



Cenicriviroc Treatment for Adults With Nonalcoholic Steatohepatitis and Fibrosis: Final Analysis of the Phase 2b CENTAUR Study

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BACKGROUND AND AIMS: Cenicriviroc (CVC) is a C-C chemokine receptors type 2 and 5 dual antagonist under evaluation for treating liver fibrosis in adults with nonalcoholic steatohepatitis (NASH). Year 1 primary analysis of the 2-year CENTAUR study showed that CVC had an antifibrotic effect without impacting steatohepatitis. Herein, we report the final data from year 2 exploratory analyses.

APPROACH AND RESULTS: This was a randomized, controlled study of adults with NASH, nonalcoholic fatty liver disease activity score ≥ 4 , and NASH Clinical Research Network stage 1-3 fibrosis. Participants in arms A and C received CVC 150 mg or placebo, respectively, for 2 years; arm B received placebo in year 1 and switched to CVC in year 2. Liver biopsy was performed at baseline, year 1, and year 2. Of 289 randomized participants, 242 entered year 2. At year 2, 24% of patients who switched to CVC and 17% who remained on placebo achieved ≥ 1 -stage fibrosis improvement and no worsening of NASH ($P = 0.37$). Twice the proportion on CVC who achieved fibrosis response at year 1 maintained benefit at year 2 (60% arm A versus 30% arm C), including 86% on CVC who had stage 3 fibrosis at baseline. Over

2 years, a similar proportion on CVC or placebo achieved ≥ 1 -stage fibrosis improvement and no worsening of NASH (15% arm A versus 17% arm C). In patients with fibrosis responses, we observed consistent reductions in levels of N-terminal type 3 collagen propeptide and enhanced liver fibrosis scores, while increases in aspartate aminotransferase-to-platelet ratio index and Fibrosis-4 scores were consistently observed in nonresponders. Safety profile was comparable across groups.

CONCLUSIONS: CVC was well tolerated, and year 2 data corroborate antifibrotic findings from year 1. The majority on CVC who achieved fibrosis response at year 1 maintained it at year 2, with greater effect in advanced fibrosis. ClinicalTrials.gov number, NCT02217475 (CENTAUR). (HEPATOLOGY 2020;72:892-905).

Nonalcoholic steatohepatitis (NASH), the progressive form of nonalcoholic fatty liver disease (NAFLD) with an estimated prevalence of 1.5%-6.5% in the general population, is characterized by inflammation and hepatocyte injury

Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; CCL2, C-C chemokine ligand type 2; CCR2, C-C chemokine receptor type 2; CI, confidence interval; CRN, Clinical Research Network; CVC, cenicriviroc; ELF, enhanced liver fibrosis; FIB-4, Fibrosis-4; IL, interleukin; ITT, intention to treat; mITT, modified ITT; NAFLD, nonalcoholic fatty liver disease; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis; OR, odds ratio; PRO-C3, N-terminal type 3 collagen propeptide; SAE, severe adverse event; TEAE, treatment-emergent adverse event.

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and has an increased risk for liver fibrosis and progression to cirrhosis.^(1,2) Fibrosis severity is the most important histological feature of NASH that is an independent predictor of long-term clinical outcomes and mortality and, if left untreated, can progress to cirrhosis and hepatocellular carcinoma, which subsequently increases overall and liver-related mortality.⁽³⁻⁶⁾ Despite recent advances in understanding the mechanisms underlying the pathogenesis of NASH, no approved, disease-modifying treatments are currently available.^(7,8)

During hepatic injury, C-C chemokine receptors type 2 (CCR2) and 5 (CCR5) and C-C chemokine ligands 2 and 5 (CCL2 and CCL5) promote liver fibrosis through activation of inflammatory signaling and immune cell infiltration.⁽⁹⁻¹¹⁾ Cenicriviroc (CVC) is a first-in-class, oral, dual CCR2/CCR5 antagonist with potent anti-inflammatory and antifibrotic activity currently in clinical development for the treatment of liver fibrosis associated with NASH.⁽¹²⁾ CVC has shown a favorable safety profile in over 1,100 trial participants, including patients with cirrhosis and

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Potential conflict of interest: Dr. Aithal consults for and advises GlaxoSmithKline and Pfizer. He advises Aegerion and Agios. He is on the speakers' bureau for Alexion. Dr. Abdelmalek consults for and received grants from Allergan, Immuron, Madrigal, NGM, Bristol-Myers Squibb, and Taiwan. She consults for Pfizer, Lexicon, and Siemens. She is on the speakers' bureau for Alexion. She received grants from Galectin, Gilead, Genfit, Boehringer Ingelheim, TARGET-NASH, Progenity, Intercept, Conatus, Shire, and Exalenz. Dr. Fischer is employed by Allergan. Dr. Francque consults for Roche, Gilead, AbbVie, Bayer, Bristol-Myers Squibb, MSD, Janssen, Actelion, Astellas, Genfit, Inventiva, Intercept, Aligos, Galmed, Echosens, Galapagos, and Genentech. Dr. Goodman received grants from Allergan, Gilead, Novartis, Bristol-Myers Squibb, and Intercept. Dr. Harrison consults for, advises, received grants from, and owns stock in Galectin, Genfit, and Madrigal. He consults for, advises, and received grants from Axcella, Cirus, CymaBay, Galmed, Gilead, HighTide, Intercept, NGM, Novartis, Novo Nordisk, and Pfizer. He consults for, advises, and owns stock in Aker and Metacrine. He consults for and advises 3V Bio, Albere, Blade, Bristol-Myers Squibb, Civi, CLDF, Contravir, Consynance, Corcept, Echosens, HistoIndex, Innovate, IQVIA, Medpace, Perspectum, Poxel, Prometheus, Prometic, Terns, and Lipocine. He received grants from Conatus, Immuron, Second Genome, and Tobira/Allergan. Dr. Korwley consults for, advises, is on the speakers' bureau of, and received grants from Gilead. He advises, is on the speakers' bureau of, and received grants from Intercept. He consults for and received grants from Conatus and Enanta. He advises and received grants from Allergan. He consults for Corcept and NGM. He advises IQVIA, Merck, and Oxford. He received grants from Zydus and Prometheus. Dr. Loomba consults for and received grants from Galmed, Madrigal, and NGM. He consults for Bird Rock, Celgene, Enanta, GRI Bio, Metacrine, Receptos, Arrowhead, and Gir. He received grants from Allergan, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi-Sankyo, Galectin, GE, Genfit, Gilead, Intercept, Janssen, Merck, Pfizer, Prometheus, Siemens, and Sirius. He is employed by Liponexus. Dr. Ratziu consults for and received grants from Intercept. He consults for Allergan, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Enanta, Galmed, Genfit, Madrigal, NGM, Novartis, Novo Nordisk, and Pfizer. He received grants from Gilead. Dr. Sanyal consults for and received grants from Allergan, AstraZeneca, Bristol-Myers Squibb, and Intercept. He consults for AbbVie, Nitto Denko, Ardelyx, Conatus, Nimbus, Echosens, Immuron, Galectin, Fractyl, Syntlogic, Novo Nordisk, Affimmune, Chemomab, and Nordic Bioscience. He received grants from Gilead, Salix, Shire, Merck, Malinckrodt, Cumberland, and Novartis. He owns stock in Genfit, Akarna, Tiziana, and Durect. He is employed by Sanyal Bioscience. Dr. Seyedkazemi is employed by Allergan. Dr. Tacke advises, is on the speakers' bureau of, and received grants from Allergan, Inventiva, and Galapagos. He advises and is on the speakers' bureau for Bayer, Boehringer Ingelheim, and Intercept. He received grants from Bristol-Myers Squibb. Dr. Wong consults for AbbVie, Allergan, Janssen, Perspectum, Pfizer, and Terns. He advises Echosens and Gilead.

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mild to severe hepatic impairment, with few reported adverse events in studies extending ≥ 48 weeks.⁽¹³⁻¹⁵⁾

The 2-year phase 2b CENTAUR study was designed to examine the efficacy and safety of once-daily treatment with CVC 150 mg compared to placebo in adult participants with NASH and liver fibrosis, for which it received fast-track designation by the Food and Drug Administration.⁽¹⁵⁾ Data from the year 1 primary analysis of the 2-year study demonstrated that CVC treatment resulted in liver fibrosis improvement without impact on underlying steatohepatitis compared to placebo (i.e., ≥ 1 -stage improvement in fibrosis and no worsening of NASH; 20% versus 10%; odds ratio [OR], 2.2; 95% confidence interval [CI], 1.11-4.35; $P = 0.02$).⁽¹⁶⁾ Moreover, CVC treatment was associated with reduced biomarkers of systemic inflammation, including C-reactive protein (CRP), interleukin (IL)-6, IL-1 β , and fibrinogen, supporting its antifibrotic and anti-inflammatory mechanism of action. Herein, we report data from the final year of the 2-year study.

Methods

STUDY DESIGN

The study design, rationale, and full eligibility criteria have been described.⁽¹⁵⁾ This was a phase 2b, randomized, double-blind, placebo-controlled, multicenter study of CVC for the treatment of adult patients with NASH and liver fibrosis. Adults aged 18-75 years with histological evidence of NASH, a NAFLD activity score (NAS) ≥ 4 with at least 1 in each component, and liver fibrosis (NASH Clinical Research Network [CRN] stages 1-3) were enrolled in 81 sites across the United States, Australia, Hong Kong, and Europe. The protocol and informed consent form (ICF) were approved by the Institutional Review Board (IRB) for each center prior to study initiation and all participants provided written informed consent. All authors had access to the data and reviewed and approved the final manuscript.

Eligible participants were randomized 2:1:1 to CVC 150 mg (arm A) or placebo (arms B and C) once daily at baseline. After year 1, participants in arm B crossed over to receive CVC, while those in arms A and C continued with their respective treatment until the end of year 2 (Supporting Fig. S1). Participants were randomized by permuted block randomization stratified

by NAS at screening (4 or ≥ 5) and fibrosis stage (≤ 2 or > 2).⁽¹⁵⁾ Liver biopsies were collected at screening, year 1, and year 2 and were read by a central study pathologist.

STUDY OUTCOMES

A complete listing of the prespecified study efficacy endpoints has been described.⁽¹⁵⁾ As the primary endpoint at year 1 (≥ 2 -point improvement in NAS with ≥ 1 -point improvement in either lobular inflammation or hepatocellular ballooning, with no worsening of fibrosis) was not met, the results from year 2 presented herein are exploratory analyses, which were not powered for statistical significance. Year 2 results mainly describe findings from the prespecified analyses focusing on proportions of participants in the intent-to-treat (ITT) population with improvement in (1) fibrosis by ≥ 1 stage, (2) fibrosis by ≥ 1 stage and no worsening of steatohepatitis (i.e., the composite endpoint), and (3) fibrosis by ≥ 2 stages and no worsening of steatohepatitis. Furthermore, *post hoc* analyses were performed to evaluate the above endpoints in the subgroup of participants with advanced fibrosis (stage 2 or 3) at baseline, in addition to analyses of fibrosis-related biomarkers and systemic markers of inflammation.

STATISTICAL ANALYSIS

Five population data sets were defined for the year 2 analysis: ITT, full analysis set, modified ITT (mITT), per protocol, and safety analysis sets (Supporting Table S1). Overall, the main efficacy analysis at the end of year 2 was based on the ITT population and included evaluation of (1) effects of 2 years of CVC treatment, comparing arm A versus arm C, and (2) effects of 1-year treatment with CVC, comparing arms A+B versus arm C (year 1 data for arms A and C and year 2 data for arm B) using a logistic regression model with factors for treatment group, NAS at screening (4 or ≥ 5), and fibrosis stage (≤ 2 or > 2). In addition, to evaluate CVC response after 1-year treatment in crossover participants, arm B versus arm C were compared for the subpopulation of placebo nonresponders (i.e., fibrosis stage 2 or 3 participants who did not achieve the ≥ 1 -stage fibrosis and NASH composite endpoint at year 1). Additional details related to methodology are included in the Supporting Information and have been described.^(15,16)

Results

PATIENT DISPOSITION AND CHARACTERISTICS

Participants were recruited from September 2014 to June 2015, and the study was completed in June 2017. Of the 812 screened, liver biopsy was conducted in 610 participants and 289 were randomized to treatment, with biopsies available for 252 and 213 participants at the end of year 1 and year 2, respectively (Fig. 1), with fewer biopsies available in arm A (82%; 99/121) compared to the other groups at the end of year 2. Baseline characteristics of the 242 participants who entered treatment at year 2 were generally comparable among the three groups, except for a higher number of patients with a history of type 2 diabetes mellitus in arm A (Supporting Table S2). At baseline, 49% (119/242) of year 2 participants were female and mean age was 54 years. Furthermore, 39% (94/242) of study participants had bridging fibrosis (NASH CRN stage 3) and 74% (178/242) had NAS ≥ 5 at screening.

EFFECTS OF 1 YEAR OF TREATMENT WITH CVC ON FIBROSIS ENDPOINTS

We had previously reported that more participants receiving CVC (arm A) achieved ≥ 1 -stage fibrosis improvement and no worsening of NASH than placebo (arm B+C) at year 1.⁽¹⁶⁾ To examine the antifibrotic response in the totality of patients treated for 1 year over the 2-year period, data were pooled for participants who received CVC for 1 year and compared to placebo (i.e., arms A+B each after 1 year of treatment versus arm C after 1 year of placebo). For this analysis, biopsies for arms A and C were from year 1 and biopsies for arm B were from year 2; all were compared against respective baseline biopsies. Among participants treated with CVC for 1 year, 27.7% (57/206) achieved the ≥ 1 -stage fibrosis endpoint versus 16.7% (12/72) of participants receiving placebo for 1 year, while ≥ 1 -stage fibrosis improvement and no worsening of NASH was achieved in 19.9% (41/206) with CVC versus 11.1% (8/72) on placebo (OR, 2.033; 95% CI, 0.894-4.622; $P = 0.09$) (Fig. 2A).

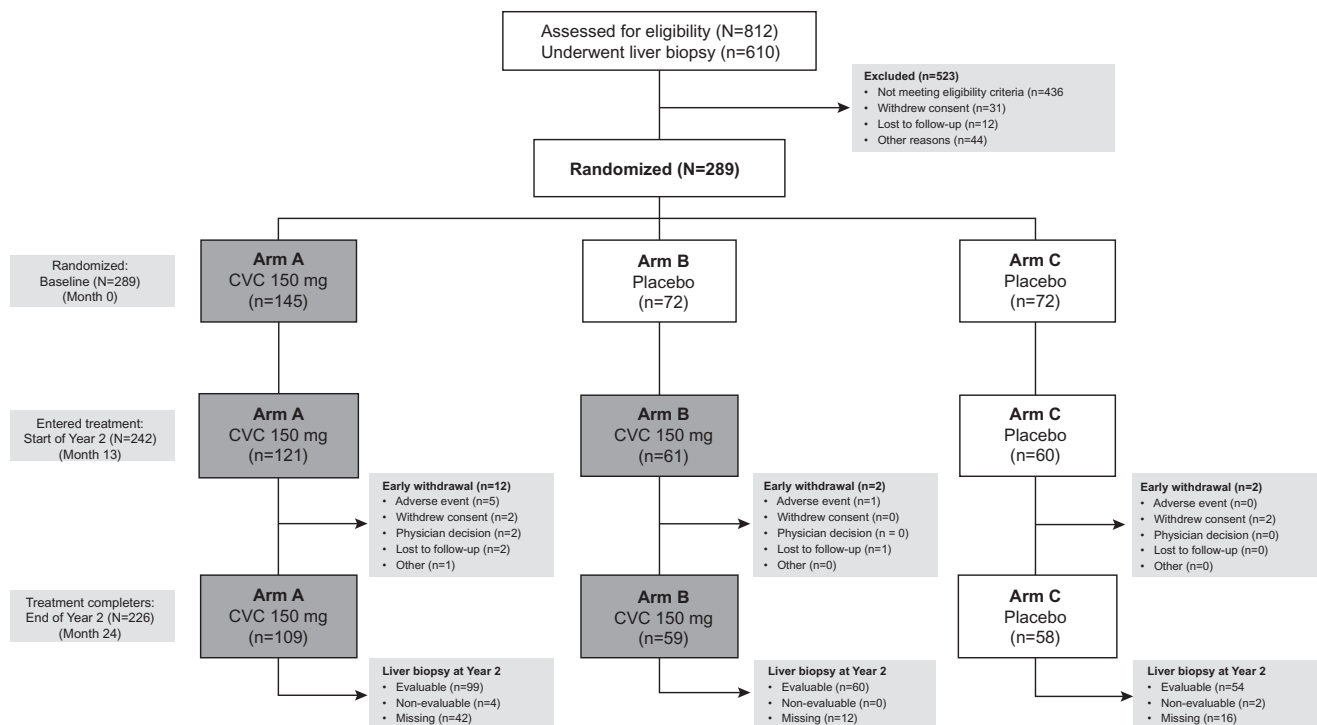


FIG. 1. Patient disposition (CONSORT flow diagram).

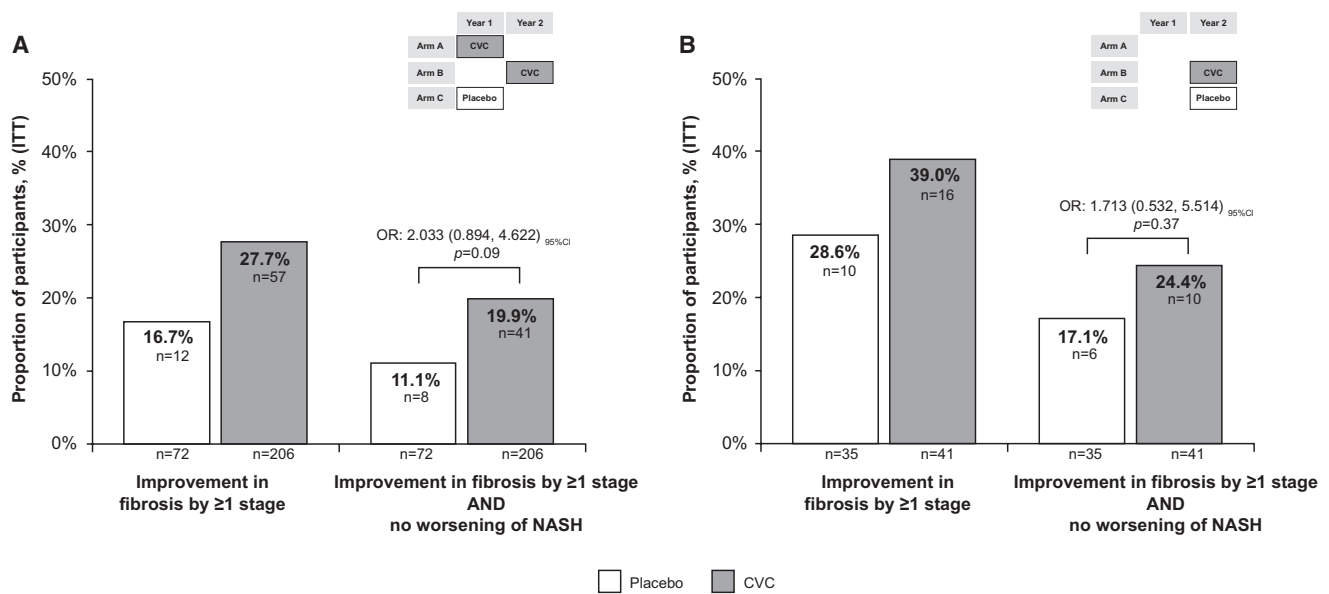


FIG. 2. Effect of 1 year of treatment with CVC on fibrosis endpoints. (A) Antifibrotic response in totality of participants treated for 1 year (arms A+B versus arm C [year 1 data for arms A and C; year 2 data for arm B]). (B) Antifibrotic response in placebo nonresponders (arm B versus arm C) during year 2. Placebo nonresponders are participants with fibrosis stage 2 or 3 who did not achieve improvement in fibrosis by ≥1 stage and no worsening of NASH at year 1 and data analyzed from year 1 to year 2. ORs, 95% CIs, and P values are from ordinal logistic regression models with factors for randomized treatment group, NAS at screening (4 or ≥5), and fibrosis stage (≤2 or >2). Data presented for the ITT population (i.e., participants who had an evaluable year 1 biopsy and who received at least one dose of study drug during year 2); participants with missing postbaseline biopsies were considered nonresponders at the respective time points.

Similarly, in the placebo crossover group during year 2 (arm B) relative to those who received placebo throughout the 2-year study (arm C) compared to baseline, 34.4% (21/61) and 19.7% (12/61) of those switching over to CVC versus 16.7% (12/72) and 11.1% (8/72) of those who remained on placebo achieved the ≥1-stage fibrosis improvement endpoint and the associated composite endpoint, respectively. Furthermore, analysis of the year 1 placebo nonresponders showed that switching to CVC during the second year of treatment was associated with improvement in fibrosis by ≥1-stage (39.0% [16/41] in arm B versus 28.6% [10/35] in arm C) and in the composite endpoint (24.4% [10/41] in arm B versus 17.1% [6/35] in arm C; OR, 1.713; 95% CI, 0.532-5.514; P = 0.37) (Fig. 2B).

EFFECTS OF 2 YEARS OF TREATMENT WITH CVC ON FIBROSIS ENDPOINTS

We next determined whether prolonged treatment with CVC for an additional year offered further

antifibrotic benefit beyond 1 year. Over the 2-year treatment period, a comparable proportion of participants receiving CVC (arm A) or placebo (arm C) achieved ≥1-stage fibrosis improvement regardless of NASH status (22.2% [26/117] versus 19.3% [11/57]), while a similar proportion achieved ≥1-stage fibrosis improvement and no worsening of NASH (12.8% [15/117] in arm A versus 14.0% [8/57] in arm C) (Fig. 3A; ITT population). Analysis of the mITT population (i.e., participants in the ITT population with evaluable biopsies at year 2) showed that a similar proportion of patients achieved both the ≥1-stage fibrosis endpoint (26.3% [26/99] versus 22.2% [12/54]) and the composite endpoint (15.2% [15/99] versus 16.7% [9/54]). To determine the impact of CVC treatment on those with advanced disease over 2 years, a *post hoc* analysis was performed of participants with baseline NASH CRN fibrosis stage 2 or 3 only. In this subpopulation, 10.8% (7/65) of CVC participants and 2.9% (1/34) of placebo participants achieved ≥2-stage fibrosis improvement and no worsening of NASH (P = 0.13) (Fig. 3B). Furthermore, when only participants with stage 3 fibrosis at baseline

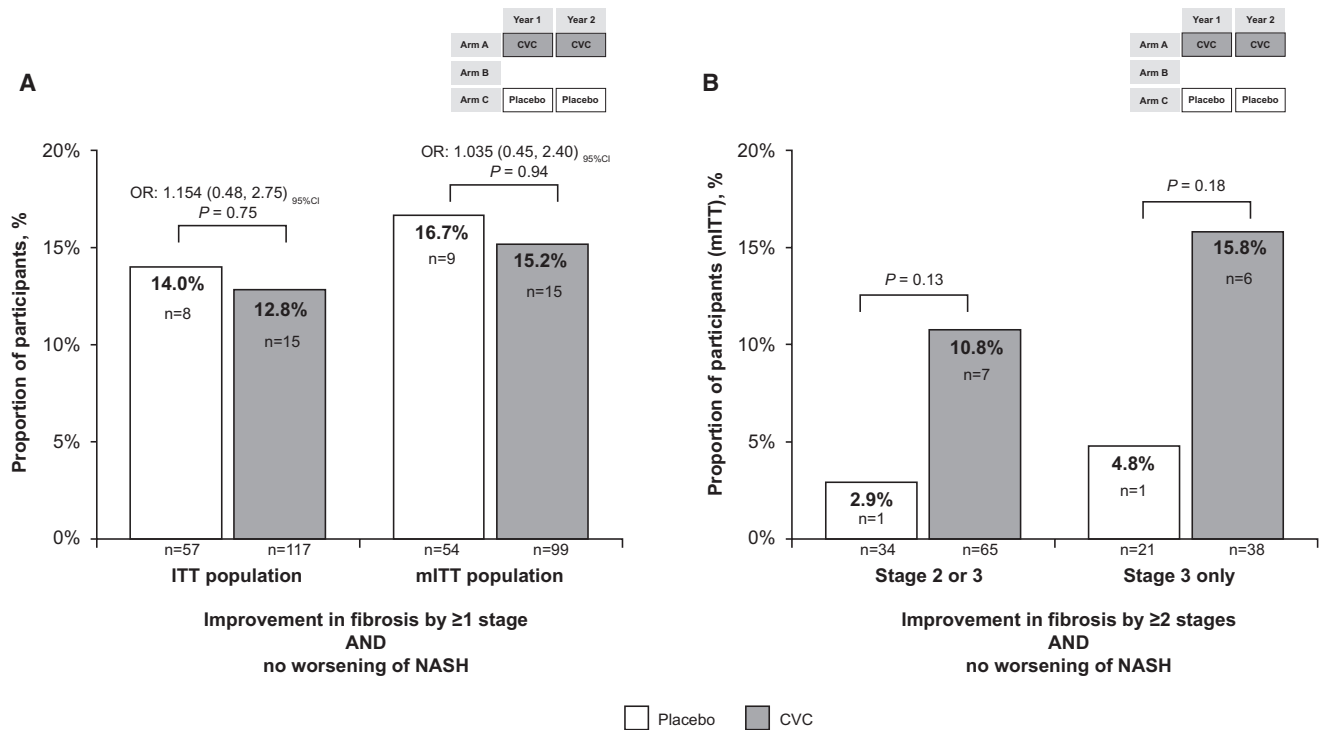


FIG. 3. Effect of 2 years of treatment with CVC on fibrosis endpoints (arm A versus arm C). (A) Improvement in fibrosis stage by ≥ 1 stage and no worsening of steatohepatitis for the ITT and mITT populations. (B) Improvement in fibrosis stage by ≥ 2 stages and no worsening of steatohepatitis among participants with baseline NASH CRN fibrosis stage 2 or 3 (excluding stage 1) for the mITT population. ORs, 95% CIs, and P values are from ordinal logistic regression models with factors for randomized treatment group, NAS at screening (4 or ≥ 5), and fibrosis stage (≤ 2 or > 2). Data presented for the ITT population (i.e., participants who had an evaluable year 1 biopsy and who received at least one dose of study drug during year 2) and the mITT population (participants who received at least one dose of study drug, had an eligible screening biopsy, and had a year 2 biopsy; used for supportive analyses); participants with missing postbaseline biopsies were considered nonresponders at the respective time points.

were included in this analysis, 15.8% (6/38) on CVC and 4.8% (1/21) on placebo achieved this endpoint ($P = 0.18$) (Fig. 3B).

DYNAMICS OF ANTIFIBROTIC RESPONSE FOLLOWING TREATMENT WITH CVC

To evaluate the durability of histological improvement over 2 years, improvement in fibrosis by ≥ 1 stage (regardless of steatohepatitis status) was assessed in participants with evaluable biopsies at baseline, year 1, and year 2. Results from this *post hoc* analysis showed that 60.0% (18/30) of participants on CVC (arm A) achieved ≥ 1 -stage fibrosis improvement at the end of year 1 and maintained this antifibrotic response at year 2 compared to the 30.0% (3/10) on placebo (arm C) (Fig. 4A,B), albeit the sample sizes were small.

Importantly, 85.7% (12/14) of participants in arm A with stage 3 fibrosis at baseline that improved by ≥ 1 stage at year 1 maintained this antifibrotic benefit at year 2 compared with 60.0% (3/5) of participants in arm C (Fig. 4A,B). Concurrent improvements in various parameters, including hepatocellular ballooning, lobular inflammation, NAS score, and portal inflammation, were observed in a majority of these 12 CVC-treated F3 participants, including 2 participants whose fibrosis improved to stage 0 by the end of year 2. A comparable proportion of those on CVC as placebo maintained the year 1 composite fibrosis endpoint at the end of year 2 (28.6% [8/28] versus 25.0% [2/8]). Among participants with fibrosis stage 2 or 3 based on year 1 biopsy, a lower proportion of those in arm A experienced worsened fibrosis at the end of year 2 compared to arm C (13.6% [8/59] versus 17.2% [5/29]).

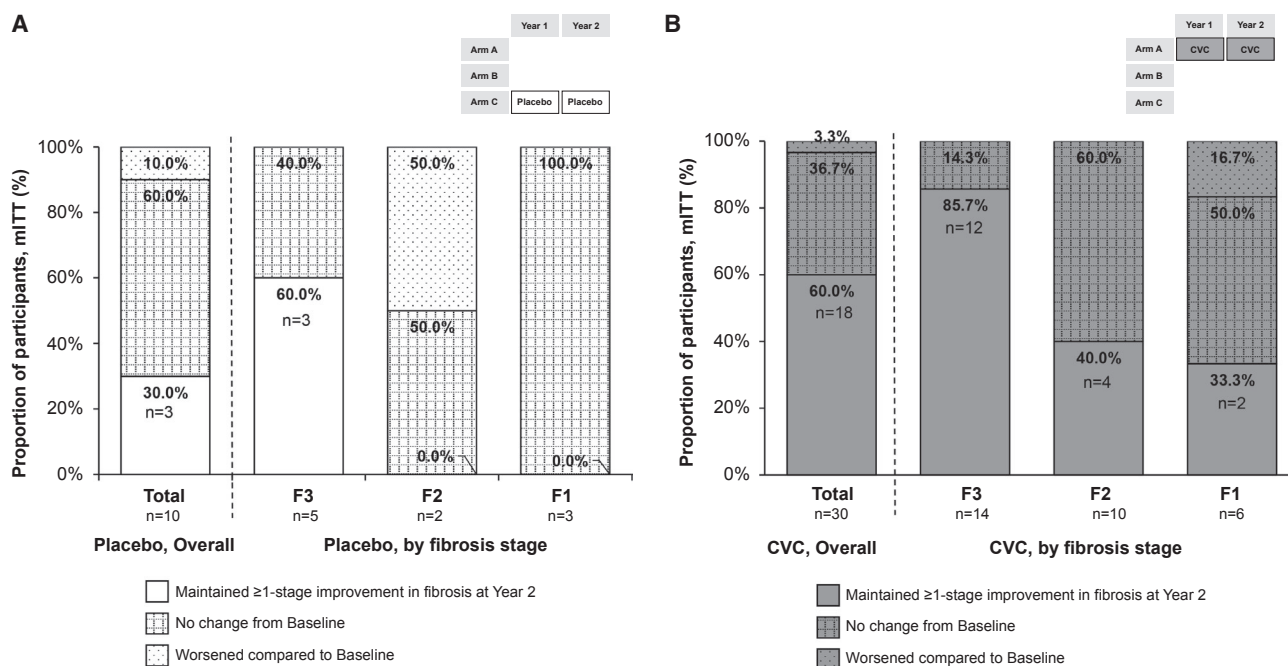


FIG. 4. Proportion of year 1 responders maintaining antifibrotic benefit at year 2 (arm A versus arm C) for the overall population and stratified by fibrosis stage at baseline in the (A) placebo and (B) CVC group. Antifibrotic benefit was defined as ≥ 1 -stage improvement in fibrosis from baseline. Note that there were 36 total responders in arm A at year 1; however, 6 participants had missing year 2 biopsy data (of whom 4 had stage 3 fibrosis at baseline) and thus were considered year 2 nonresponders and excluded from this analysis. Data presented are from *post hoc* analysis for the mITT population (participants who received at least one dose of study drug and had evaluable biopsies at baseline, year 1, and year 2); participants with missing postbaseline biopsies were considered nonresponders at the respective time points.

EFFECT OF CVC TREATMENT ON SEVERE FIBROSIS

As a greater durability of antifibrotic response was observed in participants with severe disease, a *post hoc* analysis was performed to further evaluate the effect of CVC in this subpopulation (i.e., participants with NASH CRN stage 3 at baseline and who had evaluable biopsies at all time points). At year 1, 38.0% (18/47) and 32.0% (15/47) of F3 CVC participants compared to 28.0% (14/50) and 20.0% (10/50) of F3 placebo participants achieved the ≥ 1 -stage fibrosis improvement endpoint and the composite endpoint, respectively (Supporting Fig. S2A). At year 2, 40.0% (15/38; arm A) and 50.0% (12/24; arm B) of F3 participants receiving CVC and 29.0% (6/21; arm C) receiving placebo achieved ≥ 1 -stage fibrosis improvement, while 26.0% (10/38 in arm A) and 29.0% (7/24 in arm B) on CVC and 19.0% (4/21 in arm C) on placebo achieved the composite endpoint (Supporting Fig. S2C). Additional data in F3 participants are presented in Supporting Fig. S2B,D.

EFFECT OF PLACEBO TREATMENT ON FIBROSIS

The study requirement of three serial biopsies allowed us to evaluate the course of fibrosis in the placebo group throughout the 2-year treatment period. From baseline to end of year 1 (Fig. 5A, left panel) and from baseline to end of year 2 (Fig. 5A, right panel), 20.0% and 22.2% achieved improvement in fibrosis status, while 35.0% and 22.2% experienced deterioration in fibrosis status at the end of year 1 and year 2, respectively. However, further analysis of the intermediate period from end of year 1 to end of year 2 showed erratic fluctuation of fibrosis stage in the placebo group (Fig. 5A, middle panel). The data show that of the 10 participants who had experienced 1-stage improvement in fibrosis at the end of year 1, the majority (80.0%) worsened between year 1 and year 2. Conversely, of the 15 participants who experienced worsened fibrosis at the end of year 1, the majority (53.3%) improved between year 1 and year 2. Overall, this variability of fibrosis response in the

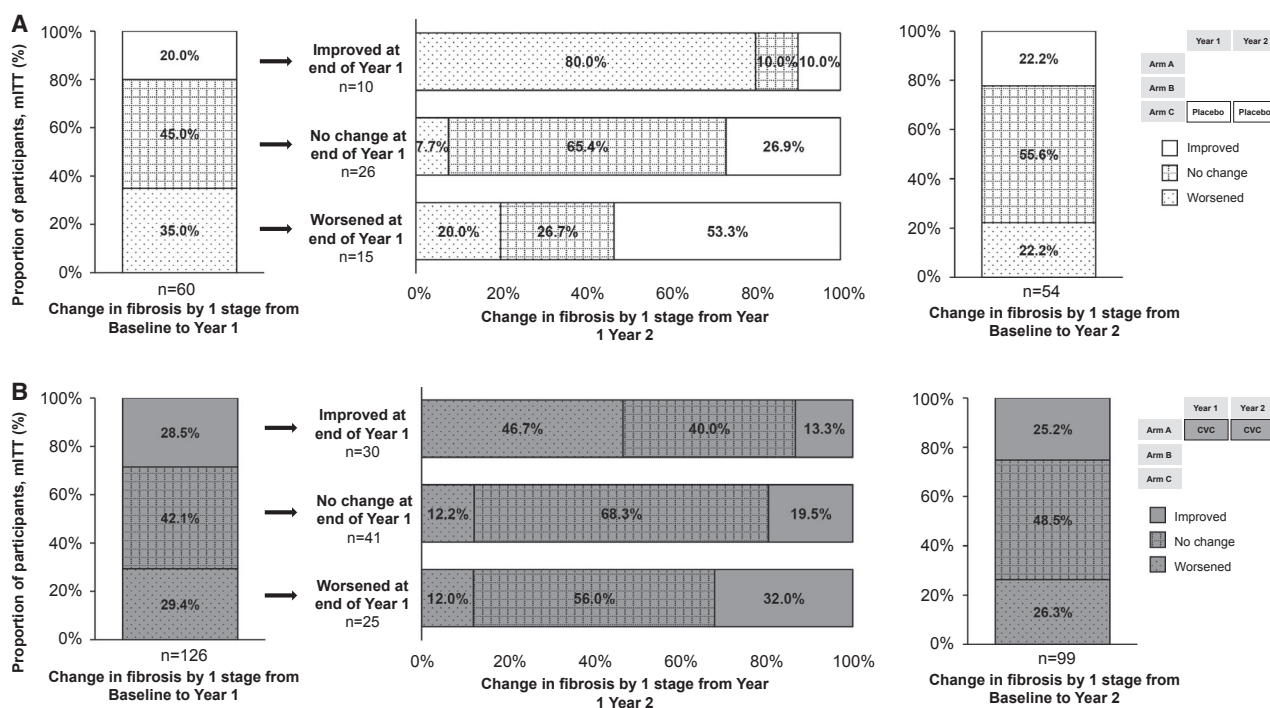


FIG. 5. Dynamics of antifibrotic response within the placebo (arm C) group and the CVC (arm A) group. Change in fibrosis by 1 stage from baseline to end of year 1 (left panels) and end of year 2 (right panels) in (A) the placebo (arm C) group and (B) the CVC (arm A) group. Fibrosis response from year 1 to year 2 in participants whose fibrosis had either improved, had no change, or worsened at end of year 1 (middle panels). Data presented for the mITT population (participants who received at least one dose of study drug and had evaluable biopsies at baseline, year 1, and year 2); participants with missing postbaseline biopsies were considered nonresponders at the respective time points.

placebo group, suggestive of a “seesaw effect,” indicates that the placebo participants who experienced improvement at year 1 were not the same participants who had fibrosis improvement at the end of year 2. In the CVC group, of the 30 participants who had experienced 1-stage improvement in fibrosis at the end of year 1, 40.0% maintained this status and 13.3% further improved between year 1 and year 2, while 32.0% of the 25 CVC patients who experienced worsened fibrosis at the end of year 1 improved between year 1 and year 2 (Fig. 5B).

CORRELATION BETWEEN ANTIFIBROTIC RESPONSE AND FIBROSIS-RELATED BIOMARKERS

Our analysis of the effect of CVC on markers of fibrosis turnover and noninvasive indices showed modest effects that were similar between

the CVC and placebo groups at year 1 and year 2. Therefore, to determine whether there was a correlation between overall changes in histology and biomarkers, data from all year 2 responders (i.e., all participants who achieved ≥ 1 -stage fibrosis improvement; total $n = 54$) were pooled from all treatment groups and compared to year 2 nonresponders (those with no change or ≥ 1 -stage fibrosis worsening; total $n = 163$) and evaluated from baseline to year 2. From a mean baseline of 14.3 ng/mL in both groups, reductions in levels of N-terminal type 3 collagen propeptide (PRO-C3) were observed in the responder group over the 2-year treatment period, while PRO-C3 levels remained near baseline levels in the nonresponder group over 2 years (Fig. 6A). Notably, baseline PRO-C3 levels were higher with advanced fibrosis (F1, 12.0 ng/mL; F2, 13.0 ng/mL; F3, 16.5 ng/mL). Correlation between histological response and fibrosis indices showed that over

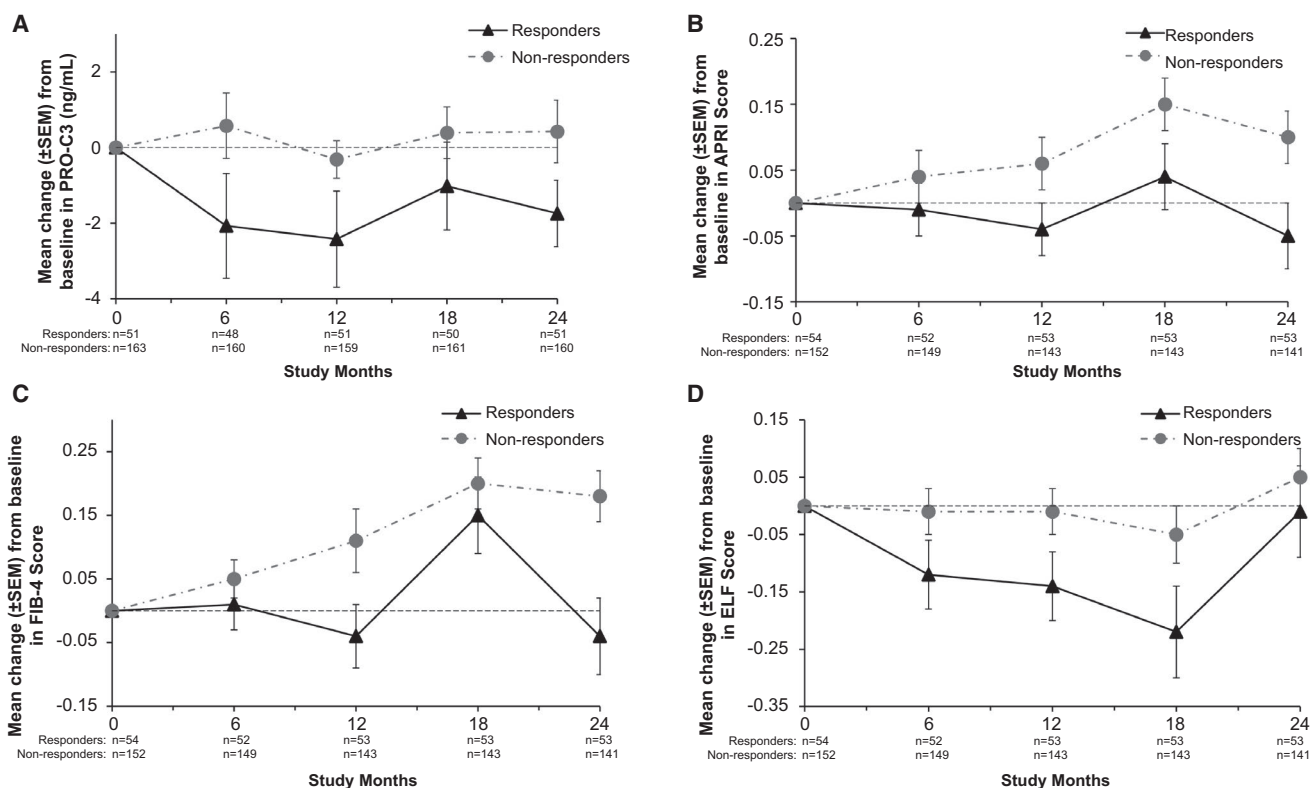


FIG. 6. Correlation between histological response and biomarkers. Mean changes (\pm SEM) in (A) PRO-C3, (B) APRI, (C) FIB-4, and (D) ELF scores from baseline to year 2 in responders and nonresponders. Histological data were stratified by year 2 responders (defined as participants who achieved ≥ 1 -stage fibrosis improvement; total $n = 54$) or nonresponders (participants who experienced no change in fibrosis or those with ≥ 1 -stage worsening in fibrosis; total $n = 163$). Data from all treatment arms (arm A [CVC] + arm B [placebo/CVC] + arm C [placebo]) were pooled in this analysis and evaluated over the 2-year treatment period. Analysis based on participants with evaluable biopsies ($n = 54$ for responders and $n = 163$ for nonresponders) and data presented at each time point for those with available samples for biomarker analyses. APRI was calculated using the following formula: (AST level [U/L]/platelet count [$10^9/L$]) \times 100. FIB-4 was calculated using the following formula: (Age [years] \times AST [U/L])/(platelet count [$10^9/L$] \times (ALT [U/L])^{1/2}). ELF data were calculated based on concentrations of N-terminal propeptide of collagen type III, hyaluronic acid, tissue inhibitor of metalloproteinase 1, and age.

2 years aspartate aminotransferase (AST)-to-platelet ratio index (APRI) and Fibrosis-4 (FIB-4) score levels remained near baseline levels for responders, while reductions in enhanced liver fibrosis (ELF) score were observed over 18 months before returning to baseline levels at year 2 (Fig. 6B-D). Conversely, from their respective baseline levels, increases in APRI and FIB-4 scores were observed over 2 years in nonresponders, while ELF score levels remained close to baseline levels.

Additional biomarker analyses were performed to further understand the clinical characteristics associated with fibrosis progression among placebo-treated participants (arm B+C, $n = 126$). Fibrosis progressors were defined as participants with ≥ 1 -stage fibrosis

worsening ($n = 37$ [arm B+C] at year 1 and $n = 21$ [arm C] at year 2), and nonprogressors were defined as those with no change or ≥ 1 -stage fibrosis improvement ($n = 89$ [arm B+C] at year 1 and $n = 16$ [arm C] at year 2). At baseline, notably higher levels of transaminases were observed among progressors compared to nonprogressors (alanine aminotransferase [ALT], 78.0 versus 60.0 IU/L; AST, 58.4 versus 44.4 IU/L), NAS ≥ 5 (89.2% versus 70.8%), hepatocellular ballooning grade 2 (64.9% versus 50.6%), and stage 1 fibrosis (64.9% versus 20.2%), albeit there was a lower proportion of participants with stage 3 fibrosis (10.8% versus 51.7%). No differences were observed between the two groups in age, body mass index, diabetes status, or stage 2 fibrosis at baseline.

EFFECT OF CVC ON MARKERS OF SYSTEMIC INFLAMMATION

In line with its function as a CCR2 and CCR5 inhibitor, increases in levels of the ligands CCL2 and CCL4 were seen in participants treated with CVC over the entire 2-year period (arm A) and in those who crossed over to CVC in the second year of treatment (arm B) (Supporting Table S3). Moreover, treatment with CVC was associated with reductions in circulating markers of systemic inflammation, such as IL-6, and in markers associated with cardiovascular outcomes, including high-sensitivity CRP and fibrinogen. From baseline, reductions in mean levels of fibrinogen were observed within the initial month of treatment in the CVC group (arm A), which were sustained until the end of the 2-year treatment period (Supporting Figs. S3). In comparison, no changes in fibrinogen levels were observed in the placebo groups (arms B and C) over the first year of treatment; however, upon crossing over to CVC treatment at the start of year 2, rapid reductions in fibrinogen were observed in arm B, which were sustained throughout the second year of treatment, while levels remained near baseline for arm C. No clinically meaningful differences were noted between the CVC and placebo treatment groups in levels of liver transaminases, fasting metabolic parameters, body weight or related parameters, or NAFLD activity score (Supporting Tables S4-S6).

SAFETY AND TOLERABILITY

The overall incidence of treatment-emergent adverse events (TEAEs) was similar in the CVC and placebo groups, the majority of which were mild to moderate in severity (Supporting Table S7). Treatment discontinuations due to TEAEs were only reported in arm A (4.1% [5/121]). Overall, a higher rate of serious adverse events (SAEs) was reported in arm C, with only one SAE resulting in premature discontinuation (arm A), no SAEs being assessed as related to treatment, and no deaths being reported throughout the 2-year study.

TEAEs related to infections were the most frequently reported events in year 2, with a higher incidence reported in arm A (Supporting Table S8), none of which were related to the respective treatments or resulted in drug withdrawal. Nasopharyngitis was reported at a higher rate in the CVC groups at year 2

(9.1% in arm A and 8.2% in arm B) compared to placebo (3.3%), while comparable rates of upper respiratory tract infection were reported in arm A and arm C (6.6% versus 5.0%), with a higher rate in arm B (8.2%) at year 2 (Supporting Table S8). Of the gastrointestinal events, nausea was reported more frequently in arm A compared to arm C (5.8% versus 3.3%), while diarrhea was more frequent in arm C (1.7% versus 8.3%). The incidence of grade 3 or 4 laboratory abnormalities was generally similar among the treatment groups (Supporting Table S9). Overall, the proportion of participants with elevations in liver biochemistry requiring further evaluation was 10.4% (15/144) in the CVC group (arm A) and 7.6% (11/144) in the placebo groups (arms B+C) during the first year of treatment. Of note, among those with elevations in liver biochemistry during year 1, two grade 3 hepatobiliary adverse events of “autoimmune hepatitis” were reported (one participant each in arm A and arm C), and one participant had a postbaseline liver biopsy suggestive of autoimmune hepatitis in arm A, none of whom continued treatment in year 2. During year 2, 3.3% (4/121) of participants in arm A, 3.3% (2/61) in arm B, and 3.3% (2/60) in arm C had elevations in liver biochemistry requiring further evaluation. Overall, exposure to study medication was comparable across all treatment groups throughout the study (Supporting Table S10). Moreover, ~85% of patients experienced a change in dosage or concomitant medications during year 2, with comparable proportions between arms A and C (86.0% and 91.7%, respectively) and 77.0% in arm B.

Discussion

Herein, we present data from the year 2 exploratory analyses, which indicate that treatment with CVC for 2 years was not associated with further improvement in fibrosis beyond the effect observed after 1 year compared to placebo. Nonetheless, the year 2 data suggest that even if no or limited additional fibrosis improvement is observed, the durability of the fibrosis benefit (those who maintained a lower fibrosis stage than at baseline, as measured 1 year later) was higher with CVC than with placebo, thus suggesting qualitative differences between pharmacologically induced fibrosis regression and fibrosis reversal owing to natural fluctuations of the disease. Moreover, the

durability of antifibrotic response obtained on CVC treatment was higher in those with advanced disease and highest in those with stage 3 fibrosis. These year 2 findings also corroborate the antifibrotic activity of CVC as was observed in year 1, as evidenced by a greater antifibrotic response in the totality of participants treated with CVC for 1 year compared to placebo (i.e., arm A+B pooled analysis versus arm C). Furthermore, among the year 1 placebo nonresponders, 39% and 24% of those who crossed over to CVC achieved ≥ 1 -stage fibrosis improvement and ≥ 1 -stage fibrosis improvement and no worsening of NASH, respectively, compared to 29% and 17% of those who remained on placebo at year 2. Over 2 years of treatment, a similar proportion on CVC or placebo achieved the ≥ 1 -stage fibrosis and NASH composite endpoint; however, a greater proportion on CVC achieved the ≥ 2 -stage fibrosis and NASH composite endpoint (10.8% versus 2.9%), albeit the sample sizes were small. Interestingly, for a ≥ 2 -stage fibrosis reduction, the difference from placebo was of the same order of magnitude after 1 and 2 years of therapy, thus suggesting that patients with a strong antifibrotic response to CVC maintained longer-term benefit.

Because liver fibrosis is independently associated with long-term clinical outcomes and fibrosis severity is associated with increasing hazard ratios for hepatic mortality, the histological benefit of CVC demonstrated here might translate into long-term clinical benefit should longer and larger studies confirm these present findings.

This study design required collection of serial biopsies over 2 years, which allowed us to further investigate two major clinical aspects of NASH and liver fibrosis: the durability of antifibrotic response in CVC-treated patients and the course of disease fluctuation in placebo-treated patients. To the first point, among those who had evaluable biopsies at all time points, 60% on CVC and 30% on placebo who achieved ≥ 1 -stage fibrosis improvement at year 1 maintained this antifibrotic benefit at year 2. This durability in response was driven mostly by participants who had stage 3 fibrosis at baseline, indicating that CVC may exert a pronounced antifibrotic effect in those with advanced disease, where CCR2/CCR5 signaling may play a greater role in the pathophysiology of fibrosis.⁽¹⁷⁾ To the second point, a pronounced “seesaw effect” in fibrosis response was evident in the placebo group, wherein the majority (80%) of those

whose fibrosis had improved by 1 stage at the end of year 1 actually worsened in the period from the end of year 1 to end of year 2, while conversely, a majority (53%) of those whose fibrosis had worsened at the end of year 1 actually improved by 1 stage at the end of year 2. Elevated liver transaminase levels at baseline were found to be associated with progression of fibrosis in the placebo groups. Fluctuations in fibrosis among participants in the placebo group may be due to the high variability in the natural course of fibrosis, particularly in patients with less severe disease, and corroborate reports from previous NASH studies that documented substantial changes in the placebo arms.⁽¹⁸⁻²⁰⁾ It also emphasizes the need for future antifibrotic trials to have large sample sizes as a small sample size in the placebo arm might lead to larger fluctuations of the response rate. Analysis of the effect of CVC on fibrosis-related biomarkers was also limited by the small sample size. However, pooling of the treatment groups allowed us to evaluate the correlation between changes in histology and fibrosis-related biomarkers. Of the evaluated biomarkers, we observed a consistent reduction in levels of PRO-C3, a propeptide that reflects formation of type III collagen, among participants with fibrosis improvement.⁽²¹⁾ The baseline PRO-C3 levels in this study of 16.5 ng/mL within the F3 population were in line with the recently reported cutoff of 15.6 ng/mL for advanced fibrosis ($\geq F3$); therefore, these exploratory analyses suggest that PRO-C3 may have prognostic value as a biomarker in NASH.⁽²²⁾

The overall safety profile of CVC was comparable to placebo and well tolerated over the 2 years. The types, severity, and frequency of TEAEs reported after 2 years of CVC treatment were consistent with those reported after 1 year of treatment, with no new safety findings identified in year 2. Overall, a comparable proportion of participants in all groups reported TEAEs, the majority of which were mild to moderate in severity; and no deaths occurred during the study. Few TEAEs resulted in study discontinuations during year 2 (all in arm A), and a similar proportion in all groups (3.3%) had elevations in liver biochemistry requiring further evaluation. Diarrhea, nausea, abdominal pain, and arthralgia were experienced more frequently in the CVC groups than the placebo group, which was consistent with prior CVC studies.^(13,14,23)

Treatment with CVC was associated with reductions in markers of systemic inflammation, providing

further evidence of its anti-inflammatory activity in response to sustained target engagement. Although the study was not designed or powered to demonstrate cardiovascular benefit of treatment, this property of CVC is potentially relevant as systemic inflammation is an important driver of adverse cardiovascular outcomes. The latter are still the most frequent cause of death in patients with NASH, and data support an independent contribution of NASH to cardiovascular disease development.⁽²⁴⁾ In the placebo-to-CVC crossover group, rapid reductions in fibrinogen were observed soon after switching to CVC, which were sustained until the end of treatment, accompanied by concurrent increases in CCL2 and CCL4. Nonetheless, there were some variations in the extent of reduction in biomarkers of systemic inflammation, which might be attributed to redundancy and compensatory mechanisms in chemokine signaling.^(17,25) However, no differences in changes in body weight or related parameters, insulin sensitivity, or fasting metabolic parameters were observed with CVC compared to placebo, suggesting that CVC likely does not worsen underlying metabolic disease or may be metabolically neutral. Consequently, treatment regimens that combine agents with anti-inflammatory and antifibrotic activities (such as CVC) with other agents that target metabolic components may represent a new paradigm in the treatment of NASH.⁽⁷⁾

In both year 1 and year 2 analyses, CVC showed a beneficial impact on fibrosis without affecting the histological features of steatohepatitis. This lack of effect on steatohepatitis may be attributed to compensatory mechanisms driven by chemokine interactions with other cognate receptors than those blocked by CVC or other pathological drivers such as hepatocyte oxidative stress, endoplasmic reticulum stress, and apoptosis that are not directly modulated by CVC.⁽²⁵⁾ It may also be that crude histological changes measured by current histological classifications (lobular inflammation of unspecified cellular origin and hepatocyte ballooning) do not capture subtle immune cell modifications induced by chemokine receptor blockade. This, together with the lack of effect of CVC on insulin resistance or associated metabolic changes opens the possibility of further benefit from combination therapies with other agents that target liver metabolism and steatohepatitis such as farnesoid X receptor (FXR) agonists, peroxisome proliferator-activator receptor agonists, or fibroblast growth factor-21.^(7,25)

One such combination treatment with tropifexor (an FXR agonist) and CVC is currently under way in a phase 2 study of adult patients with NASH and liver fibrosis (TANDEM study, NCT03517540).

The key limitation of our study was a higher attrition rate than was anticipated over the 2 years of treatment (23% versus 15%), which might be associated with the protocol requirement of three serial biopsies over a 2-year period. While currently the gold standard in assessing clinical benefit and disease severity, liver biopsies are otherwise painful and invasive and may be associated with complications.^(26,27) Moreover, the missing liver biopsy data predominantly affected the CVC group (arm A), which limited the evaluation of the year 2 data, particularly among the year 1 responders without evaluable biopsies at year 2, who thus were considered nonresponders at year 2. This is an important reminder of the need to identify diagnostic and prognostic biomarkers independent of histological sampling. Another limitation of the study was the limited sample size of patients with severe disease; nonetheless, our *post hoc* analysis on ≥ 2 -stage fibrosis improvement without impact on underlying steatohepatitis suggests that patients with stage 3 fibrosis may potentially be the ideal target population for CVC. Based on these limitations and our overall observations from the phase 2b CENTAUR study, the ongoing AURORA phase 3 study (NCT03028740) was designed to evaluate and confirm the efficacy and safety of CVC for the treatment of liver fibrosis in adults with NASH. The AURORA study differs from CENTAUR in two main aspects: (1) the phase 3 study population specifically includes patients who are likely to benefit from treatment with CVC (i.e., those with stage 2 or 3 fibrosis) and excludes patients with stage 1 fibrosis who comprised 34% of the CENTAUR population and (2) the primary outcomes focus on improvement of liver fibrosis (i.e., improvement in fibrosis by ≥ 1 stage and no worsening of steatohepatitis). Nevertheless, data from CENTAUR support the timing of liver biopsy for the AURORA study, which will be collected at baseline, year 1 (primary endpoint analysis), and year 5 (end of study). Notably, previous phase 2 trials were designed for a single, short-term evaluation of histological endpoints. In contrast, CENTAUR is a unique attempt to assess the durability of the antifibrotic response beyond the initial, 1-year evaluation

together with the variability of the placebo response in the long term. In current phase 3 trials, follow-up data beyond the interim analysis will only be available several years from now.

In conclusion, treatment with CVC resulted in an early antifibrotic benefit, which was maintained particularly in the subset of patients with advanced fibrosis. The drug was well tolerated, with a similar safety profile as placebo. The present results provide additional evidence of the potential of CVC as a safe and efficacious pharmacologic treatment for liver fibrosis in adults with NASH, requiring validation in a larger phase 3 trial. These results also identify CVC as a relevant partner for future combinations with agents that target the metabolic components of NASH, an important consideration given the multifactorial pathogenesis of this disease.

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Data Availability Statement: Data reported in this manuscript are available within the article and its Supporting Information. Allergan will share deidentified patient-level data and/or study-level data, including protocols and clinical study reports, for phase 2-4 trials completed after 2008 that are registered on ClinicalTrials.gov or EudraCT. The indication studied in the trial must have regulatory approval in the United States and/or the European Union, and the primary manuscript from the trial must be published prior to data sharing. To request access to the data, the

researcher must sign a data use agreement. All shared data are to be used for noncommercial purposes only. More information can be found at <http://www.allerganclinicaltrials.com/>.

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Supporting Information

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