

Tropifexor plus cenicriviroc combination versus monotherapy in non-alcoholic steatohepatitis: Results from the Phase 2b TANDEM study

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Trial registration

NCT03517540, [ClinicalTrials.gov](https://clinicaltrials.gov)

Keyword (5/5 that do not appear in the title)

NAFLD; NASH; randomized trial; digital pathology; histology; fibrosis

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List of abbreviations

| | |
|------------------|---|
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| AI | Artificial Intelligence |
| AST | Aspartate aminotransferase |
| AUC | Area under the drug concentration-time curve in plasma |
| BMI | Body mass index |
| CCR2/5 | C-C chemokine receptor types 2/5 |
| CI | Confidence interval |
| C _{max} | Maximum concentration |
| C _{min} | Minimum concentration |
| COVID-19 | Coronavirus disease 2019 |
| CRN | Clinical Research Network |
| CVC | Genecriviroc |
| ELF | Enhanced liver fibrosis |
| EMA | European Medicines Agency |
| EOS | End of study |
| EOT | End of treatment |
| FDA | Food and Drug Administration |
| FGF19 | Fibroblast growth factor 19 |
| FIB-4 | Fibrosis 4 |
| FXR | Farnesoid X receptor |
| GGT | Gamma-glutamyl transferase |
| HbA1c | Glycosylated hemoglobin |
| HDL-C | High-density lipoprotein cholesterol |
| HFF | Hepatic fat fraction |
| HOMA-IR | Homeostatic model assessment for insulin resistance |
| LDL-C | Low-density lipoprotein cholesterol |
| MRI | Magnetic resonance imaging |
| MRI-PDFF | Magnetic resonance imaging-proton density fat fraction |
| N | Total number of patients |
| n | Number of Patients per group |
| NAFLD | Non-alcoholic fatty liver disease |
| NAS | NAFLD activity score |
| NASH | Non-alcoholic steatohepatitis |
| PGIC | Patient global impression of change |
| PGIS | Patient global impression of severity |
| PK | Pharmacokinetic |
| PRO | Patient-reported outcome |
| SAE | Serious adverse event |
| SD | Standard deviation |
| SHG/TPEF | Second harmonic generation/two-photon excitation fluorescence |
| TEAE | Treatment-emergent adverse event |
| TXR | Tropifexor |
| VAS | Visual analog scale |

Graphic abstract

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Abstract

Background & Aims

With distinct mechanisms of action, the combination of tropifexor (TXR) and cenicriviroc (CVC) may provide an effective treatment for non-alcoholic steatohepatitis. This randomized, multicenter, double-blind, phase 2b study assessed the safety and efficacy of TXR and CVC combination, compared with respective monotherapies.

Approach & Results

Patients (N=193) were randomized 1:1:1:1 to once-daily TXR 140 μ g (TXR₁₄₀), CVC 150 mg (CVC), TXR 140 μ g+CVC 150 mg (TXR₁₄₀+CVC), or TXR 90 μ g+CVC 150 mg (TXR₉₀+CVC), for 48 weeks. The primary and secondary endpoints were safety and histological improvement, respectively.

Rates of adverse events (AEs) were similar across treatment groups. Pruritus was the most frequently experienced AE, with highest incidence in the TXR₁₄₀ group (40.0%). In TXR and combination groups, alanine aminotransferase (ALT) decreased from baseline to 48 weeks (geometric mean change: -21%, TXR₁₄₀; -16%, TXR₁₄₀+CVC; -13%, TXR₉₀+CVC; +17%, CVC). Reductions in body weight observed at Week 24 (mean changes from baseline: TXR₁₄₀, -2.5 kg; TXR₁₄₀+CVC, -1.7 kg; TXR₉₀+CVC, -1.0 kg; CVC, -0.1 kg) were sustained to Week 48. At least one-point improvement in fibrosis stage/steatohepatitis resolution without worsening of fibrosis was observed in 32.3%/25.8%, 31.6%/15.8%, 29.7%/13.5%, and 32.5%/22.5% of patients in the TXR₁₄₀, CVC, TXR₁₄₀+CVC and TXR₉₀+CVC groups, respectively.

Conclusion

The safety profile of TXR+CVC combination was similar to respective monotherapies, with no new signals. TXR monotherapy showed sustained ALT and body weight decreases. No substantial incremental efficacy was observed with TXR+CVC combination on ALT, body weight, or in histological endpoints compared with monotherapy.

Introduction

Non-alcoholic steatohepatitis (NASH) is a progressive form of non-alcoholic fatty liver disease (NAFLD), one of the most common chronic liver diseases worldwide.^{1,2} It is a chronic inflammatory condition accompanied by hepatocyte damage and varying degrees of fibrosis, which may progress to cirrhosis.^{3,4} Pathogenic mechanisms of NASH are complex and may involve insulin resistance, accumulation of lipids, lipotoxicity, oxidative stress and injury, and gut microbiota disruption.⁵⁻⁷

Therapies targeting different pathogenic pathways in NASH are under investigation including nuclear receptor agonists like farnesoid X receptor (FXR), antioxidants, anti-inflammatory agents, anti-fibrotic agents, and modulators of the tumor necrosis factor- α pathway, among others.^{3,8,9}

There are no approved therapies globally for NASH, with many of the investigational agents studied to date either failing to meet histological endpoints or demonstrating limited efficacy.^{8,10} Given the complex pathophysiological processes that underpin NASH, it is hypothesized that combination therapy targeting multiple distinct mechanisms may effectively control the disease.³

Tropifexor (TXR), a potent non-bile acid FXR agonist, has been shown to be highly efficacious in animal models,^{11,12} and well tolerated at single doses up to 3000 μg in healthy volunteers with a pharmacokinetic (PK) profile suitable for once-daily dosing.¹³ In the Phase 2a/b FLIGHT-FXR study, sustained decreases in alanine aminotransferase (ALT) and hepatic fat fraction (HFF) were observed in patients treated with TXR versus placebo.¹⁴ Further, the therapeutic effect of FXR agonism in NASH has been demonstrated in clinical trials, with the bile acid derivative obeticholic acid resulting in fibrosis reduction and improvement in the key features of steatohepatitis.^{15,16}

Cenicriviroc (CVC), a potent inhibitor of C-C chemokine receptor types 2/5 (CCR2/5), has demonstrated antifibrotic and anti-inflammatory properties in animal models.¹⁷⁻¹⁹ In the Phase 2b CENTAUR study in patients with NASH, 1-year treatment with CVC resulted in an improvement in fibrosis without worsening of steatohepatitis, reduction of biomarkers of inflammation, and comparable safety and tolerability versus placebo.²⁰ With distinct and complimentary mechanisms of action, the combination of TXR and CVC might improve efficacy

while maintaining safety, thereby leading to potential additive effects. In a preclinical model of diet-induced NASH (streptozotocin administered to neonatal mice, followed by a high fat diet), treatment with the combination of TXR and CVC showed synergistic reduction in inflammation and ballooning versus monotherapy.²¹ In a drug-drug interaction study in healthy volunteers, this combination exhibited acceptable safety and tolerability versus the respective monotherapy; however, the co-administration of CVC reduced TXR peak drug concentration (C_{max}) and area under the concentration-time curve (AUC) by 35% at steady-state, while TXR did not influence CVC pharmacokinetics.²² Therefore, it is important to consider exposure differences when comparing the performance of TXR alone and in combination with CVC.

The purpose of this study was to assess the safety and efficacy of the TXR and CVC combination in patients with non-cirrhotic NASH compared with respective monotherapies.

Methods

Study design and treatments

TANDEM (NCT03517540) was a 48-week, Phase 2b randomized, multicenter, double-blind study conducted between September 2018 (first patient, first visit) and October 2020 (last patient, last visit) in 65 centers across 17 countries. The study design of TANDEM has been reported in detail previously²³ and is also illustrated in **Supplementary Figure 1**. All eligible patients were randomized to one of four treatment arms (TXR 140 μ g once daily [qd; TXR₁₄₀]; CVC 150 mg qd [CVC]; TXR 140 μ g+CVC 150 mg qd [TXR₁₄₀+CVC]; TXR 90 μ g+CVC 150 mg qd [TXR₉₀+CVC]) at a ratio of 1:1:1:1 in a blinded, unbiased manner using Interactive Response Technology. Randomization was stratified by participation in magnetic resonance imaging-proton density fat fraction (MRI-PDFF) assessment, which allowed for a balanced number of patients who underwent MRI-PDFF in each treatment arm. Investigators, persons performing the assessments, and the Novartis clinical trial team were blinded to the identity of study treatments from the time of randomization until final database lock.

The original study treatment duration was 48 weeks. A protocol amendment allowed treatment to continue for up to approximately 8 additional weeks for patients who were unable to attend the study site for the scheduled Week 48 end-of-treatment (EOT) assessments, including EOT liver biopsy, due to coronavirus disease-2019 (COVID-19) pandemic-related restrictions, which

included temporary closures of clinics. The study protocol and all amendments were reviewed by an Independent Ethics Committee or Institutional Review Board for each center, and the study was conducted according to the ICH E6 Guidelines for Good Clinical Practice that have their origin in the Declaration of Helsinki. All patients provided written informed consent before any study-specific procedures were performed.

Study population

Male and female patients aged ≥ 18 years (at the time of the screening visit) weighing between 50 and 200 kg were eligible to participate in the study. Other key inclusion criteria were (i) an adequate liver biopsy sample for evaluation by a central reader, (ii) presence of NASH as demonstrated by histologic evidence, and (iii) presence of fibrosis stages F2/F3 as demonstrated on a liver biopsy with evaluation by a central reader during the screening period (as per NASH clinical research network [CRN] staging criteria).²⁴ Alternatively, a historical biopsy was used if it was performed within 6 months prior to screening and evaluable by a central reader.

Key exclusion criteria included (i) current or history of significant alcohol consumption for a period of more than three consecutive months within 1 year prior to screening (>20 g/day in females and >30 g/day in males), (ii) uncontrolled diabetes (glycosylated hemoglobin [HbA1c] $\geq 9\%$ at screening), (iii) clinical evidence of hepatic decompensation or severe liver impairment, (iv) previous diagnosis of other forms of chronic liver disease or a history of autoimmune liver disease, and (v) women of child-bearing potential or pregnant/lactating women.

Study endpoint

The primary objective/endpoint of TANDEM was to evaluate the safety and tolerability of TXR plus CVC in patients with NASH and fibrosis (stages F2/F3) by monitoring adverse events (AEs), vital signs, and laboratory values during 48 weeks of treatment as compared to TXR and CVC monotherapy. This primary objective was chosen as this was the first study to investigate combined FXR agonism with CCR2/5 antagonism in patients with NASH. The secondary endpoints of this study were to evaluate the proportion of patients who had at least a one-point improvement in fibrosis stage (NASH CRN) without worsening of steatohepatitis and the proportion of patients with resolution of steatohepatitis without worsening of fibrosis, after 48

weeks of treatment. Exploratory endpoints included were previously reported²³ and provided in the **Supplementary Information**.

Study assessments

Safety assessments were performed to assess the occurrence of AEs, serious AEs (SAEs), AEs leading to study discontinuation or dose reduction, AEs of special interest (AESIs), changes in vital signs, and changes in laboratory data. AEs, SAEs, and vital signs were assessed at screening; baseline; Weeks 2, 4, 6, 8, 12, 16, 24, 32, 40, and 48; and post-treatment follow-up at Week 52.

To assess treatment-induced changes, paired liver biopsies (baseline and EOT) were reviewed by a central pathologist (blinded to visits and treatment) to score fibrosis staging and grading of steatohepatitis features (steatosis, lobular inflammation, and hepatocyte ballooning). Real-time readings of liver biopsies were also performed at baseline to assess eligibility for entry into the study and after treatment completion. See **Supplementary Information** for further details on liver biopsy readings.

The NAFLD activity score (NAS) was calculated according to the NASH CRN criteria,²⁴ which included steatosis (0–3), lobular inflammation (0–3), and hepatocyte ballooning (0–2), giving a range of 0–8 for the NAS.

MRI-PDFF was performed optionally in a subset of patients to quantify HFF at screening. All MRI scans were performed locally and sent to the central MRI laboratory for evaluation. Anthropometric assessments included height and body weight.

Blood samples and fasting blood samples were collected to assess liver biochemistry, which included ALT, aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and lipid panels (i.e., total cholesterol, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], triglycerides, free glycerol, and free fatty acids).

A number of non-invasive tests were performed to assess liver damage and function. See **Supplementary Information** for further details.

Patient-reported outcomes (PROs) included the visual analog scale (VAS) for itch, VAS for sleep disturbance due to itch, Patient Global Impression of change (PGIC; end of study [EOS] only), and Patient Global Impression of severity (PGIS).

Pre- and post-dose PK plasma samples were collected at specified time intervals over the study duration (Weeks 4, 8, 12, 24, and 48). See **Supplementary Information** for further details.

Statistical analysis

Summary tables are presented by treatment group and analysis visit (as applicable) using descriptive statistics. Continuous variables are summarized by arithmetic mean and standard deviation (SD) unless otherwise stated. The number and percentage of patients in each category are presented for categorical variables for each treatment group and all patients (total).

There were no pre-specified hypotheses and statistical models in this study. The primary safety variables were analyzed descriptively using a summary table of absolute and relative frequencies, overall and by preferred term (for the occurrence of AEs, SAEs, and AEs leading to study discontinuation or dose reduction) and using a summary table of absolute and relative frequencies, overall and by type of AEs (for AESIs). Only treatment-emergent adverse events (TEAEs) were considered for the analysis.

Due to the nature of the primary objective, the assessment was made based on the whole safety profile and not on quantitatively formulated hypotheses for distinct parameters. Therefore, the sample size was based on the feasibility with respect to expected speed of enrollment and duration of the study.

For power considerations, events with a true incidence of 30% and above are likely to be observed (almost 100% probability) in a group of 50 patients (size of each treatment group). Events with true incidences below 10% down to 3% are still very likely to be observed, while events with less than 50% probability are observed only if the true incidence is less than about 2.5%.

For the secondary objectives, the difference in the proportion of patients on the different TXR plus CVC regimens who achieved at least a one-point improvement in fibrosis stage and/or resolution of steatohepatitis at Week 48 was compared with TXR and CVC monotherapy patients. Treatment differences between TXR+CVC combination therapy and monotherapy with TXR or CVC were evaluated using a Cochran-Mantel-Haenszel test that controlled for baseline fibrosis stage (F2/F3).

For the PK analysis, dose-response and exposure-response relationships for TXR, CVC, and TXR+CVC combination therapy with key selected safety (e.g., ALT and AST) and efficacy endpoints including biomarkers (e.g., FGF19, GGT, etc.) were explored.

Post hoc digital pathology and artificial intelligence (AI) analyses of treatment-induced changes in steatosis, hepatocyte ballooning, and liver fibrosis

Unstained, formalin-fixed sections from paired liver biopsies (baseline and EOT) were examined using second harmonic generation/two-photon excitation fluorescence (SHG/TPEF) microscopy with computer-assisted analyses. The liver sections were de-paraffinized, and tissue scanning was performed on Genesis[®]200 (a fully automated, stain-free multiphoton fluorescence imaging microscope) and analyzed using AI-based algorithms (HistoIndex Pte. Ltd) to quantitatively assess qFibrosis, qSteatosis, and qBallooning, as described previously.²⁵⁻²⁷ Additional analyses were also performed including (i) quantitation of fibrosis dynamics in different zones of liver lobules from baseline to Week 48, (ii) co-localization analysis to assess the relationship between treatment-induced changes of fibrosis in relation steatosis changes, and (iii) co-localization analysis to assess the relationship between treatment-induced changes of fibrosis and hepatocyte ballooning, as described previously.²⁷

To compare steatosis and liver fibrosis changes from baseline and after 48 weeks of treatment, as assessed by NASH CRN scoring and by AI digital quantitation (qSteatosis and qFibrosis), patients in the four treatment arms were categorized as *Progressor, No Change, or Regressor* (P/N/R analysis). The qSteatosis and qFibrosis results were expressed both by categorical steatosis grade (qS0 to qS3) and fibrosis stage (qF0 to qF4), respectively, as well as a continuous value. For steatosis, progression was defined as increase of ≥ 1 grade from baseline to Week 48 or an increase of ≥ 1 standard error of the mean (for qSteatosis as a continuous value); regression was defined as a decrease of ≥ 1 grade or decrease of ≥ 1 standard error of mean (for qSteatosis as a continuous value). For fibrosis, progression was defined as an increase of ≥ 1 stage or an increase of ≥ 1 standard error of the mean (for qFibrosis as a continuous value); regression was defined as decrease of ≥ 1 stage or ≥ 1 standard error of mean (for qFibrosis as a continuous value). See **Supplementary Information** for further details.

Results

Patient disposition and baseline demographics

Overall, 643 patients were screened for study inclusion, with 193 patients (30.0%) meeting the entry criteria for randomization. Of the 193 patients who were randomized to study treatment, 158 patients (81.9%) completed the study (**Figure 1**).

Baseline patient demographics and characteristics are displayed in **Table 1**. Across treatment groups, mean ages of patients ranged from 54 to 55 years, most patients were female (60.0%–64.6%), except in the TXR₉₀+CVC group (47.9% were female), and most were Caucasian (82.0%–91.7%). Across treatment groups, 82.4% of patients were reported to have diabetes and 55.4% were taking concomitant lipid-reducing medication.

Based on baseline liver biopsies and NASH CRN histological scoring, F3 fibrosis was present in 64.0%, 79.2%, 78.7%, and 62.5% of patients in the TXR₁₄₀, CVC, TXR₁₄₀+CVC, and TXR₉₀+CVC groups, respectively. All patients had NAS: steatosis (1 or 2), with lobular inflammation (1, 2, or 3), and hepatocyte ballooning (1 or 2). The mean NAS total score was 5.2 in the TXR₁₄₀ and TXR₉₀+CVC groups, and 5.4 in the CVC and TXR₁₄₀+CVC groups.

Safety

Rates of AEs were similar across treatment groups. Overall, 85.5% of patients experienced at least one AE (**Table 2**).

The proportion of patients who experienced pruritus was the highest in the TXR₁₄₀ group (40.0%) and was lower in the TXR₁₄₀+CVC group (31.9%). Similar patterns were noted for fatigue and urinary tract infection.

Overall, 21 of 193 patients (10.9%) discontinued from study treatment due to an AE, with most discontinuations occurring in the TXR₁₄₀ group (9/50, 18.0%) and in the TXR₁₄₀+CVC group (8/47, 17.0%).

The AEs that attributed to the most discontinuations from study treatment were pruritus (TXR₁₄₀ [4/50, 8.0%]; TXR₁₄₀+CVC [2/47, 4.3%]) and flatulence (TXR₁₄₀+CVC [2/47, 4.3%]); all other AEs leading to discontinuation were single occurrences. SAEs were reported in 22 of 193 patients (11.4%) overall and the incidence was the highest in the TXR₉₀+CVC group. Most SAEs were single occurrences, except for two patients who experienced SAEs due to COVID-19 (TXR₉₀+CVC group). Of the 22 patients with SAEs, only one patient had an SAE that was

attributed by the investigator to study treatment (spondylitis, TXR₁₄₀ group). A cerebrovascular accident was reported in one participant each in the TXR₁₄₀+CVC and TXR₉₀+CVC groups.

Liver tests, hepatic fat fraction, and fibrosis markers

In the TXR and combination groups, a decrease in ALT (**Figure 2A**), AST (**Figure 2B**) and GGT (**Figure 2C**) from baseline was noted during the 48-week period. Approximately 50% of patients underwent MRI-PDFF. At both Weeks 24 and 48, reductions in HFF were observed in all TXR-containing groups, with the highest percentage reduction observed with TXR₁₄₀+CVC combination therapy (**Figure 2D**). Reductions of at least a 30% in HFF at Weeks 24 and 48, as measured by PDFF, were observed more frequently in all TXR-containing groups compared to CVC monotherapy group (**Figure 2E**). At Weeks 24 and 48, the number of patients with at least a 30% reduction in HFF was the highest in the TXR₁₄₀+CVC (11/21, 52%) and TXR₁₄₀ (6/16, 38%) groups (**Figure 2E**).

There were no consistent changes from baseline to Week 48 for liver stiffness (via Fibroscan[®]), enhanced liver fibrosis (ELF) scores, fibrosis biomarker test scores, NAFLD fibrosis scores, or magnetic resonance elastography-derived liver stiffness from baseline to Week 48 with any TXR-containing dose. At Week 48, although there was a slight reduction in post-treatment mean fibrosis-4 (FIB-4) from baseline (change from baseline: -0.02) in the TXR₁₄₀+CVC group, when compared with the change from baseline in the monotherapy and TXR₉₀+CVC groups, the change was not considered meaningful. Further details of fibrosis markers and other biomarker results are given in **Supplementary Figures 2–3**.

Liver histology

At least a one-point improvement in fibrosis stage was observed in 32.3% (10/31), 31.6% (12/38), 29.7% (11/37), and 32.5% (13/40) of patients in the TXR₁₄₀, CVC, TXR₁₄₀+CVC, and TXR₉₀+CVC groups, respectively (**Figure 3A**). Steatohepatitis resolution without worsening of fibrosis was observed in 25.8% (8/31), 15.8% (6/38), 13.5% (5/37), and 22.5% (9/40) of patients in the TXR₁₄₀, CVC, TXR₁₄₀+CVC, and TXR₉₀+CVC groups, respectively (**Figure 3B**). There was no evidence that patients who received combination therapy demonstrated a higher likelihood of at least a one stage improvement in fibrosis (NASH CRN staging) or achieving resolution of steatohepatitis after 48 weeks of treatment compared with patients who received

monotherapy treatment, based on paired biopsy readings. The odds ratio and 95% confidence interval (CI) was similar in the TXR₉₀+CVC group compared with CVC (1.21, 95% CI: 0.41, 3.61) and lowest in the TXR₁₄₀+CVC group compared with TXR₁₄₀ (0.8, 95% CI: 0.25, 2.63). Similar results were reported based on real-time biopsies (see **Supplementary Figure 4**) and for the histologic endpoint based on the FDA/EMA definition of resolution of steatohepatitis without worsening of fibrosis (NASH CRN staging) (see **Supplementary Table 1**).

The proportion of patients with paired biopsy results at Week 48 with at least two-point improvement in fibrosis (NASH CRN staging) regardless of steatohepatitis status or without worsening of steatohepatitis at 48 weeks of treatment were considered not to be clinically meaningful (see **Supplementary Table 2**). Changes in individual histological features of NASH are shown in **Supplementary Table 3**.

At Week 48, no consistent changes in liver collagen morphometry were observed in combination treatment groups, with the highest response in the TXR₁₄₀+CVC group compared with TXR₁₄₀ monotherapy group (0.7 [adjusted mean difference vs TXR₁₄₀]).

Digital quantitation and AI analyses of treatment-induced changes in steatosis, ballooning, and liver fibrosis

Paired liver biopsies from 144 patients (TXR₁₄₀, N=30; CVC, N=37; TXR₁₄₀+CVC, N=37; TXR₉₀+CVC, N=40) were analyzed. P/N/R analyses revealed that TXR₁₄₀ alone or in combination with CVC had a greater effect in reducing steatosis than CVC monotherapy. The TXR antisteatotic effect observed in the TXR₁₄₀ group was significantly greater than the other three treatment groups based on the NASH CRN scoring (**Figure 4A**), as well as numerically higher with the digital quantitation of qSteatosis changes (**Figure 4B**). No significant difference was present between groups when assessing liver fibrosis changes from baseline to Week 48 either with the NASH CRN scoring or with qFibrosis (stage and continuous value) digital quantitation (**Figure 4 C and D**).

In-depth analyses of fibrosis changes in different zones of liver lobule demonstrated that TXR₁₄₀ achieved greater fibrosis reduction overall, and in the periportal area (−33%) and in zone 2 (−28%) (**Figure 5A**). The antifibrotic effect of CVC monotherapy was seen mainly in the periportal (28%), pericentral (24%), and central vein (28%) areas (**Figure 5A**). In the

colocalization analyses, significant fibrosis reduction was observed only in association with steatosis reduction in all treatment groups. The effect of TXR₁₄₀ monotherapy was seen mainly in zone 1 and zone 2 (**Figure 5B**); the effect of CVC monotherapy appeared uniform in all three zones of liver lobule (**Figure 5C**), while both TXR₁₄₀+CVC and TXR₉₀+CVC treatment groups showed an additive effect, achieving the greatest fibrosis reduction near steatosis in all three zones of the liver lobule, with the TXR₁₄₀+CVC group showing the greatest treatment-induced changes (**Figure 5D and E**).

There were no notable changes in the number of ballooned hepatocytes from baseline to Week 48 with any of the four treatment regimens, irrespective of whether patients had a high or low number of ballooned hepatocytes. (**Supplementary Figure 5A**). Treatment-induced changes of fibrosis in relation to hepatocyte ballooning, in the four treatment arms, were evaluated by simultaneous measurement of fibrosis and hepatocyte ballooning in colocalization analyses. A marked increase of qBallooning area (as observed in the TXR₁₄₀+CVC group) was associated with a relative increase (%) in fibrosis area near ballooned hepatocytes, while improvement in qBallooning area was associated with reduction of the nearby collagen fibers. In the subset of patients who had improved qBallooning grade, the TXR₁₄₀ group showed the highest improvement in qBallooning area (67% reduction) and in nearby fibrosis (62% reduction), compared with the other treatment groups. (**Supplementary Figure 5B and C**).

Lipid parameters, body weight, and HOMA-IR

Mean LDL-C increased (**Figure 6A**) and mean HDL-C decreased (**Figure 6B**) from baseline in the TXR₁₄₀ group and both combination treatments, but there was less change with CVC. In both cases, the treatment effect was apparent by Week 4 and near maximum by Week 12 with little change thereafter. At Week 48, in the TXR₁₄₀ group and combination treatment groups, the mean increase in LDL-C from baseline ranged between 0.43 and 0.56 mmol/L (17–22 mg/dL) and the mean decrease in HDL-C from baseline ranged between 0.07 and 0.20 mmol/L (3 and 8 mg/dL). For the other lipids (total cholesterol, triglycerides, free glycerol, and free fatty acids), there was very little change from baseline or a mild-to-moderate worsening in lipid levels during the study, with little suggestion of a difference between treatment groups (**Supplementary Figure 6**). At baseline, the proportion of patients taking lipid lowering agents was higher in combination

treatment arms (70.2% [TXR₁₄₀+CVC]; 60.4% [TXR₉₀+CVC]) compared with monotherapy arms (44.0% [TXR₁₄₀]; 47.9% [CVC]). During the treatment period none of the patients started a statin as a new medication in any treatment arm.

A reduction in body weight from baseline was evident with TXR-containing groups by Week 4. By Week 24, the following mean changes from baseline were reported: TXR₁₄₀, -2.5 kg; TXR₁₄₀+CVC, -1.7 kg; TXR₉₀+CVC, -1.0 kg; CVC, -0.1 kg. These reduction patterns were sustained until Week 48 (**Figure 6C**).

Median HOMA-IR scores at baseline ranged between 4.60 and 6.63 across treatment groups, with the highest baseline score in the TXR₁₄₀ group. At Week 24, HOMA-IR scores improved in the TXR₁₄₀ and CVC groups with a change from baseline of -0.78 and -0.16, respectively, while scores in the combination therapy groups increased (change from baseline: 0.68 and 0.80, respectively). At Week 48, the HOMA-IR score decreased in the TXR₁₄₀ group only (change from baseline: -0.49) with no difference from baseline in the CVC group and somewhat lower scores in both combination therapy groups (0.34 and 0.57, respectively; see **Supplementary Table 4**).

Patient-reported outcomes

There were no differences in the VAS scores for itch intensity and sleep disturbance due to itch across treatment groups. For patients who responded to the global PGIS questionnaire, results at Weeks 12, 24, and 48 were similar to those at baseline across all treatment groups; most patients rated their symptoms as very mild, mild, or moderate. In patients who responded to the PGIC questionnaire, most in the CVC and TXR₁₄₀+CVC groups indicated that their symptoms were “about the same” (30/44, 68.2%, and 21/41, 51.2%, respectively).

Pharmacokinetics

No marked difference was present in the TXR pre-dose mean plasma concentration range for the TXR₁₄₀ dose level (1.56 to 1.95 ng/mL) when dosed either alone or in combination with CVC (1.33 to 1.91 ng/mL). Reduced TXR pre-dose concentrations were observed in the TXR₉₀+CVC group (1.04 to 1.13 ng/mL), broadly in proportion to the reduced dose of TXR (**Supplementary Figure 7A**). Post-dose mean TXR drug concentration ranges were reduced by ~10% in the TXR₁₄₀+CVC study arm (1.61 to 1.98 ng/mL) (**Supplementary Figure 7B**) compared to the TXR₁₄₀ group (1.91 to 2.23 ng/mL).

Plasma concentrations ranges of CVC in pre- and post-dose PK samples were comparable across each of the study arms (pre-dose concentration range, 179 to 204 ng/mL for the CVC group, 160 to 198 ng/mL for the TXR₉₀+CVC group, and 165 to 229 ng/mL for the TXR₁₄₀+CVC group). Furthermore, CVC plasma concentrations were consistent throughout the study (post-dose concentration range, 181–219 ng/mL for the CVC group, 167–215 ng/mL TXR₉₀+CVC group, and 174–226 ng/mL for the TXR₁₄₀+CVC group) (**Supplementary Figure 7C & 7D**).

Discussion

This study was a 48-week, randomized, double-blind, multicenter trial with the primary objective to evaluate the safety and tolerability of TXR+CVC in patients with NASH and fibrosis as compared to TXR and CVC monotherapy. The safety profiles of the combination therapies of TXR₁₄₀+CVC and TXR₉₀+CVC were similar to those of monotherapy with TXR and CVC, with no additional emergent safety signals compared to those identified and reported in previous monotherapy studies, and no deaths were reported.^{14, 20}

Overall, pruritus, nausea, and fatigue were the most frequently experienced AEs, with the highest incidence of pruritus observed in the TXR monotherapy group and notably lower with TXR₁₄₀+CVC combination treatment. The observed reduction of post-dose TXR levels (~10%) in the presence of CVC may explain this. A previous drug-drug interaction study²² showed reduced systemic TXR exposure of 35% for C_{max} and AUC and most likely reflects the true reduction in TXR exposure for the combination, but not monotherapy arms. This may also have had an impact on the observed efficacy of combination therapy as dosed in this trial (discussed below), with a higher TXR dose of 200 µg potentially resulting in greater efficacy than that observed with TXR at a dose of 140 µg. Most SAEs were single occurrences. The AE most frequently leading to discontinuation from study treatment was pruritus. Other studies investigating FXR agonists^{14-16, 28, 29} have also noted pruritus as a common AE, indicating that it may be a class effect of agonism by FXR.

There was a decrease in ALT, AST, and GGT in the TXR monotherapy and combination groups from baseline during the 48-week period, while in the CVC monotherapy group, no such reduction was observed. A similar decrease in ALT from baseline with TXR was observed in the FLIGHT-FXR study.¹⁴ With a number of studies suggesting that a ≥30% relative reduction in

HFF measured by MRI-PDFF may be associated with histologic response in NASH trials,^{30,31} it is interesting to note that in our study, this level of reduction in HFF was observed in several of the FXR containing arms without notable histologic response. At Week 24, the number of patients with a $\geq 30\%$ reduction in HFF measured by MRI-PDFF was highest in the TXR₁₄₀+CVC group (52.4%); however, at Week 48, the highest number of patients with a $\geq 30\%$ reduction in HFF was seen in the TXR₁₄₀ monotherapy group (37.5%). No meaningful change over the study period was observed in non-invasive markers of liver fibrosis.

Although the observed fibrosis improvement was in the same range as in other placebo controlled monotherapy studies with CVC or TXR,^{14,20} in our study neither of the combination therapies (TXR₁₄₀+CVC or TXR₉₀+CVC) increased the likelihood of improvement of fibrosis or resolution of steatohepatitis, based on the central pathologist's assessment, when compared with either TXR or CVC monotherapy. In the CENTAUR study, ≥ 1 stage improvement in fibrosis without worsening of steatohepatitis at 1 year was observed in twice as many patients on CVC (20%) compared to placebo.²⁰ Interim results of the Phase 3 AURORA study (NCT03028740), designed to evaluate and confirm the efficacy and safety of CVC for the treatment of liver fibrosis in adults with NASH, showed a lack of efficacy.³²

Although we did not see synergistic efficacy with these therapies when used in combination, this does not exclude such an effect in other combinations. As the effects of CVC on metabolic components of NASH are thought to be limited³³ and its antifibrotic activity did not perform as expected in the AURORA Phase 3 study, a TXR combination with another compound with potent antimetabolic activity may have provided greater synergy and efficacy. Additionally, it is worth noting that in our study, most patients had markers of progressive NASH at baseline, with stage 3 fibrosis, a proportion that is higher than in other non-cirrhotic trials investigating NASH. When considering more advanced NASH, a trial involving patients with advanced fibrosis or cirrhosis (fibrosis stage 3-4), combination therapy with firsocostat (an acetyl-CoA carboxylase inhibitor), and cilofexor (an FXR agonist) resulted in greater improvements in histology and clinically relevant biomarkers versus either agent alone or placebo, although, as with our trial, the histological endpoint was not met.²⁹

The post hoc digital pathology and AI analyses provided useful mechanistic details in the evaluation of NASH treatment with compounds of different mechanisms of action. TXR alone was shown to have greater impact in reducing steatosis than CVC monotherapy, consistent with

TXR effects in reducing liver enzymes and HFF; the antifibrotic activity of TXR monotherapy was seen mainly in zone 1 and zone 2 of the liver lobule, while CVC showed antifibrotic effects uniformly in all 3 zones of the liver lobule. Although no significant difference in liver fibrosis stage was observed between the four treatment groups over the study period using conventional microscopy, digital quantitation analysis of fibrosis changes in different zones of the liver lobule revealed that the combination of TXR and CVC had an additive effect, achieving the greatest fibrosis reduction near steatosis in all 3 zones of the liver lobule, compared with each monotherapy group, with the TXR₁₄₀+CVC group showing the greatest treatment-induced changes. Similarly, the use of AI/machine learning analyses of liver biopsies from the ATLAS trial provided greater details than the conventional microscopy and the NASH CRN scoring in evaluating the effects of another combination therapy.³⁴ The effects seen in different liver lobules in our trial using digital pathology and AI analyses may not have been detected using conventional microscopy.

The co-localization analyses assessing treatment-induced changes of fibrosis in relation to steatosis or hepatocyte ballooning, in the four treatment arms, confirmed the association that fibrosis regression occurs in cases with reduction of steatosis and hepatocyte ballooning, as described previously.²⁷ Overall, these data illustrate the granularity and the additional information that can be obtained by applying AI digital pathology for quantitative assessment of NASH features and liver fibrosis in general and the advantage of its use in clinical trials, along with the standard diagnostic assessment of liver histology. The clinical relevance of AI digital measurements of the NASH features, especially for liver fibrosis progression or regression, will have to be established in future studies in relation to liver-related clinical outcomes.

The treatment effect on changes in lipid levels related to TXR treatment was apparent by Week 4, near maximum by Week 12, and with little change thereafter. This was similar to the stabilization of changes in lipid levels after Week 12 in the FLIGHT-FXR study.¹⁴ There were no consistent changes in triglycerides in any treatment group. These effects are in line with those observed with other FXR agonists. There was a sustained reduction in body weight in the TXR-containing groups, although the COVID-19 pandemic related restrictions introduced mid-study may have attenuated the effects seen with TXR on weight loss. PROs were similar across all treatment groups.

PK data from this study confirm a similar pre-dose exposure between TXR₁₄₀ monotherapy and TXR₁₄₀ combination therapy and a trend for a higher TXR exposure in samples collected post-dose for the TXR₁₄₀ monotherapy group. Study endpoints that are similar for the TXR₁₄₀ monotherapy and TXR₁₄₀+CVC combination group (e.g., lipids, ALT, GGT) may be more dependent on C_{min}, whereas for the stronger effects seen in the TXR₁₄₀ monotherapy group (e.g., pruritus, weight loss), the higher total exposure (AUC and C_{max}) may contribute.

Limitations of this study include a small number of patients, limiting the power to address histological change, with the COVID-19 pandemic effect further decreasing effective sample size, and leading to missed visits and central lab assessments.

Conclusions

TXR monotherapy showed sustained decrease in ALT and body weight, but there was no substantial incremental efficacy with the combination of TXR and CVC either on ALT or body weight reduction nor in histological endpoints when compared to the monotherapy arms. The TANDEM study demonstrated that the safety profile of this combination therapy (TXR+CVC) was similar to that of each of the monotherapies. There were no new safety signals compared to those already reported in monotherapy studies.

Author contributions

All authors were involved in the preparation and critical review of the manuscript and approved the final version for submission. All authors were involved in the interpretation of data in the manuscript. All authors agreed to be accountable for all aspects of the work and attest to the accuracy and integrity of the work. Acquisition of clinical data and investigators in the clinical study: Quentin M Anstee, Kathryn J Lucas, Sven Francque, Manal F Abdelmalek, Arun J Sanyal, Vlad Ratziu, Adrian C Gadano, Michael Charlton, Edward Mena, Jörn M Schattenberg, Mazen Nouredin, Donald Lazas, George BB Goh, Shiv Kumar Sarin, Yusuf Yilmaz. Digital data analyses and interpretation: Elaine Chng, Nikolai V Naoumov. Conception, design, and/or statistical/data analysis, and/or clinical conduct of the trial: Mary Rinella, Rohit Loomba, Miljen Martic, Rowan Stringer, Jossy Kochuparampil, Li Chen, Gerardo Rodriguez-Araujo, Nikolai V Naoumov, Clifford Brass, Marcos C Pedrosa.

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Conflicts of Interest

Quentin M Anstee, on behalf of Newcastle University, consults for Alimentiv, Akero, AstraZeneca, Axcella, 89Bio, Boehringer Ingelheim, Bristol Myers Squibb, Galmed, Genfit, Genentech, Gilead, GlaxoSmithKline, Hanmi, HistoIndex, Intercept, Inventiva, Ionis, IQVIA, Janssen, Madrigal, Medpace, Merck, NGMBio, Novartis, Novo Nordisk, PathAI, Pfizer, Pharmanest, Prosciento, Poxel, Resolution Therapeutics, Roche, Ridgeline Therapeutics, RTI, Shionogi, and Terns. He received grants from AstraZeneca, Boehringer Ingelheim, and Intercept. He is on the speakers’ bureau for Fishawack, Integritas Communications, Kenes, Novo Nordisk, Madrigal, Medscape, and Springer Healthcare. He receives royalties from Elsevier.

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The remaining authors have nothing to report.

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Figure 1. CONSORT flow diagram of participant disposition by treatment group

^aIf a patient completed the 8-week extension, the patient was also counted as having completed the 4-week extension. CVC, cenicriviroc; N, number of patients in group; n, number of patients with outcome; TXR₉₀, tropifexor 90 µg; TXR₁₄₀, tropifexor 140 µg

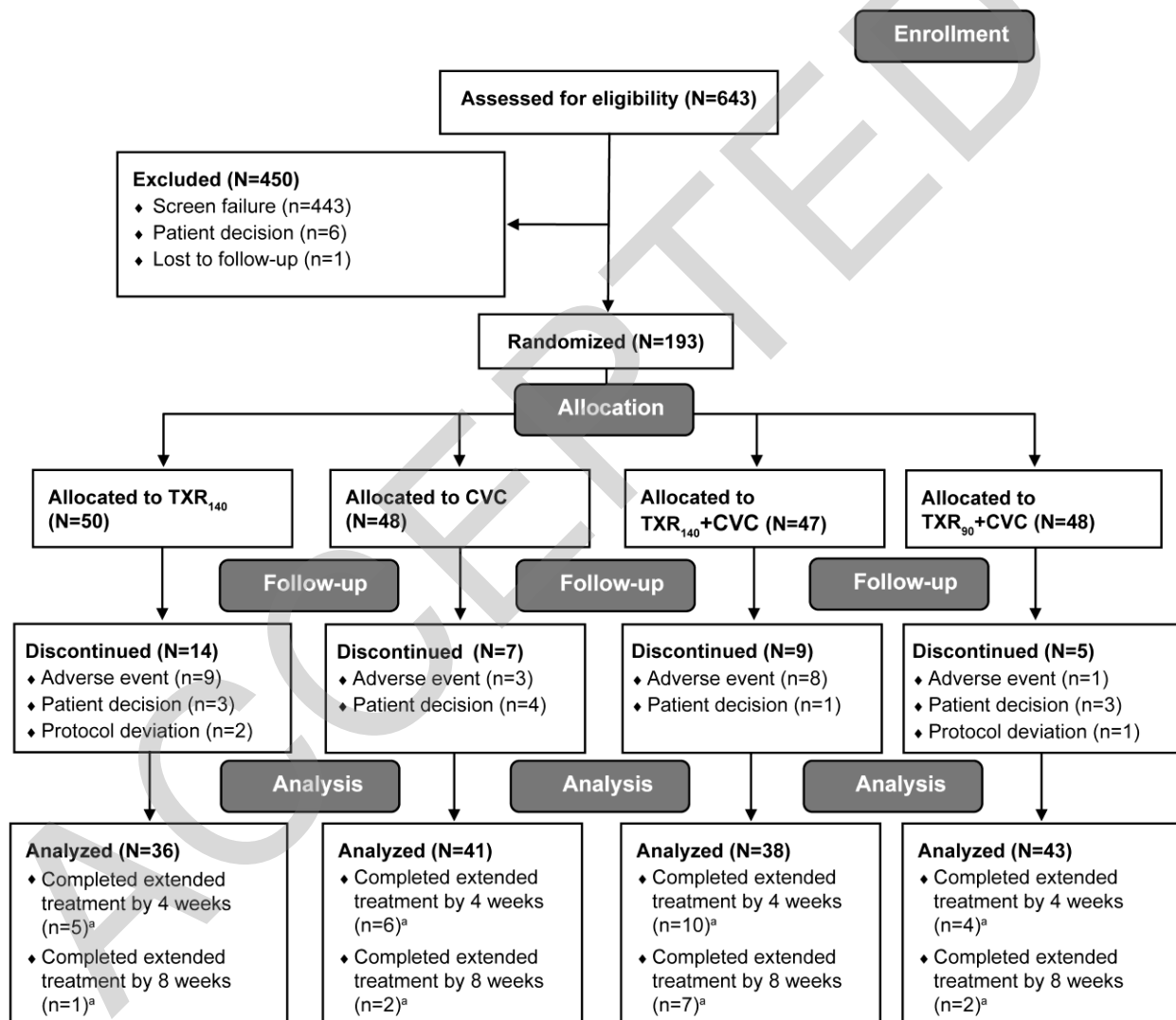


Figure 2. Geometric mean percentage change from baseline (95% CI) up to Week 48 in all groups and change in hepatic fat fraction at Weeks 24 and 48

(A) Geometric mean percentage change (95% CI) in ALT; (B) Geometric mean percentage change (95% CI) in AST; (C) Geometric mean percentage change (95% CI) in GGT; (D) Geometric mean percentage change from baseline in hepatic fat fraction; (E) Patients with at least a 30% reduction in hepatic fat fraction.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CVC, cenicriviroc; GGT, gamma-glutamyl transferase; HFF, hepatic fat fraction; n, number of patients in group; TXR₉₀, tropifexor 90 μg; TXR₁₄₀, tropifexor 140 μg

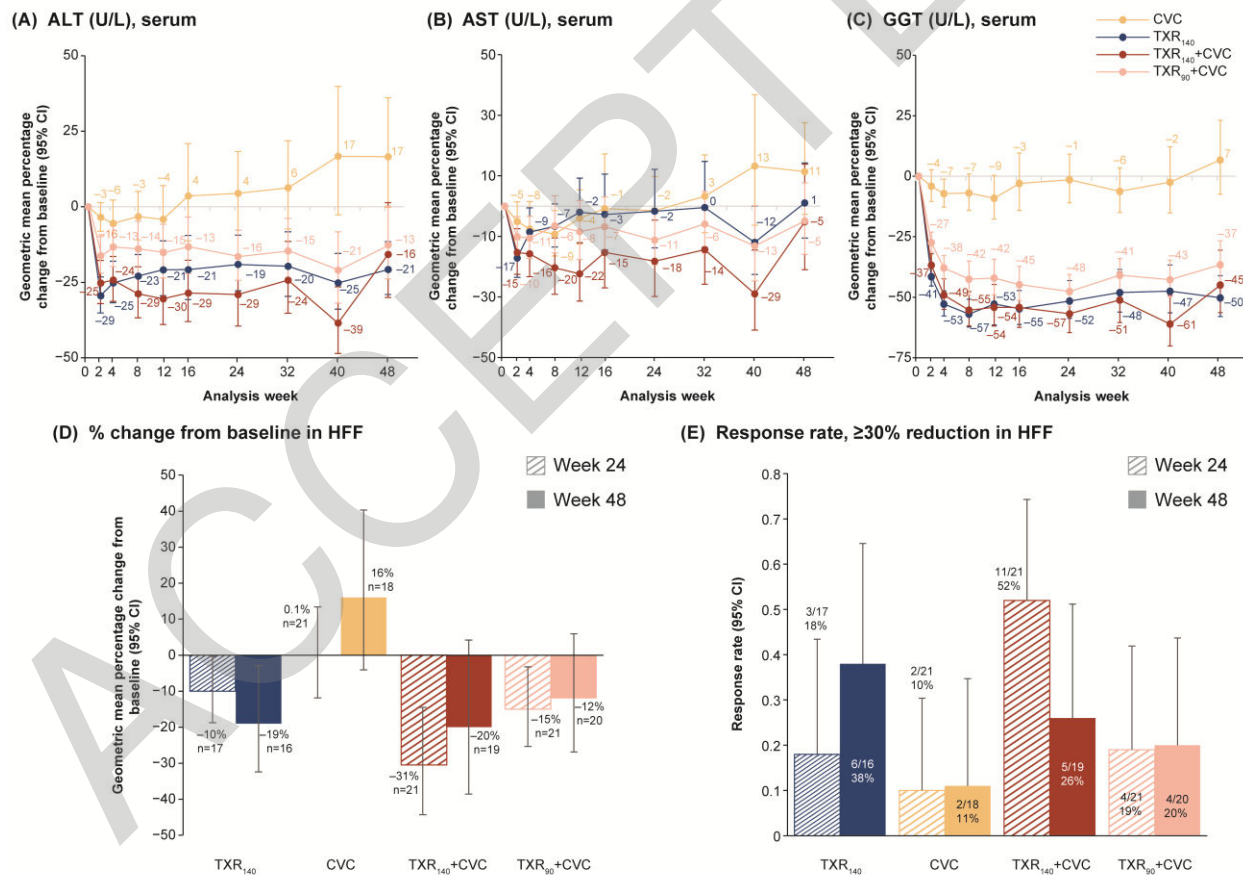
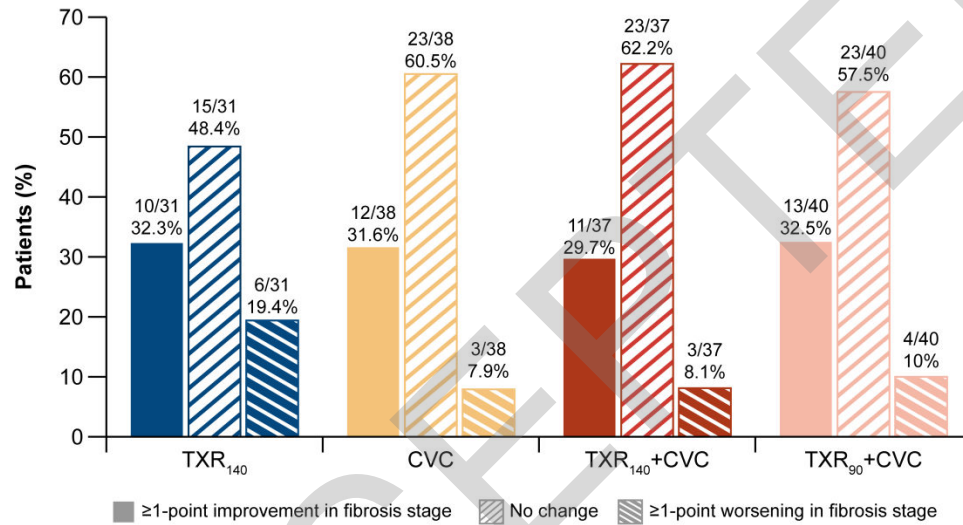


Figure 3. Participants' histological response at Week 48 in all groups based on NASH CRN staging

(A) Proportion of patients with change in fibrosis stage; (B) Proportion of patients with steatohepatitis resolution.

CRN, clinical research network; CVC, cenicriviroc; NASH, non-alcoholic steatohepatitis; TXR₉₀, tropifexor 90 g; TXR₁₄₀, tropifexor 140 µg

(A) Fibrosis change, regardless of steatohepatitis status – Paired reading



(B) Steatohepatitis resolution (diagnostic category) – Paired reading

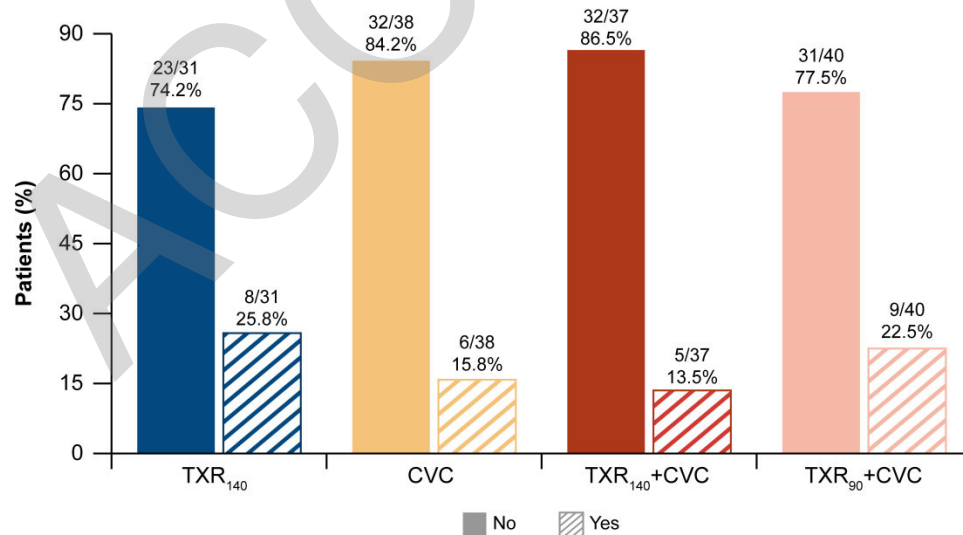


Figure 4. Changes in steatosis and liver fibrosis as assessed by NASH CRN scoring and by digital quantification from baseline to Week 48

(A) P/N/R analysis of steatosis changes based on the NASH CRN scoring; (B) P/N/R analysis of steatosis changes based on the digital quantitation and expressed as qSteatosis grade or qSteatosis as a continuous value; (C) P/N/R analysis of fibrosis changes based on the NASH CRN scoring; (D) P/N/R analysis of fibrosis changes based on the digital quantitation and expressed as qFibrosis stage or qFibrosis as a continuous value. *p*-values obtained by comparing each treatment arm versus TXR 140 μg monotherapy using a Chi-square test.

CRN, Clinical Research Network; CVC, cenicriviroc; n, number of patients per group; NASH, non-alcoholic steatohepatitis; P/N/R, Progressive/No-change/Regressive; qF, qFibrosis; qS, qSteatosis; SHG/TPEF, second harmonic generation/two-photon excitation fluorescence microscopy; TXR₉₀, tropifexor 90 μg; TXR₁₄₀, tropifexor 140 μg.

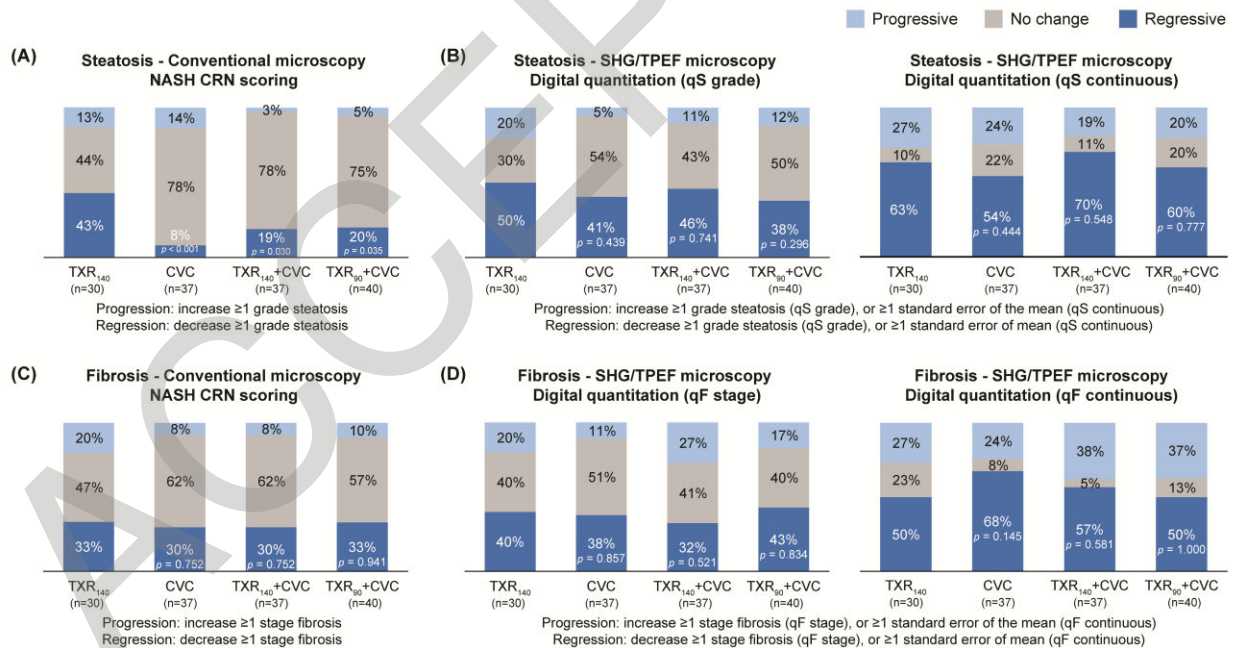


Figure 5. Treatment-induced fibrosis changes in different zones of liver lobules and co-localization analysis of steatosis and fibrosis changes from baseline to Week 48

(A) Digital quantification of fibrosis dynamics as a percentage change of fibrosis area in different zones of the liver lobule. The periportal and pericentral areas are set at 100 μm from the portal tract and the central vein, respectively, and the region in between is the Zone 2 area.

$p > 0.05$ each treatment group versus TXR₁₄₀ treatment group (Chi-square test); (B–E) Co-localization analysis of steatosis and fibrosis in zone 1, 2, and 3 of liver lobules. Patients were divided into two subgroups: those with “unchanged” or “increased” qSteatosis and those with “reduced” qSteatosis. Wilcoxon rank test was used for p -values comparing baseline to Week 48 changes.

CVC, cenicriviroc; n, number of patients per group; TXR₉₀, tropifexor 90 μg; TXR₁₄₀, tropifexor 140 μg.

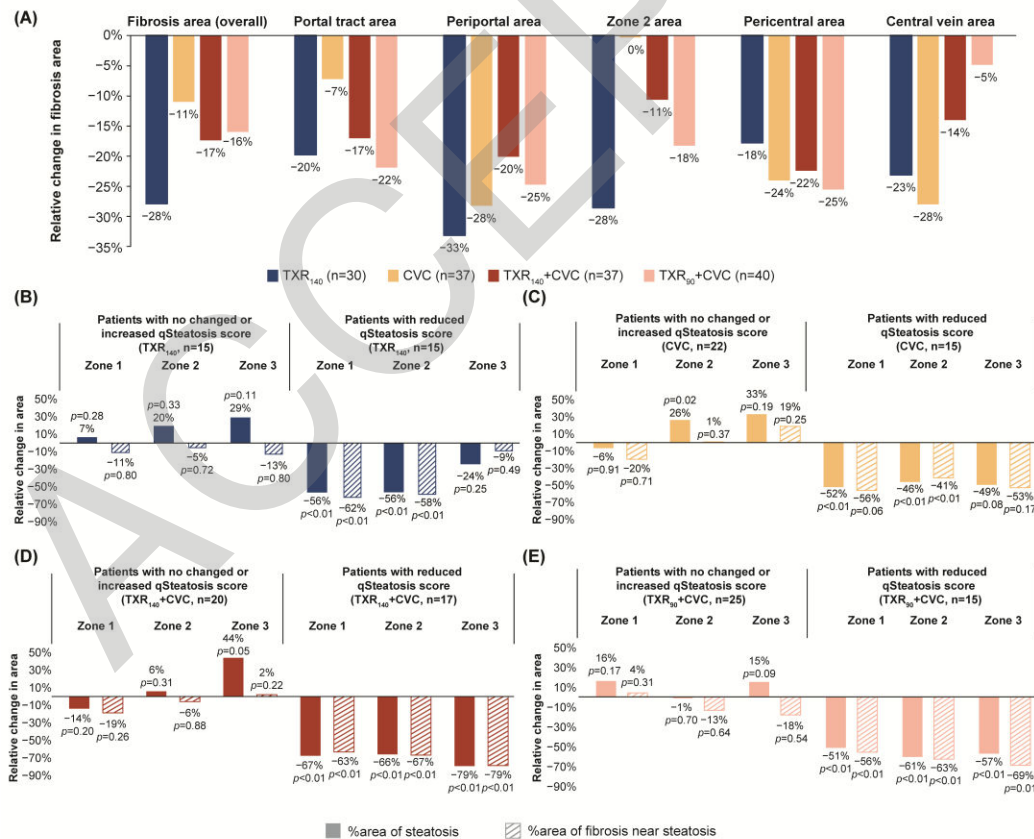
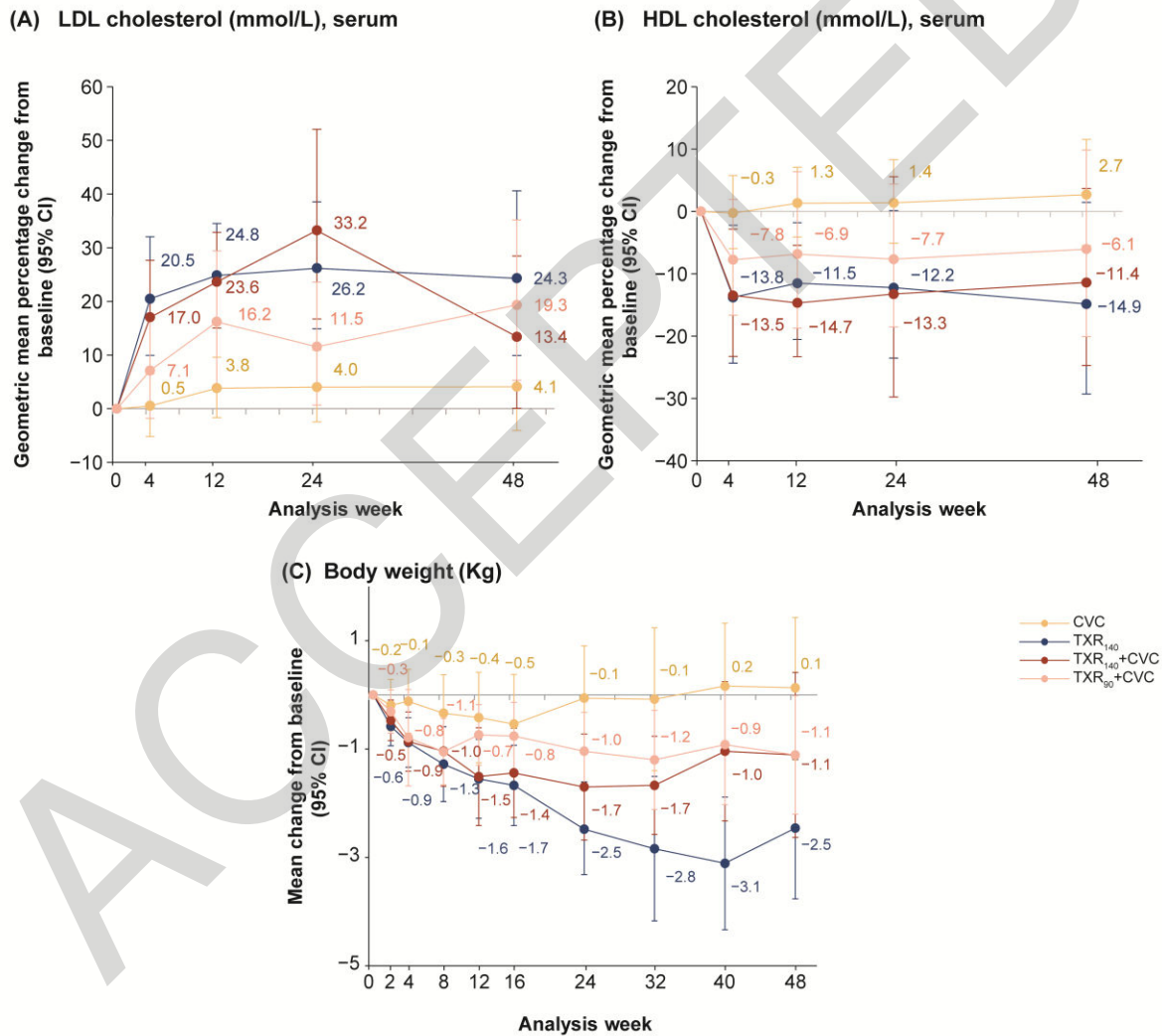


Figure 6. Change in lipid parameters and body weight up to Week 48

(A) Geometric mean percentage change (95% CI) in LDL cholesterol; (B) Geometric mean percentage change (95% CI) in HDL cholesterol; (C) Mean change from baseline (95% CI) in body weight up to Week 48 in all groups.

CI, confidence interval; CVC, cenicriviroc; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TXR₉₀, tropifexor 90 µg; TXR₁₄₀, tropifexor 140 µg.



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Table 1. Demographics and baseline characteristics

| Demographics and baseline characteristics | TXR₁₄₀ N=50 | CVC N=48 | TXR₁₄₀+CVC N=47 | TXR₉₀+CVC N=48 |
|---|-----------------------------------|---------------------|---------------------------------------|--------------------------------------|
| Age (years), mean (±SD) | 54.8±13.4 | 53.7±11.8 | 54.7±12.7 | 54.9±12.3 |
| Male, n (%) | 20 (40.0) | 17 (35.4) | 18 (38.3) | 25 (52.1) |
| Race, n (%) | | | | |
| Caucasian | 41 (82.0) | 44 (91.7) | 40 (85.1) | 43 (89.6) |
| Asian | 7 (14.0) | 4 (8.3) | 5 (10.6) | 5 (10.4) |
| Black | 1 (2.0) | 0 (0.0) | 2 (4.3) | 0 (0.0) |
| Unknown | 1 (2.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| BMI (kg/m²), mean (±SD) | 33.7±6.6 | 35.7±8.4 | 34.7±6.9 | 34.3±7.3 |
| Diabetes, n (%) | 39 (78.0) | 41 (85.4) | 39 (83.0) | 40 (83.3) |
| Lipid lowering medication, n (%) | 22 (44.0) | 23 (47.9) | 33 (70.2) | 29 (60.4) |
| AST, mean (±SD) | 38.6±18.0 | 35.1±13.0 | 42.1±25.2 | 41.4±25.8 |
| ALT, mean (±SD) | 49.1± 25.3 | 40.9±15.7 | 51.1±28.6 | 51.8±33.0 |
| ELF, mean (±SD) | 9.6±0.8 | 9.5±1.0 | 9.4±0.7 | 9.6±0.8 |
| HOMA-IR, mean (±SD) | 8.4±7.6 | 7.0±4.8 | 7.1±6.2 | 10.5±14.5 |
| FIB-4, mean (±SD) | 1.3±0.7 | 1.3±0.6 | 1.4±0.9 | 1.3±0.8 |
| Histological characteristics | | | | |
| Fibrosis (NASH CRN), real-time biopsy^a, n (%) | | | | |
| Stage 1 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Stage 2 | 17 (34.0) | 10 (20.8) | 10 (21.3) | 17 (35.4) |
| Stage 3 | 32 (64.0) | 38 (79.2) | 37 (78.7) | 30 (62.5) |
| Stage 4 | 1 (2.0) | 0 (0.0) | 0 (0.0) | 1 (2.1) |
| NASH diagnosis by CRN, n (%) | 50 (100.0) | 48 (100.0) | 47 (100.0) | 48 (100.0) |
| NAS total score (mean±SD) | 5.2±0.93 | 5.4±0.82 | 5.4±1.06 | 5.2±1.02 |
| Steatosis, n (%) | | | | |
| 1 (5%–33%) | 42 (84.0) | 38 (79.2) | 39 (83.0) | 41 (85.4) |

| | | | | |
|---|-----------|-----------|-----------|-----------|
| 2 (34%–66%) | 8 (16.0) | 10 (20.8) | 8 (17.0) | 7 (14.6) |
| Lobular inflammation, n (%) | | | | |
| 1 (<2 foci/*field) | 3 (6.0) | 2 (4.2) | 3 (6.4) | 4 (8.3) |
| 2 (2–4 foci/*field) | 24 (48.0) | 24 (50.0) | 18 (38.3) | 25 (52.1) |
| 3 (>4 foci/*field) | 23 (46.0) | 22 (45.8) | 26 (55.3) | 19 (39.6) |
| Hepatocyte ballooning, n (%) | | | | |
| 1 (Mild, few) | 17 (34.0) | 11 (22.9) | 12 (25.5) | 13 (27.1) |
| 2 (Moderate, many) | 33 (66.0) | 37 (77.1) | 35 (74.5) | 35 (72.9) |
| <p>^aReal-time readings of liver biopsies were performed at baseline to assess eligibility for entry into the study.</p> <p>ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRN, clinical research network; CVC, cenicriviroc; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4; HOMA-IR, homeostatic model assessment for insulin resistance; N, number of patients in group; n, number of patients with outcome; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; SD, standard deviation; TXR₉₀, tropifexor 90 µg; TXR₁₄₀, tropifexor 140 µg.</p> | | | | |

ACCEPTED

Table 2. Occurrence of AEs during the study and TEAEs with $\geq 10\%$ incidence, by preferred term

| Events, n (%) | TXR ₁₄₀ N=50 | CVC N=48 | TXR ₁₄₀ +CVC N=47 | TXR ₉₀ +CVC N=48 | Total N=193 |
|---|----------------------------|-------------|---------------------------------|--------------------------------|----------------|
| Patients with at least one AE | 42 (84.0) | 41 (85.4) | 40 (85.1) | 42 (87.5) | 165 (85.5) |
| Patients with at least one SAE | 5 (10.0) | 3 (6.3) | 4 (8.5) | 10 (20.8) | 22 (11.4) |
| AE as reason for discontinuation | 9 (18.0) | 3 (6.3) | 8 (17.0) | 1 (2.1) | 21 (10.9) |
| TEAEs, (incidence of $\geq 10\%$ in any treatment group), n (%) | | | | | |
| Pruritus | 20 (40.0) | 10 (20.8) | 15 (31.9) | 10 (20.8) | 55 (28.5) |
| Nausea | 2 (4.0) | 6 (12.5) | 7 (14.9) | 6 (12.5) | 21 (10.9) |
| Fatigue | 7 (14.0) | 4 (8.3) | 5 (10.6) | 4 (8.3) | 20 (10.4) |
| Arthralgia | 6 (12.0) | 3 (6.3) | 6 (12.8) | 1 (2.1) | 16 (8.3) |
| Constipation | 5 (10.0) | 2 (4.2) | 6 (12.8) | 3 (6.3) | 16 (8.3) |
| Urinary tract infection | 7 (14.0) | 3 (6.3) | 2 (4.3) | 4 (8.3) | 16 (8.3) |
| Abdominal pain | 5 (10.0) | 3 (6.3) | 5 (10.6) | 2 (4.2) | 15 (7.8) |
| Upper respiratory tract infection | 3 (6.0) | 2 (4.2) | 5 (10.6) | 5 (10.4) | 15 (7.8) |
| Asthenia | 4 (8.0) | 2 (4.2) | 5 (10.6) | 3 (6.3) | 14 (7.3) |
| Back pain | 1 (2.0) | 3 (6.3) | 5 (10.6) | 4 (8.3) | 13 (6.7) |
| Diarrhea | 2 (4.0) | 7 (14.6) | 4 (8.5) | 0 (0.0) | 13 (6.7) |
| Abdominal pain upper | 3 (6.0) | 2 (4.2) | 5 (10.6) | 2 (4.2) | 12 (6.2) |
| A patient with multiple occurrences of an AE is counted only once. | | | | | |
| AE, adverse event; CVC, cenicriviroc; N, number of participants in group; n, number of participants with outcome; SAE, serious AE; TEAE, treatment-emergent AE; TXR ₉₀ , tropifexor 90 μg ; TXR ₁₄₀ , tropifexor 140 μg . | | | | | |