatment of non-alcoholic steatohepatitis and fibrosis: a meta-analysis with fragility index of phase 2 randomised placebo-controlled trials

We have read with interest the excellent review by Trauner and Fuchs on the novel therapeutic approaches that are currently developed for treating non-alcoholic steatohepatitis (NASH).¹ Although there are no licensed pharmacotherapies for NASH, long-acting fibroblast growth factor-21 (FGF-21) analogues are being evaluated to treat NASH because FGF-21 is a pleiotropic liver-derived hormone regulating lipid metabolism, insulin sensitivity and energy homeostasis, all mechanisms closely implicated in NASH development.²

To quantify the magnitude of the possible hepatoprotective effects of FGF-21 analogues, we systematically searched three electronic databases from the inception date to 1 September 2023 to identify phase-2 randomised controlled trials (RCTs) examining the efficacy of FGF-21 analogues on the US Food and Drug Administration defined histological endpoints for conditional approval of new

drugs for NASH, that is, NASH resolution without worsening of fibrosis or ≥ 1 stage fibrosis improvement without worsening of NASH. We also calculated the fragility index (FI) to establish the robustness of the trial's data.³ More details of the systematic review are reported in online supplemental material.

We included five phase-2 placebo-controlled RCTs^{4–8} involving 602 obese adults with biopsy-confirmed NASH and stages F1–F4 fibrosis, most of whom had diabetes (446 randomly assigned to FGF-21 analogues and 156 assigned to placebo). Online supplemental figure 1 shows the results of the literature research and study selection. The main characteristics of the eligible RCTs are summarised in table 1. Three RCTs^{6–8} were in phase 2b, whereas two^{4,5} were in phase 2a with histological endpoints available only for a subset of individuals. Figure 1 shows the treatment effects of FGF-21 analogues on resolution of NASH without worsening of fibrosis (figure 1A, n=3 RCTs^{6–8}) or ≥ 1 stage fibrosis improvement without worsening of NASH (figure 1B, n=5 RCTs^{4–8}) compared with placebo. Treatment with once-weekly subcutaneous FGF-21 analogues for 16–48 weeks resulted in a significantly higher percentage of patients with NASH resolution with no worsening of fibrosis, or ≥ 1 stage

fibrosis improvement without worsening of NASH than placebo (especially using common-effects models). However, it should be noted that the FI for both histological endpoints was small, suggesting that the findings are weak. Specifically, the FI for the ≥ 1 stage fibrosis improvement was 3 (ie, only three participants from the active-comparator arm should be re-assigned to the placebo arm to change the result from significant to non-significant), while the FI for the resolution of NASH was 8.

The FI measures the robustness (or fragility) of the results from a clinical trial using dichotomous outcomes. The FI represents the minimum number of participants whose status needs to change from an 'event' to a 'non-event' (or vice versa) so that the results switch from statistically significant to non-significant. Whether few participants are needed to hamper the significance of a result, the strength of evidence for affirming the superiority of a specific treatment over a placebo might be questionable. When we looked at the efficacy of pioglitazone or semaglutide in achieving resolution of NASH or ≥ 1 stage fibrosis improvement without worsening of NASH, we found that the FI for pioglitazone for NASH resolution with no worsening of fibrosis was 11, while the FI for ≥ 1 stage fibrosis improvement was

Table 1 Main characteristics of the phase-2 RCTs examining the efficacy of long-acting FGF-21 analogues for treating adult individuals with biopsy-confirmed NASH and different stages of fibrosis included in the meta-analysis

Author, (ref.)	Phase	Molecule (dosage: once a week subcutaneously), trial name	Sample size (n) (mean age; mean BMI; percentage of men; prevalence of diabetes)	Trial duration	Risk of bias*
Harrison <i>et al</i> ⁴	2a	Efruxifermin (28 mg, 50 mg, or 70 mg weekly), BALANCED	42 obese adults with biopsy-confirmed NASH and stage F1-F3 fibrosis: n=40 in the efruxifermin-treated group; n=2 in the placebo group	16 weeks	Low
Harrison <i>et al</i> ⁵	2a	Efruxifermin (50 mg weekly), BALANCED Cohort C	17 obese adults with biopsy-confirmed NASH and stage F4 fibrosis (compensated cirrhosis): n=12 in the efruxifermin-treated group; n=5 in the placebo group	16 weeks	Low
Loomba <i>et al</i> ⁶	2b	Pegbelfermin (10 mg, 20 mg, or 40 mg weekly), FALCON 1	197 obese adults with biopsy-confirmed NASH and stage F3 fibrosis: n=148 in the pegbelfermin-treated group (mean age 57 years; mean BMI 35.7 kg/m ² ; 41% were men; 70% had T2DM); n=49 in the placebo group (mean age 57 years; mean BMI 35.2 kg/m ² ; 41% men; 74% had T2DM)	24 weeks	Low
Abdelmalek <i>et al</i> ⁷	2b	Pegbelfermin (10 mg, 20 mg, or 40 mg weekly), FALCON 2	154 obese adults with biopsy-confirmed NASH and stage F4 fibrosis (compensated cirrhosis): n=115 in the pegbelfermin-treated group (mean age 59 years; mean BMI 35.6 kg/m ² ; 36% were men; prevalence of T2DM 71%); n=39 in the placebo group (mean age 61 years; mean BMI 35.2 kg/m ² ; 39% men; 78% had T2DM)	48 weeks	Low
Loomba <i>et al</i> ⁸	2b	Pegozafermin (15 mg, 30 mg weekly or 44 mg once every 2 weeks), ENLIVEN	192 obese adults with biopsy-confirmed NASH and stage F2 or F3 fibrosis: n=131 in the pegozafermin-treated group (mean age 55 years; mean BMI 36.0 kg/m ² ; 36% were men; prevalence of T2DM 65%); n=61 in the placebo group (mean age 56 years; mean BMI 38.1 kg/m ² ; 45% men; 69% had T2DM)	24 weeks	Low

Ref. #4 and #5 did not provide mean age, mean BMI and percentage of men and known T2DM because the histological endpoints were available only in a small subset of individuals. In these two trials, the primary study endpoints were changes from baseline in liver fat content (as assessed by MRI-PDFF), liver stiffness and other non-invasive biomarkers of liver fibrosis.

*Risk of bias was assessed using the Cochrane risk-of-bias tool for each eligible RCT.¹¹

FGF-21, fibroblast growth factor-21; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.

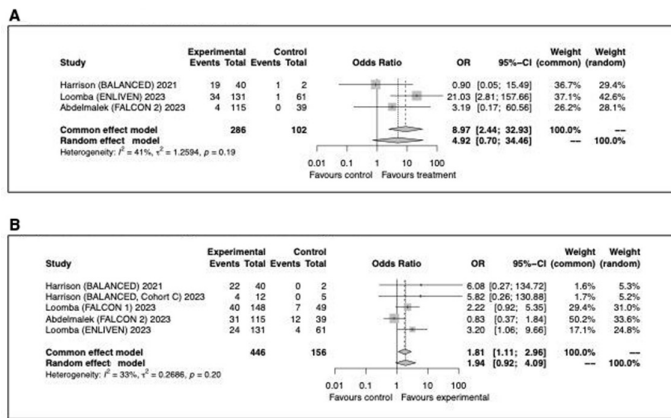


Figure 1 Forest plots and pooled estimates of the effects of long-acting FGF-21 analogues on the histological resolution of NASH with no worsening of fibrosis ((A), n=3 RCTs^{6–8}) or the improvement in fibrosis of one stage or more without worsening of NASH ((B), n=5 RCTs^{4–8}) compared with placebo. The pooled and individual effect sizes for all RCTs are expressed as OR and 95% CIs, as estimated by both common-effects and random-effects models. For the active-comparator group (ie, participants using FGF-21 analogues), we calculated the individual effect sizes of each RCT by combining the treatment effect data of variable dosages of FGF-21 analogues into a single group (to avoid including individuals in the placebo group several times in the analysis). With regard to this, it is important to note that before combining the data of the active-comparator group for each RCT, we have previously tested in a multivariate meta-regression analysis that neither the different type nor the different dosage of FGF-21 analogue used in each RCT were significant predictors of the observed effects of this drug class on the histological liver endpoints. FGF-21, fibroblast growth factor-21; NASH, non-alcoholic steatohepatitis; RCT, non-alcoholic steatohepatitis.

6.⁹ In a phase-2b placebo-controlled RCT testing semaglutide,¹⁰ we found that the FI of semaglutide for the resolution of NASH without worsening of fibrosis was 8.

In conclusion, the results of this meta-analysis suggest that FGF-21 analogues are a promising treatment option for adults with biopsy-confirmed NASH and fibrosis. However, based on the FI of the trials' data, uncertainty remains about the robustness and clinical benefit of FGF-21 analogues. Future large phase-3 RCTs with long-term follow-up are needed to have more robust findings.

Alessandro Mantovani ¹, Herbert Tilg ², Giovanni Targher ^{1,3}

¹Endocrinology and Metabolism, Department of Medicine, University of Verona, Verona, Italy

²Department of Internal Medicine I, Gastroenterology, Hepatology, Endocrinology & Metabolism, Medizinische Universität Innsbruck, Innsbruck, Austria

³Metabolic Diseases Research Unit, IRCCS Sacro Cuore Don Calabria Hospital, Negrar di Valpolicella, Italy

Correspondence to Professor Giovanni Targher, Endocrinology and Metabolism, University of Verona Department of Medicine, Verona, Italy; giovanni.targher@univr.it

Contributors AM and GT planned the study, performed the statistical analyses and wrote the first draft of the manuscript. HT contributed to the interpretation of the results. All authors edited, reviewed and approved the final version of the manuscript. GT is the guarantor of this work, and,

as such, had full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests HT is an associate editor of the journal and GT is an editorial board member of the journal.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; internally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.



OPEN ACCESS

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work

non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/gutjnl-2023-331115>).



To cite Mantovani A, Tilg H, Targher G. Gut Epub ahead of print: [please include Day Month Year]. doi:10.1136/gutjnl-2023-331115

Received 11 September 2023

Accepted 14 September 2023

Gut 2023;0:1–2. doi:10.1136/gutjnl-2023-331115

ORCID iDs

Alessandro Mantovani <http://orcid.org/0000-0002-7271-6329>

Herbert Tilg <http://orcid.org/0000-0002-4235-2579>

Giovanni Targher <http://orcid.org/0000-0002-4325-3900>

REFERENCES

- Trauner M, Fuchs CD. Novel therapeutic targets for cholestatic and fatty liver disease. *Gut* 2022;71:194–209.
- Geng L, Lam KSL, Xu A. The therapeutic potential of FGF21 in metabolic diseases: from bench to clinic. *Nat Rev Endocrinol* 2020;16:654–67.
- Atal I, Porcher R, Boutron I, et al. The statistical significance of meta-analyses is frequently fragile: definition of a fragility index for meta-analyses. *J Clin Epidemiol* 2019;111:32–40.
- Harrison SA, Ruane PJ, Freilich BL, et al. Efruxifermin in non-alcoholic Steatohepatitis: a randomized, double-blind, placebo-controlled, phase 2A trial. *Nat Med* 2021;27:1262–71.
- Harrison SA, Ruane PJ, Freilich B, et al. A randomized, double-blind, placebo-controlled phase IIa trial of efruxifermin for patients with compensated NASH cirrhosis. *JHEP Rep* 2023;5:100563.
- Loomba R, Sanyal AJ, Nakajima A, et al. Pegbelfermin in patients with nonalcoholic steatohepatitis and stage 3 fibrosis (FALCON 1): a randomized phase 2B study. *Clin Gastroenterol Hepatol* 2023.
- Abdelmalek MF, Sanyal AJ, Nakajima A, et al. Pegbelfermin in patients with nonalcoholic steatohepatitis and compensated cirrhosis (FALCON 2): A randomized phase 2B study. *Clin Gastroenterol Hepatol* 2023.
- Loomba R, Sanyal AJ, Kowdley KV, et al. Randomized, controlled trial of the FGF21 analogue pegozafermin in NASH. *N Engl J Med* 2023;389:998–1008.
- Musso G, Cassader M, Paschetta E, et al. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: a meta-analysis. *JAMA Intern Med* 2017;177:633–40.
- Newsome PN, Buchholtz K, Cusi K, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med* 2021;384:1113–24.
- Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for systematic reviews of interventions. *Cochrane Database Syst Rev* 2019;10:ED000142.