# 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 pleotropic 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,

**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 *et al*[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 *et al*[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 *et al*[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 *et al*[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 *et al*[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.

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 reassigned to the placebo arm to change the result from significant to non-significant), while the FI for the resolution of NASH was 8.

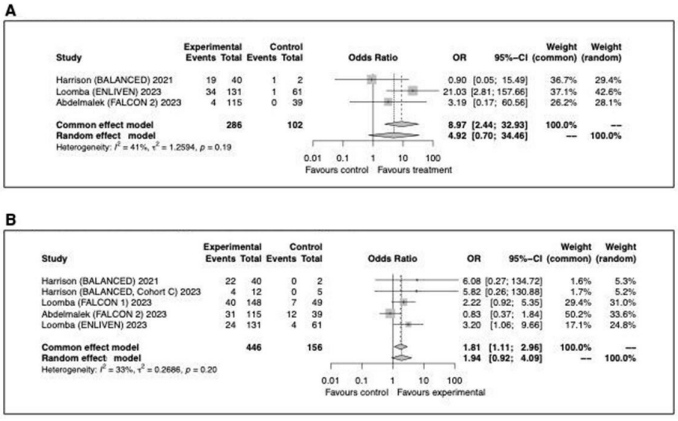


**Figure 1** Forest plots and pooled estimates of the effects of long-acting FGF-21 analogues on the histological resolution of NASH with no worsening of fibrosis ((A), n=3 RCTs[6–8]) or the improvement in fibrosis of one stage or more without worsening of NASH ((B), n=5 RCTs[4–8]) compared with placebo. 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.

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 of pioglitazone for NASH resolution with no worsening of fibrosis was 11, while the FI for ≥1 stage fibrosis improvement was 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.

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