A Randomized, Placebo-Controlled Trial of Cenicriviroc for Treatment of Nonalcoholic Steatohepatitis with Fibrosis

Scott L. Friedman [scott.friedman@mssm.edu],[1*] Vlad Ratziu [vlad.ratziu@inserm.fr],[2*] Stephen A. Harrison [stephenharrison87@gmail.com],[3] Manal F. Abdelmalek [manal.abdelmalek@duke.edu],[4] Guruprasad P. Aithal [Guru.Aithal@nuh.nhs.uk][5] Juan Caballeria [CABALLER@clinic.ub.es],[6] Sven Francque [sven.francque@uza.be],[7] Geoffrey Farrell [geoff.farrell@anu.edu.au],[8] Kris V. Kowdley [kris.kowdley@swedish.org],[9] Antonio Craxi [antonio.craxi@unipa.it],[10] Krzysztof Simon [krzysimon@gmail.com],[11,12] Laurent Fischer [laurent.fischer@allergan.com],[13] Liza Melchor-Khan [Flordeliza.Melchor-Khan@allergan.com],[13] Jeffrey Vest [j.vest@medpace.com],[14] Brian L. Wiens [Brian.Wiens@allergan.com],[13] Pamela Vig [Pamela.Vig@allergan.com],[13] Star Seyedkazemi [star.seyedkazemi@allergan.com],[13] Zachary Goodman [zachary.goodman@inova.org],[15] Vincent Wai-Sun Wong [wongv@cuhk.edu.hk],[16] Rohit Loomba [roloomba@ucsd.edu],[17,18] Frank Tacke [frank.tacke@gmx.net],[19] Arun Sanyal [arun.sanyal@vcuhealth.org],[20]† and Eric Lefebvre [Eric.Lefebvre@allergan.com][13]†

[1]Division of Liver Diseases, Icahn School of Medicine at Mount Sinai, NY, USA; [2]Hôpital Pitié Salpêtrière and Université Pierre et Marie Curie, Paris, France; [3]Pinnacle Clinical Research, San Antonio, TX, USA; [4]Division of Gastroenterology & Hepatology, Department of Medicine, Duke University, Durham, NC, USA; [5]Nottingham Digestive Diseases Centre, National Institute for Health Research (NIHR), Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and University of Nottingham, UK; [6]Liver Unit, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Centro de Investigación en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain; [7]Gastroenterology and Hepatology, Antwerp University Hospital, University of Antwerp,

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/hep.29477

Belgium; [8]Liver Research Group, Australian National University Medical School at the Canberra Hospital, Canberra, Australian Capital Territory, Australia; [9]Liver Care Network, Swedish Medical Center, Seattle, WA, USA; [10]Department of Gastroenterology, DiBiMIS, University of Palermo, Palermo, Italy; [11]Division of Infectious Diseases and Hepatology, Faculty of Medicine and Dentistry, Wrocław Medical University, Poland; [12]Department of Infectious Diseases, J. Gromkowski Provincial Specialist Hospital in Wrocław, Poland; [13]Tobira Therapeutics, Inc., South San Francisco, CA, USA; [14]Medpace, Inc., Cincinnati, OH, USA; [15]Center for Liver Diseases, Inova Fairfax Medical Campus, Falls Church, VA, USA; [16]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong; [17]Division of Gastroenterology, Department of Medicine, University of California at San Diego, La Jolla, CA, USA; [18]NAFLD Research Center, Department of Medicine, University of California at San Diego, La Jolla, CA, USA; [19]Department of Medicine III, University Hospital Aachen, Aachen, Germany; [20]Department of Gastroenterology, Virginia Commonwealth University, Richmond, VA, USA

**Joint first authors; †Joint last authors*

Keywords: NASH, NAFLD, CVC, nonalcoholic fatty liver, inflammation

Footnote page

Contact information: Scott L. Friedman, M.D., Division of Liver Diseases, Box 1123, Icahn School of Medicine at Mount Sinai, 1425 Madison Ave., Room 11-70c, New York, NY 10029-6574, United States of America; Phone: +1 (212) 659-9501; Fax: +1 (212) 849 2574; Email: Scott.Friedman@mssm.edu

Abbreviations: NASH, nonalcoholic steatohepatitis; CVC, cenicriviroc; NAS, nonalcoholic fatty liver disease activity score; CRN, Clinical Research Network; T2DM, type 2 diabetes mellitus.

Financial support: The CENTAUR study was sponsored by Tobira Therapeutics, a subsidiary of Allergan plc. Authors who were employees of Tobira Therapeutics were involved in study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analyses; obtained funding; administrative, technical or material support; and study supervision.

Abstract

The aim of this study was to evaluate cenicriviroc (CVC), a dual antagonist of C-C chemokine receptor types 2 and 5, for treatment of nonalcoholic steatohepatitis (NASH) with liver fibrosis.

A randomized, double-blind, multinational phase 2b study enrolled subjects with NASH, a nonalcoholic fatty liver disease activity score [NAS] ≥4, and liver fibrosis (stages 1–3, NASH Clinical Research Network) at 81 clinical sites. Subjects (N = 289) were randomly assigned CVC 150 mg or placebo. Primary outcome was ≥2-point improvement in NAS and no worsening of fibrosis at year 1. Key secondary outcomes were: resolution of steatohepatitis and no worsening of fibrosis; improvement in fibrosis by ≥1 stage and no worsening of steatohepatitis. Biomarkers of inflammation and adverse events were assessed.

Full study recruitment was achieved. The primary end point of NAS improvement in the intent-to-treat population and resolution of steatohepatitis was achieved in a similar proportion of subjects on CVC (N = 145) and placebo (N = 144) (16% vs 19%, $P = 0.52$ and 8% vs 6%, $P = 0.49$, respectively). However, the fibrosis end point was met in significantly more subjects on CVC than placebo (20% vs 10%; $P = 0.02$). Treatment benefits were greater in those with higher disease activity and fibrosis stage at baseline. Biomarkers of systemic inflammation were reduced with CVC. Safety and tolerability of CVC were comparable to placebo.

Conclusions: After 1 year of CVC treatment, twice as many subjects achieved improvement in fibrosis and no worsening of steatohepatitis compared with placebo. Given the urgent need to develop antifibrotic therapies in NASH, these findings warrant phase 3 evaluation. ClinicalTrials.gov no: NCT02217475 (CENTAUR).

Nonalcoholic fatty liver disease is now the most common cause of liver disease, with a prevalence of 25% globally.(1) Nonalcoholic steatohepatitis (NASH), the more severe form of the disease, is characterized by the presence of steatosis, lobular and/or portal inflammation, hepatocyte injury (ie, ballooning), and fibrosis.(2) The presence of liver fibrosis confers an increased risk of disease progression to cirrhosis, liver failure, and hepatocellular carcinoma, with a higher mortality.(3, 4) Fibrosis stage is the only histological feature of NASH independently linked to an increased likelihood of liver-related and all-cause (eg, cardiovascular disease) mortality in recent studies.(3-5) Therefore, reducing liver fibrosis is expected to improve the long-term clinical outcomes of patients with NASH.(6) Among pharmacological treatments currently undergoing evaluation, a number have reported improvement in histological features of NASH,(6-9) but only obeticholic acid improved fibrosis in a randomized clinical study in adults with noncirrhotic NASH.(10)

Cenicriviroc (CVC) is an oral, dual antagonist of C-C motif chemokine receptor types 2 and 5. Preclinical(11-14) and clinical evidence(15-17) support its anti-inflammatory and antifibrotic properties, which are mediated by C-C motif chemokine receptor types 2 and 5 blockade. CVC has demonstrated antifibrotic activity in animal models of liver and renal fibrosis.(11) These findings are supported in patients by improvements in noninvasive markers of hepatic fibrosis (aspartate aminotransferase-to-platelet ratio index, fibrosis-4, and enhanced liver fibrosis test) observed in post hoc analyses of a 48-week phase 2b study in HIV-infected subjects.(18, 19) Furthermore, extensive clinical experience using CVC, with over 1000 subjects treated to date, indicates a favorable safety profile including in subjects with cirrhosis and mild-to-moderate (Child-Pugh A or B) hepatic impairment.(17, 20)

CVC-mediated antagonism of C-C motif chemokine receptor type 2 is expected to reduce the recruitment, migration, and infiltration of pro-inflammatory monocytes and macrophages at the site of liver injury.(14, 15) C-C motif chemokine receptor type 5 antagonism by CVC is expected to additionally impair the migration, activation, and proliferation of collagen-producing activated hepatic stellate cells/myofibroblasts.(21) We designed the phase 2 CENTAUR study to test the efficacy and safety of CVC in adults with NASH and liver fibrosis; results from the year 1 primary analysis are reported here.

Methods

Study Design

The study design, rationale, and procedures of CENTAUR (NCT02217475) have been reported previously.(15) This is a phase 2b, randomized, double-blinded, placebo-controlled, and multinational study. The protocol was approved by the Institutional Review Board or Independent Ethics Committee for each center. The study is being conducted in accordance with the Declaration of Helsinki and with all applicable laws/regulations of the study locations; all subjects gave written informed consent. Data were analyzed by Medpace, Inc., and the sponsor. Authors had access to the data and participated in drafting the manuscript; editorial support was funded by the sponsor and provided by independent medical writers under author guidance. All authors approved the manuscript and assume full responsibility for data accuracy and completeness.

Subjects were randomized to receive CVC 150 mg or a matched placebo once daily. After 1 year, half of the subjects receiving placebo crossed over to CVC, based on preplanned randomization, for a second year of treatment. At baseline, eligible subjects were assigned to the treatment arms using permuted block randomization stratified by nonalcoholic fatty

liver disease activity score (NAS) at screening (4 or ≥5) and fibrosis stage (≤2 or >2). Subjects were randomized 2:1:1 to arm A (CVC 150 mg once daily for 2 years), arm B (placebo for 1 year then CVC 150 mg for 1 year), or arm C (placebo for 2 years). Randomization was accomplished via interactive voice response system.

Subjects, the sponsor, investigators and all site personnel involved with dispensing study medication, carrying out study procedures, evaluating subjects, entering study data and/or evaluating study data remain blinded to individual treatment assignment until all subjects complete the 2-year study and the database is locked for all study data. CVC and matching placebo provided by the sponsor were visually indistinguishable and the packaging identical except for a unique bottle identification number. We report herein the results at year 1 of treatment, comparing CVC to placebo.

Adult subjects with histological evidence of NASH, a NAS ≥4 with ≥1 in each component, and liver fibrosis (NASH Clinical Research Network [CRN] stages 1 to 3) were enrolled at 81 clinical sites in Australia, Belgium, France, Germany, Hong Kong, Italy, Poland, Spain, the UK, and the USA. Subjects had either type 2 diabetes mellitus (T2DM), a high body mass index (>25 kg/m^2) with ≥1 criteria of the metabolic syndrome (National Cholesterol Education Program definition), or bridging fibrosis (NASH CRN stage 3) and/or high disease activity (NAS ≥5). The screening and year 1 liver biopsies were read by a central pathologist, who remained blinded to individual subject treatment assignment. Screening biopsies were not reread at the time year 1 biopsies were assessed; however, biopsy sequence was not blinded, due to logistical challenges.

The study protocol instructed sites to provide and review patient education materials about NASH and liver fibrosis by the National Institute of Diabetes and Digestive Kidney Diseases

(NIDDK) at the screening visit, but relied on local standard of care for implementing diet and lifestyle intervention in randomized subjects. Subjects were excluded from the study if they had bariatric surgery in the past 5 years, or planned bariatric surgery during the trial. Alcohol consumption (current drinker, former drinker or never consumed) was recorded at baseline and at subsequent visits. Height of subjects was recorded at screening and month 12; body weight was monitored at regular intervals (screening, baseline, and at months 3, 6, and 12 during treatment period 1 [ie, year 1]). Change in body mass index was calculated for CVC and placebo recipients.

Treatment of T2DM and dyslipidemia was allowed with certain restrictions or precautions, depending on the co-administered drug and its drug–drug interaction potential with CVC. The use of frequently administered concomitant medications, including biguanides, glucose lowering drugs (excluding insulin), hydroxymethylglutaryl CoA reductase inhibitors and angiotensin II inhibitors, were noted throughout year 1 of the study and are listed in Supplementary Table S1. Pioglitazone and high-dose vitamin E (>400 UI/day) were disallowed due to potential confounding effects on efficacy.

Study Outcomes

The primary outcome evaluated hepatic histological improvement at year 1 relative to the screening biopsy (defined by ≥2-point improvement in NAS with ≥1-point reduction in either lobular inflammation or hepatocellular ballooning), and no worsening of fibrosis stage (ie, no progression of NASH CRN fibrosis stage). This end point was based on previously published phase 2b trials in NASH.(9, 10) Two key secondary outcomes were prospectively selected based on regulatory guidance and were evaluated at year 1: (1) complete resolution of steatohepatitis (histopathologic interpretation of fatty liver disease, or simple or isolated steatosis and no steatohepatitis) and no worsening of fibrosis stage; (2) improvement in

fibrosis by ≥1 stage (NASH CRN system) and no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocellular ballooning grade).

Other secondary outcomes included: change in fibrosis stage (NASH CRN and Ishak systems); change in histological scores for steatosis, lobular inflammation, and hepatocellular ballooning; change in collagen morphometry on liver biopsy; safety and tolerability of CVC; change in liver biochemistry and fasting metabolic parameters. Inflammatory biomarkers were also assessed.

A tertiary objective of the study was to evaluate the change from baseline in liver stiffness through non-invasive methods (eg, ultrasound transient elastography, two-dimensional magnetic resonance elastography, acoustic radiation force impulse). Unfortunately, most sites did not have access to these methods at the time of initiation of the study; therefore, only a limited number of subjects had available data.

The Supplementary Appendix provides details on CENTAUR study objectives (Supplementary Table S2) and efficacy end points (Supplementary Figure 1).

Statistical Analyses

To assess CVC efficacy for the primary end point the original required sample size was 252 subjects, assuming a 20% response rate for placebo and a 36% response rate for CVC at year 1. The study over-enrolled by 15% but, due to an anticipated dropout rate of 15%, this sample size was still expected to provide at least an 80% power to demonstrate superiority (for a 2-sided type 1 error rate of 0.05) of CVC versus placebo.

The primary efficacy end point was analyzed using logistic regression, which included terms for treatment and the two stratification variables (ie, baseline NAS of 4 or ≥5 and fibrosis stage ≤2 or >2). A preordered, step-down approach was used (Supplementary Figure 2). If statistical significance was achieved at $\alpha = 0.05$, two-sided for the primary end point, a composite analysis on the sum of the two key secondary end points was to be performed with an ordinal logistic regression model. If statistical significance was achieved for the summation, a parallel, simultaneous analysis for each key secondary end point was to be performed. The type I error rate was controlled for the key secondary end points by only testing the composite analysis if the primary end point was positive, and only testing each secondary end point if the composite analysis was also positive.

Supportive analyses were planned in the modified intent-to-treat population, consisting of all subjects in the intent-to-treat population with evaluable biopsies, and with the full analysis set, compiling all subjects with evaluable biopsies at both baseline and year 1.

A post hoc analysis of various factors that might affect response (including baseline characteristics, demographics, laboratory tests, and histological features) was conducted without control of the type I error rate. In a logistic regression model, potential predictors were added to the model in a stepwise selection process if the *P* value was less than or equal to 0.30 after adjustment for all previously included factors. When all such factors were found, those with resulting *P* values less than or equal to 0.05 were considered nominally significant after adjustment for all other potential predictors.

Results

Subjects

This phase 2b, randomized, double-blinded, placebo-controlled, multinational study was initiated in September 2014 and fully enrolled by June 2015. It is currently ongoing and will be conducted over 2 years, with the primary analysis having been performed at year 1 (cut-off date July 2016). A total of 812 subjects were screened; 610 underwent liver biopsy and 289 were randomized to treatment (Figure 1). At the end of year 1, 252 subjects had available screening and year 1 biopsies. The primary efficacy analysis, reported in the intent-to-treat population, comprised all randomized subjects.

Baseline demographics and disease characteristics are presented in Table 1. With the exception of T2DM, the treatment groups were well balanced. Overall, 51% (146/289) of subjects had T2DM, 95% (273/289) had body mass index >25 kg/m^2 with ≥1 criteria of the metabolic syndrome, and 38% (111/289) had bridging fibrosis (NASH CRN stage 3). A total of 72% (208/289) of subjects met ≥3 criteria of the metabolic syndrome. The majority of subjects had NAS ≥5 (74% [214/289]) and 67% (193/289) had fibrosis stage 2 or 3 at screening.

Primary and Key Secondary Outcomes

At year 1, a similar proportion of subjects receiving CVC or placebo achieved the primary end point of hepatic histological improvement in NAS by ≥2 points and no worsening of fibrosis stage (16% vs 19%; odds ratio, 0.82 [95% confidence interval, 0.44–1.52]; P = 0.52; Figure 2A).

Analysis of the key secondary end points was conducted as prespecified and is presented for full disclosure of data, although the primary end point was not met. The composite secondary end point (summation of 'complete resolution of steatohepatitis and no worsening of fibrosis stage' and 'improvement in fibrosis stage by ≥1 stage and no worsening of steatohepatitis') was achieved by significantly more subjects receiving CVC than those receiving placebo (18% vs 10%; odds ratio 1.93 [95% confidence interval 1.04–3.61]; $P = 0.04$). When the two key secondary end points were analyzed separately, a similar proportion of subjects achieved complete resolution of steatohepatitis and no worsening of fibrosis stage (8% vs 6%; odds ratio 1.40 [95% confidence interval 0.54–3.63]; $P = 0.49$), while twice as many subjects on CVC achieved improvement in fibrosis stage by ≥1 stage and no worsening of steatohepatitis compared with those on placebo (20% vs 10%; odds ratio 2.20 [95% confidence interval 1.11–4.35]; $P = 0.02$; Figure 2B).

Subgroup Analyses for Key Secondary Fibrosis End Point

CVC provided antifibrotic benefits in both fibrosis strata (stages ≤2 and >2; Figure 2C and Figure 3). When subjects with baseline fibrosis stages 2 and 3 were pooled, CVC benefits were significant ($P < 0.05$; Figure 2D and Figure 3). CVC treatment benefits were consistent across prespecified subgroups; the greatest treatment benefits were in subjects with baseline NAS ≥5 and those with prominent hepatocellular ballooning, relative to those with baseline NAS =4 and few ballooned cells (Figure 2E, Figure 2F and Figure 3).

A post hoc analysis was conducted to evaluate the effect of biopsy length (<15 mm or ≥15 mm), in the modified intent-to-treat population (Supplementary Table S3). The majority of liver biopsies collected at baseline (78–83%) and year 1 (79–82%) had a length of ≥15 mm, a length above which sampling variability is expected to be lower.

Findings from this post hoc analysis were generally consistent with the main results, except for the smaller subset of subjects with a year 1 liver biopsy length of <15 mm, where placebo response was higher than in other subgroups (22%; 6/27 placebo-treated subjects). In contrast, the most pronounced treatment benefits were observed in the larger subset of subjects with a year 1 liver biopsy of ≥15 mm; improvement in fibrosis by ≥1 stage and no worsening of steatohepatitis was achieved by 24% (78/103) of CVC-treated subjects compared to 9% (9/99) of placebo-treated subjects. In this subgroup, the odds ratio (CVC/placebo) was 3.21 (95% confidence interval 1.41–7.28).

A post hoc analysis of predictors of response determined that the factors most strongly associated with improvement in fibrosis stage and no worsening of steatohepatitis at year 1 were treatment (ie, receiving CVC), a higher fibrosis stage at baseline, mild or no portal inflammation at baseline, and a higher baseline body mass index ($P < 0.050$ for each, after adjustment for the other predictors). Although differences were observed in subgroups for gender, region, and presence of T2DM, these factors were not associated with response to CVC.

Other Secondary End Points

Change in Fibrosis Stage

The shift in fibrosis stage from baseline to year 1 was assessed using the NASH CRN and Ishak systems (Supplementary Figure 3). The proportion of subjects with a decrease in fibrosis stage was 29% for CVC and 19% for placebo using the NASH CRN system; and 35% and 22%, respectively, using the Ishak system. A total of 27 and 20 subjects in the CVC and placebo groups, respectively, improved by one NASH CRN fibrosis stage (33 and 23 subjects, respectively, improved by one Ishak fibrosis stage). Eight and three subjects in the

CVC and placebo groups, respectively, improved by two fibrosis stages on the NASH CRN system; ten and four subjects, respectively, improved by two stages on the Ishak system. Ten subjects achieved resolution of fibrosis with CVC compared with five subjects on placebo (both systems). Two subjects progressed to cirrhosis with CVC compared with five subjects on placebo (both systems).

Collagen Area by Morphometry on Liver Biopsy

Change from baseline to year 1 in collagen area by morphometry was analyzed as prespecified in the study protocol. A post hoc analysis was then performed to evaluate the change in collagen area from baseline to year 1, according to histologic response (ie, improvement in NASH CRN or Ishak stage) in subjects with paired liver biopsies. At baseline, the mean (standard deviation) collagen area was relatively low in both groups: 2.37 (1.827) for CVC and 2.49 (2.389) for placebo. Although mean (standard deviation) changes from baseline to year 1 were small in both groups (0.02 [2.357] for CVC and –0.14 [2.389] for placebo), a larger proportion of subjects receiving CVC had a reduction in collagen and improvement in fibrosis by at least 1 stage compared to those receiving placebo (NASH CRN: CVC = 28/121 [23%], placebo = 18/123 [15%]; Ishak: CVC = 36/121 [30%], placebo = 22/123 [18%]). Moreover, there was good correspondence between improvement in fibrosis stage and reduction in collagen area by morphometry; of those subjects who achieved an improvement in fibrosis stage (whether in the CVC or placebo groups), the majority (80% for CVC group, 75% for placebo) had a concordant reduction in collagen area. When assessed similarly by Ishak, 84% of CVC and 79% of placebo subjects had a concordant improvement in both fibrosis stage and collagen area.

Another post hoc analysis was conducted using only slides with liver biopsy tissue surface of ≥5 mm^2, where sampling variability is expected to be lower. In subjects with collagen

morphometry of ≥2% at baseline, all subjects achieving at least one stage improvement in fibrosis (NASH CRN) had concordant reduction in collagen at year 1. However, there was substantial variability in changes in collagen between baseline and year 1 in subjects with <2% collagen morphometry at baseline which represents a sizeable portion of all CENTAUR subjects (Supplementary Figure S4).

Improvement in NAS

Changes in histological scores at the end of year 1 for CVC versus placebo for steatosis, lobular inflammation, and hepatocellular ballooning are reported in Supplementary Table S4. No notable differences in the individual components of NAS were observed.

Body weight, Liver and Fasting Metabolic Parameters and Noninvasive Hepatic Fibrosis Markers

There were no meaningful differences in body weight or body mass index (mean change [standard deviation] from baseline to year 1) between groups (-0.24 [4.177] kg for CVC and -0.08 [4.301] for placebo for body weight; -0.13 [1.493] kg/m^2 for CVC and -0.01 [1.751] kg/m^2 for placebo for body mass index). Changes from baseline to year 1 in liver transaminases, fasting metabolic parameters, and noninvasive hepatic fibrosis markers (nonalcoholic fatty liver disease fibrosis score, fibrosis-4, aspartate aminotransferase-to-platelet count ratio index, and enhanced liver fibrosis test) were modest, and similar between the CVC and the placebo groups (Table 2 and Supplementary Tables S5 and S6).

A post hoc analysis was conducted to explore the relationship between change in fibrosis indices and improvement in liver histology. Changes from baseline to year 1 in fibrosis indices were calculated for subjects who improved in fibrosis by ≥1 stage at year 1

(NASH CRN), and for subjects who did not (Supplementary Table S6). This post hoc analysis was not powered to demonstrate a difference for treatment (CVC or placebo) and/or subgroup (histological improvement or not). In general, more favorable changes (ie, smaller mean increases or larger mean decreases) in fibrosis indices (nonalcoholic fatty liver disease fibrosis score, fibrosis-4, aspartate aminotransferase-to-platelet ratio index, enhanced liver fibrosis) were observed in subjects in whom fibrosis improved by ≥1 stage at year 1 relative to subjects in whom fibrosis did not improve. These observations were noted in subjects who received CVC and in those who received placebo.

Biomarkers of inflammation

Marked reductions in circulating biomarkers of systemic inflammation (high-sensitivity C-reactive protein, interleukin-6, fibrinogen, interleukin-1ß) and of monocyte activation (soluble cluster of differentiation 14) were observed with CVC (vs placebo) (Table 2). Reciprocal increases in chemokine (C-C motif) ligands 2 and 4 were observed in CVC-treated subjects only, confirming potent C-C motif chemokine receptor types 2 and 5 blockade, as described previously.(16, 17, 22)

A post hoc analysis was conducted to evaluate correlations between change in markers of inflammation, where pronounced treatment differences were observed (ie, high-sensitivity C-reactive protein, interleukin-6, fibrinogen, interleukin-1ß and soluble cluster of differentiation 14), and change in markers of insulin sensitivity (ie, hemoglobin A1c, homeostatic model of assessment of insulin resistance and adipose tissue insulin resistance). The results showed limited, if any, relationship (Spearman rank correlation of 0.20 or less for almost all comparisons; data not shown).

Safety and Tolerability

The safety population comprised all 288 subjects who were randomized and received at least one dose of study drug. The incidence of treatment-emergent adverse events was similar in both groups, and in general mild or moderate in severity (Supplementary Table S7).

Twenty-six treatment-emergent serious adverse events were reported (CVC, n = 16; placebo, n = 10). All serious adverse events but one (grade 2 arrhythmia; subject remained on blinded treatment) were considered not related to treatment. The incidence of treatment-emergent grade 3 or 4 laboratory abnormalities was generally similar between groups. Grade 4 uric acid elevations, which occurred in subjects with increased baseline values, and asymptomatic grade 3 amylase elevations were observed more frequently in the CVC than placebo group (7.6% vs 4.2% and 4.2% vs 0.7%, respectively) (Supplementary Table S7). No treatment-emergent adverse events of pancreatitis were reported in subjects with grade 3 amylase elevations.

Changes from baseline in liver biochemistry and fasting metabolic parameters are reported in Supplementary Table S5.

Discussion

NASH is highly prevalent globally and represents an unmet medical need, based on related morbidity and mortality burdens, and the lack of approved therapies.(1) CENTAUR prospectively analyzed and reported on composite clinical efficacy end points currently being evaluated in phase 3 NASH studies (NCT02548351, NCT02704403, NCT03028740; https://clinicaltrials.gov), and demonstrated a benefit on fibrosis in subjects with NASH after only 1 year of treatment. Although the primary outcome was not met, twice as many

subjects on CVC than placebo achieved the clinically important key secondary outcome of improvement in fibrosis by ≥1 stage and no worsening of steatohepatitis. Fibrosis is the only histological feature that has been independently associated with clinical outcomes in longitudinal cohorts.(3-5) CENTAUR exclusively enrolled subjects with NASH and liver fibrosis; additionally, subjects were required to have active metabolic dysfunction (T2DM or metabolic syndrome), a well-known risk factor for disease progression. The primary outcome was chosen based on the standard established in prior phase 2 studies that assessed the efficacy of NASH therapies.(9, 10) Improvement in fibrosis by ≥1 stage and no worsening of steatohepatitis was selected as one of the two key secondary outcomes, both because of its association with clinical outcomes and to inform the phase 3 program. Greater CVC treatment benefits were observed in subjects with higher disease activity and fibrosis stage (ie, NAS ≥5, prominent hepatocellular ballooning, moderate-to-severe fibrosis); these observations help identify which patients are most likely to benefit from CVC treatment and are aligned with known risk factors of disease progression. The majority of subjects who achieved an improvement in fibrosis stage also achieved a reduction in collagen area by morphometry, supporting findings from secondary efficacy end points related to improvement in fibrosis.

The safety and tolerability of NASH therapies are paramount, as the condition is typically asymptomatic and patients are often being treated for comorbidities including T2DM and cardiovascular disease. In CENTAUR, the incidence of treatment-emergent adverse events and laboratory abnormalities was comparable between CVC and placebo. The most frequently reported treatment-emergent adverse events of at least moderate severity (ie, fatigue, diarrhea, and headache) were consistent with the extensive clinical experience with CVC in prior studies.(16, 17, 22) Changes in fasting metabolic parameters from baseline

were relatively small and comparable between groups, indicating that CVC is not likely to worsen pre-existing metabolic disease in NASH patients.

The results of CENTAUR are potentially paradigm-shifting, as they challenge the common assumption that the antifibrotic effects of NASH agents can only be observed by improving the underlying metabolic liver disease. Instead, the beneficial impact of CVC on fibrosis without affecting the histological features of steatohepatitis at year 1 reinforces the rationale for directly targeting inflammatory and fibrotic mechanisms. The antifibrotic activity of CVC observed here is consistent with findings in several animal models of chronic liver injury.(11) While the study didn't meet the primary end point at year 1, it nonetheless underscores the evolving principles of clinical-trial design that increasingly look to assign end points that are aligned with the mechanism of action.

Based on its mechanism of action, the lack of effect of CVC on lobular inflammation was unexpected and will need to be further explored. One possible explanation may be that the impact of CVC on the composition of immune cells in the inflamed lobule, as well as the noncellular components of inflammation (ie, chemokines and soluble mediators), cannot be fully characterized by the H&E stain alone (used to grade the degree of lobular inflammation). Detailed characterization of immune cell subsets will be valuable in the future to further clarify the impact of CVC on hepatic inflammation. Although the NAS has been widely used to evaluate early treatment effects in phase 2 studies, it does not distinguish targeted effects of CVC on C-C motif chemokine receptor type 2-expressing monocyte-derived macrophages, as previously demonstrated in models of liver injury.(12, 14) Specifically, activities of chemokine signaling, including intrahepatic monocyte and macrophage recruitment, and fibrogenesis, occur downstream of liver-cell injury and metabolic dysregulation in the pathophysiology of NASH; therefore, they may not be

reflected in the traditional histological features of the NAS, including steatosis, lobular inflammation, and hepatocellular ballooning. Therefore, further evaluation using cell-specific markers will be required to elucidate the effects of CVC on immune cells in patients.

Importantly, a broad mechanistic impact of CVC on inflammatory signaling is underscored by reductions in circulating markers of systemic inflammation (ie, high-sensitivity C-reactive protein, interleukin-6, fibrinogen) and soluble cluster of differentiation 14 (a marker of monocyte activation), which is consistent with previous studies in subjects with HIV infection.(17, 22)

In this study in subjects with NASH, a large histological data set of 252 paired biopsies was available for year 1 evaluation in the modified intent-to-treat population. All liver biopsies were read centrally by a single pathologist, thereby reducing reader variability. Limitations of our study include: differences in responses among subgroups (eg, region, sex, and T2DM) that may reflect the multifactorial nature of the disease; the study sample size; and the inherent variability of liver biopsy sampling,(23) which will require further investigation in subsequent studies.

Improvement in fibrosis stage has been reported in phase 2 NASH randomized clinical trials, as early as 24 weeks.(10, 24, 25) These and similar studies have also demonstrated that a small but significant proportion of subjects, up to approximately 20%,(8-10) will have spontaneous improvement on placebo. This improvement has often been attributed to increased clinical monitoring, motivation, and compliance to diet and lifestyle changes of subjects participating in such trials. Therefore, the observation that some placebo subjects improved in the CENTAUR study is neither unexpected nor out of line with other reported results.

In conclusion, CVC showed a significant antifibrotic benefit at year 1 and was well tolerated. Although the primary end point of the study was not met, the fact that the CENTAUR year 1 study results showed that CVC provided clinically meaningful benefits and resulted in twice as many subjects achieving 'improvement in fibrosis by ≥1 stage and no worsening of steatohepatitis' as compared with placebo, suggests that the study did in fact show proof of concept, warranting phase 3 development of CVC. If this benefit is corroborated by the continued follow-up over the planned second year of treatment, and subsequent confirmatory trials, CVC will represent an important advance in the treatment of liver fibrosis in patients with NASH.

Trial registration: CENTAUR; NCT02217475

The full clinical trial protocol can be accessed as a supplemental attachment.

The study was sponsored by Tobira Therapeutics, a subsidiary of Allergan plc. The sponsor provided funding for the study and provided the study drug.

References

1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016 Jul;64(1):73-84.

2. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Am J Gastroenterol 2012 Jun;107(6):811-826.

3. Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015 Aug;149(2):389-397.

4. Ekstedt M, Hagström H, Nasr P, Fredrikson M, Stål P, Kechagias S, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2015 May;61(5):1547-1554.

5. Younossi ZM, Stepanova M, Rafiq N, Makhlouf H, Younoszai Z, Agrawal R, et al. Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality. Hepatology 2011 Jun;53(6):1874-1882.

6. Ratziu V, Goodman Z, Sanyal A. Current efforts and trends in the treatment of NASH. J Hepatol 2015 Apr;62(1 Suppl)(1 Suppl):S65-S75.

7. Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, et al. Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus: A Randomized, Controlled Trial. Ann Intern Med 2016 Jun 21.

8. Ratziu V, Harrison SA, Francque S, Bedossa P, Lehert P, Serfaty L, et al. Elafibranor, an agonist of the peroxisome proliferator-activated receptor-α and -δ, induces resolution of nonalcoholic steatohepatitis without fibrosis worsening. Gastroenterology 2016;150(5):1147-1159.

9. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010 May 6;362(18):1675-1685.

10. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet 2015 Mar 14;385(9972):956-965.

11. Lefebvre E, Moyle G, Reshef R, Richman LP, Thompson M, Hong F, et al. Antifibrotic effects of the dual CCR2/CCR5 antagonist cenicriviroc in animal models of liver and kidney fibrosis. PLoS One 2016;11(6):e0158156.

12. Puengel T, Krenkel O, Mossanen J, Longerich E, Lefebvre E, Trautwein C, et al. The dual CCR2/CCR5 antagonist cenicriviroc ameliorates steatohepatitis and fibrosis in

vivo by inhibiting the infiltration of inflammatory monocytes into injured liver. J Hepatol 2016;64:s159-s182.

13. Tacke F, Poulin D, Jenkins H, Wolfgang G, Lefebvre E. Oral, dual CCR2/CCR5 antagonist, cenicriviroc, leads to dose-dependent decreases in monocyte recruitment in a thioglycollate-induced model of peritonitis. Poster number 8 presented at AASLD and Industry Colloquium: Novel Targets and Therapies in Liver Disease, 20 March 2015, Durham, NC, USA.

14. Mossanen JC, Krenkel O, Ergen C, Govaere O, Liepelt A, Puengel T, et al. Chemokine (C-C motif) receptor 2-positive monocytes aggravate the early phase of acetaminophen-induced acute liver injury. Hepatology 2016 Jun 15;64(5):1667-1682.

15. Friedman SL, Sanyal A, Goodman Z, Lefebvre E, Gottwald M, Fischer L, et al. Efficacy and safety study of cenicriviroc for the treatment of non-alcoholic steatohepatitis in adult subjects with liver fibrosis: CENTAUR Phase 2b study design. Contemp Clin Trials 2016;47:356-365.

16. Lefebvre E, Gottwald M, Lasseter K, Chang W, Willett M, Smith PF, et al. Pharmacokinetics, safety, and CCR2/CCR5 antagonist activity of cenicriviroc in participants with mild or moderate hepatic impairment. Clin Transl Sci 2016 May 12;9(3):139-148.

17. Thompson M, Saag M, Dejesus E, Gathe J, Lalezari J, Landay AL, et al. A 48-week randomized Phase 2b study evaluating cenicriviroc vs. efavirenz in treatment-naive HIV-infected adults with CCR5-tropic virus. AIDS 2016 Mar 27;30(6):869-878.

18. Sherman KE, Abdel-Hameed E, Rouster SD. CCR2/CCR5 antagonism with cenicriviroc decreases fibrosis scores in HIV-infected patients. Presented at HEP DART 2015, Frontiers in Drug Development for Viral Hepatitis, 6 December 2015, Hawaii, USA.

19. Thompson M, Chang W, Jenkins H, Flynt A, Gottwald M, Lefebvre E. Improvements in APRI and FIB-4 fibrosis scores correlate with decreases in sCD14 in HIV-1 infected adults receiving cenicriviroc over 48 weeks. Hepatology 2014 Oct;60(Suppl 1)(Suppl 1):424A.

20. Lefebvre E, Smith P, Willett MS, Lasseter KC, Chang W, Gottwald MD. Pharmacokinetics and safety of multiple-dose cenicriviroc, a novel, oral, once-daily CCR2 and CCR5 antagonist, in adults with mild or moderate hepatic impairment. Hepatology 2014 Oct;60(1 Suppl):23-24.

21. **Marra F, Tacke F.** Roles for chemokines in liver disease. Gastroenterology 2014 Sep;147(3):577-594.

22. Lalezari J, Gathe J, Brinson C, Thompson M, Cohen C, Dejesus E, et al. Safety, efficacy, and pharmacokinetics of TBR-652, a CCR5/CCR2 antagonist, in HIV-1-infected, treatment-experienced, CCR5 antagonist-naive subjects. J Acquir Immune Defic Syndr 2011 Jun 1;57(2):118-125.

23. Ratziu V, Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. Gastroenterology 2005 Jun;128(7):1898-1906.

24. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006 Nov 30;355(22):2297-2307.

25. Loomba R, Lawitz E, Mantry PS, Jayakumar S, Caldwell SH, Arnold H, et al. GS-4997, an Inhibitor of Apoptosis Signal-Regulating Kinase (ASK1), Alone or in Combination with Simtuzumab for the Treatment of Nonalcoholic Steatohepatitis (NASH): A Randomized, Phase 2 Trial [Abstract]. Hepatology 2016 Dec;1119A-1120A.

Tables

Table 1. Baseline Demographics and Disease Characteristics of Randomized Subjects per Treatment Group

CVC, cenicriviroc; HbA1c, hemoglobin A1c; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH CRN, nonalcoholic steatohepatitis Clinical Research Network; SD, standard deviation.

[a]One subject was randomized in error without an adequate screening biopsy.

Table 2. Change from Baseline to Year 1 in Biomarkers of Systemic Inflammation, Monocyte/Macrophage Activation, CCR2 and CCR5 Blockade and Hepatocellular Apoptosis (PP population)

CI, confidence intervals; CCL2, chemokine (C-C motif) ligand 2; CCL4, chemokine (C-C motif) ligand 4; CK-18, cytokeratin 18; CVC, cenicriviroc; hs-CRP, high-sensitivity C-reactive protein; IL-1β, interleukin-1 beta; IL-6, interleukin-6; PP, per protocol; sCD14, soluble cluster of differentiation 14; sCD163, soluble cluster of differentiation 163.

Figures

Figure 1. Subject disposition (CONSORT flow diagram).

[a]The disposition of four subjects who withdrew early (one for protocol deviation, one lost to follow-up, one due to physician's decision, one other) cannot be reported in specific treatment arm as the study is ongoing and remains blinded.

[b]Liver biopsy sample too small or fragmented, therefore inadequate for assessment of efficacy end points.

[c]A subject was randomized in error without an adequate screening biopsy.

Figure 2. Primary end point and key secondary end point of improvement in fibrosis by ≥1 stage and no worsening of steatohepatitis at Year 1 (ITT analysis), with subgroup analyses for the key secondary end point (mITT population). (*A*) Subjects meeting the primary end point (improvement in NAS and no worsening of fibrosis); (*B*) Subjects meeting the key secondary end point of improvement in fibrosis by ≥1 stage and no worsening of steatohepatitis. Missing biopsies were counted as treatment failure. (*C,D,E,F*) Response for the key secondary end point by baseline: (*C*) fibrosis stage (NASH CRN system); (*D*) fibrosis stages 2 and 3 pooled (NASH CRN system); *(E)* NAS stratification and *(F)* prominent hepatocellular ballooning. OR are presented with 95% CI and *P* values, and were calculated using a logistic regression model with factors for randomized treatment group, NAS at screening (4 or ≥5), and fibrosis stage (≤2 or >2).

CI, confidence intervals; CVC, cenicriviroc; ITT, intent-to-treat; mITT, modified intent-to-treat; NAS, nonalcoholic fatty liver disease activity score; NASH CRN, nonalcoholic steatohepatitis Clinical Research Network; OR, odds ratio.

Figure 3. Subgroup analyses for the key secondary end point of improvement in fibrosis by ≥1 stage and no worsening of steatohepatitis (mITT population). Response by baseline NAS stratification, fibrosis stage (NASH CRN system), hepatocellular ballooning grade, lobular inflammation, steatosis, gender, age, BMI, type 2 diabetes mellitus status, PNPLA3 genotype, and region.

BMI, body mass index; CI, confidence intervals; CVC, cenicriviroc; mITT, modified intent-to-treat; NAFLD, nonalcoholic fatty liver disease; NAS, nonalcoholic fatty liver disease activity score; NASH CRN, nonalcoholic steatohepatitis Clinical Research Network; OR, odds ratio; PNPLA3, patain-like phospholipase domain-containing protein 3.

[a]OR and 95% CI not calculable.

Writing assistance: Editorial support was provided by Catrina Milgate, Sandra Whitelaw and Camille Bonomelli of Alpharmaxim Healthcare Communications.

Acknowledgments: The investigators thank the study subjects for their participation, and the CENTAUR study team.

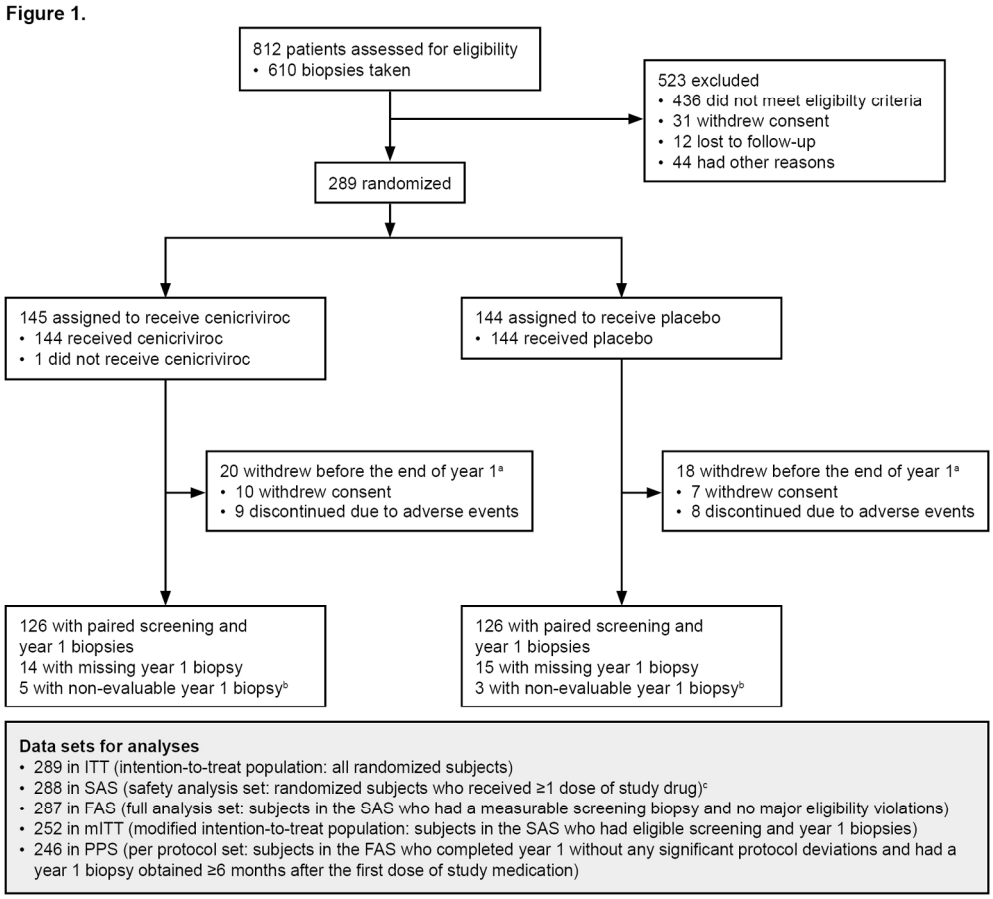

Figure 1. Subject disposition (CONSORT flow diagram).
[a]The disposition of four subjects who withdrew early (one for protocol deviation, one lost to follow up, one due to physician's decision, one other) cannot be reported in specific treatment arm as the study is ongoing and remains blinded.
[b]Liver biopsy sample too small or fragmented, therefore inadequate for assessment of efficacy end points.
[c]A subject was randomized in error without an adequate screening biopsy.

165x150mm (300 x 300 DPI)

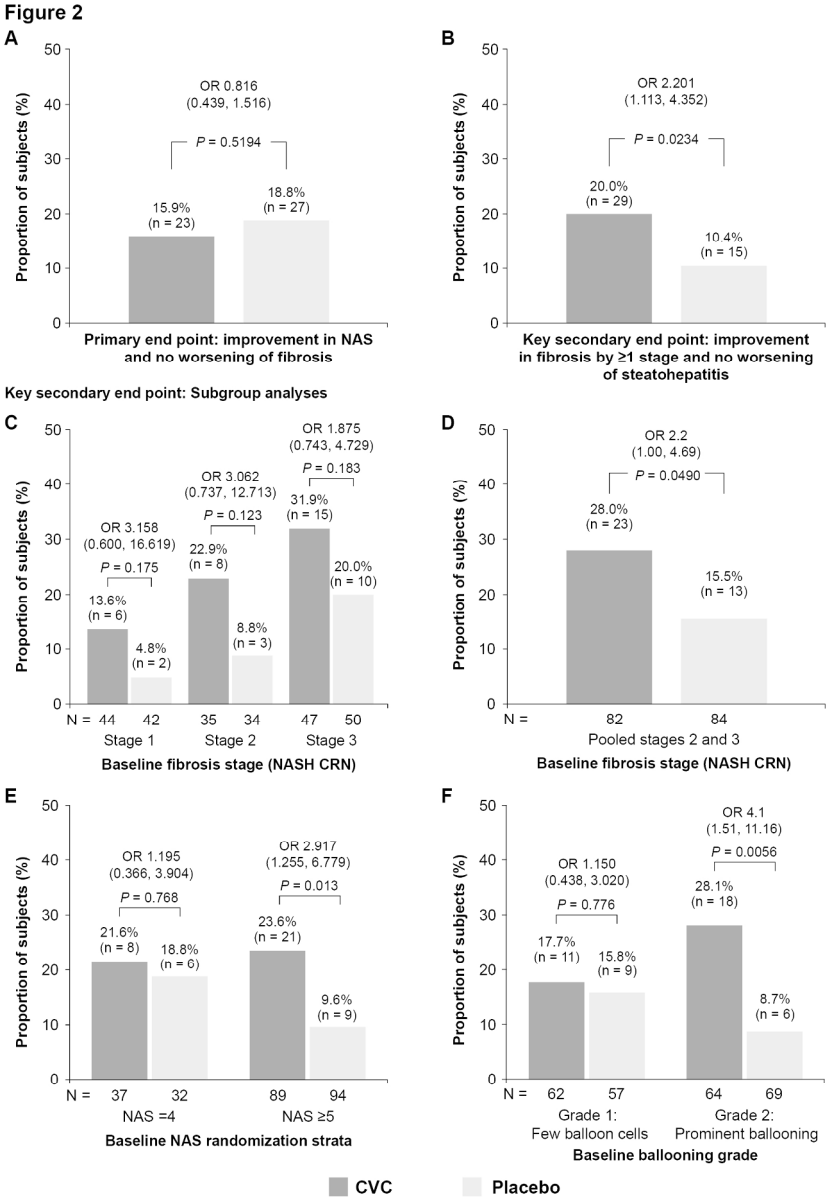

Figure 2. Primary end point and key secondary end point of improvement in fibrosis by ≥1 stage and no worsening of steatohepatitis at Year 1 (ITT analysis), with subgroup analyses for the key secondary end point (mITT population). (A) Subjects meeting the primary end point (improvement in NAS and no worsening of fibrosis); (B) Subjects meeting the key secondary end point of improvement in fibrosis by ≥1 stage and no worsening of steatohepatitis. Missing biopsies were counted as treatment failure. (C,D,E,F) Response for the key secondary end point by baseline: (C) fibrosis stage (NASH CRN system); (D) fibrosis stages 2 and 3 pooled (NASH CRN system); (E) NAS stratification and (F) prominent hepatocellular ballooning. OR are presented with 95% CI and P values, and were calculated using a logistic regression model with factors for randomized treatment group, NAS at screening (4 or ≥5), and fibrosis stage (≤2 or >2).

173x250mm (300 x 300 DPI)

Figure 3

	CVC	Placebo
Overall mITT population	29/126 (23%)	15/126 (12%)
NAFLD activity score		
NAS =4	8/37 (22%)	6/32 (19%)
NAS ≥5	21/89 (24%)	9/94 (10%)
Fibrosis stage (NASH CRN)		
Stage 1	6/44 (14%)	2/42 (5%)
Stage 2	8/35 (23%)	3/34 (9%)
Stage 3	15/47 (32%)	10/50 (20%)
Fibrosis stage 2/3 (NASH CRN)		
Stage 2/3	23/82 (28%)	13/84 (16%)
Hepatocellular ballooning		
Grade 1 (few balloon cells)	11/62 (18%)	9/57 (16%)
Grade 2 (prominent ballooning)	18/64 (28%)	6/69 (9%)
Lobular inflammation		
Grade 1 (<2 foci/200x)	1/6 (17%)	1/4 (25%)
Grade 2 (2–4 foci/200x)	17/66 (26%)	7/61 (12%)
Grade 3 (>4 foci/200x)	11/54 (20%)	7/61 (12%)
Steatosis		
Grade 1 (5–33%)	21/89 (24%)	10/81 (12%)
Grade 2 (>33–66%)	8/31 (26%)	4/41 (10%)
Grade 3 (>66%)[a]	0/6 (0%)	1/4 (25%)
Gender		
Male	19/69 (28%)	7/59 (12%)
Female	10/57 (18%)	8/67 (12%)
Age		
< Median age (56 yr)	14/59 (24%)	9/66 (14%)
≥ Median age (56 yr)	15/67 (22%)	6/60 (10%)
BMI		
≤30 kg/m^2	7/32 (22%)	3/34 (9%)
>30–≤35 kg/m^2	8/51 (16%)	5/45 (11%)
>35–≤40 kg/m^2	6/22 (27%)	4/28 (14%)
>40 kg/m^2	7/19 (37%)	3/19 (16%)
Type 2 diabetes status		
Present	17/74 (23%)	10/57 (18%)
Not present	12/52 (23%)	5/69 (7%)
PNPLA3 genotype		
Wild type (CC)	6/30 (20%)	4/32 (13%)
G allele (GG+CG)	20/86 (23%)	10/87 (12%)
Region		
USA	16/75 (21%)	10/70 (14%)
Rest of world	13/51 (26%)	5/56 (9%)

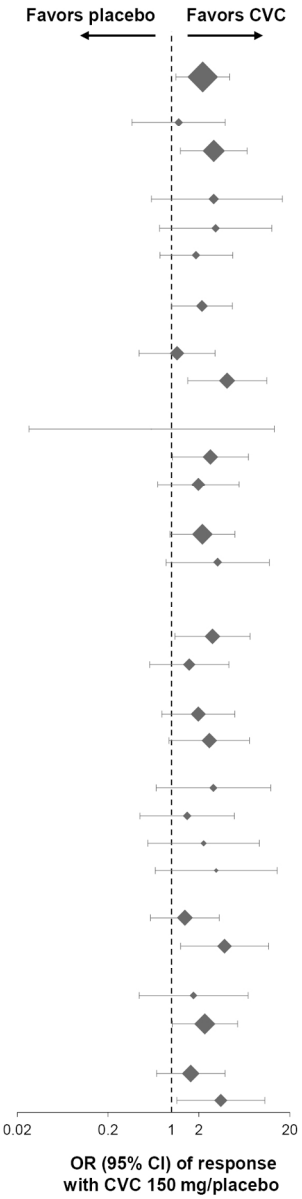

Figure 3. Subgroup analyses for the key secondary end point of improvement in fibrosis by ≥1 stage and no worsening of steatohepatitis (mITT population). Response by baseline NAS stratification, fibrosis stage (NASH CRN system), hepatocellular ballooning grade, lobular inflammation, steatosis, gender, age, BMI, type 2 diabetes mellitus status, PNPLA3 genotype, and region.

142x195mm (300 x 300 DPI)

HEP-17-0693

Table 1. Baseline Demographics and Disease Characteristics of Randomized Subjects per Treatment Group

	CVC 150 mg (N = 145)	Placebo (N = 144)	All (N = 289)[a]
Demographics			
Mean age — year (SD)	54.6 (10.2)	53.7 (11.0)	54.1 (10.6)
Female — no. (%)	73 (50.3)	79 (54.9)	152 (52.6)
Race or ethnicity — no. (%)			
White	129 (89.0)	121 (84.0)	250 (86.5)
Black or African American	5 (3.4)	3 (2.1)	8 (2.8)
Asian	6 (4.1)	15 (10.4)	21 (7.3)
Hispanic	23 (15.9)	25 (17.4)	48 (16.6)
Serum biochemistry			
Mean alanine aminotransferase — U/L (SD)	61.3 (35.2)	65.5 (39.6)	63.4 (37.5)
Mean aspartate aminotransferase — U/L (SD)	43.7 (22.0)	48.3 (24.0)	46.0 (23.1)
Mean alkaline phosphatase — U/L (SD)	79.0 (20.9)	80.8 (27.8)	79.9 (24.5)
Mean gamma-glutamyl transferase — U/L (SD)	69.6 (79.0)	65.2 (43.5)	67.4 (63.7)
Mean total bilirubin — mg/dL (SD)	0.510 (0.531)	0.483 (0.273)	0.496 (0.422)
Lipids			
Triglycerides			
Mean — mg/dL (SD)	180.3 (149.0)	174.5 (110.1)	177.4 (130.8)
>150 mg/dL — no. (%)	70 (48.3)	71 (49.3)	141 (48.8)
Mean cholesterol — mg/dL (SD)			
Total	192.5 (48.9)	187.9 (47.4)	190.2 (48.1)

HEP-17-0693

High-density lipoprotein	42.1 (12.2)	40.9 (13.2)	41.5 (12.7)
Low-density lipoprotein	121.9 (44.4)	118.7 (42.8)	120.3 (43.6)
Very-low-density lipoprotein	36.1 (30.0)	34.9 (22.0)	35.5 (26.3)
Metabolic factors			
Mean body weight — kg (SD)	95.1 (20.4)	97.1 (21.9)	96.1 (21.1)
Mean body mass index — kg/m^2 (SD)	33.6 (5.7)	34.1 (7.2)	33.9 (6.5)
Mean HbA1c — % (SD)	6.71 (1.36)	6.37 (1.15)	6.54 (1.27)
Type 2 diabetes mellitus — no. (%)	82 (57.2)	64 (44.4)	146 (50.5)
≥3 criteria of metabolic syndrome — no. (%)	104 (71.7)	104 (72.2)	208 (72.0)
Histological features			
NAFLD activity score			
Mean total (SD)	5.3 (1.1)	5.4 (1.0)	5.3 (1.0)
Mean steatosis (SD)	1.4 (0.6)	1.4 (0.5)	1.4 (0.6)
Mean lobular inflammation (SD)	2.4 (0.6)	2.4 (0.6)	2.4 (0.6)
Mean hepatocellular ballooning (SD)	1.5 (0.5)	1.5 (0.5)	1.5 (0.5)
NAS			
=4 — no. (%)	39 (26.9)	35 (24.3)	74 (25.6)
≥5 — no. (%)	106 (73.1)	108 (75.0)	214 (74.0)
Fibrosis stage (NASH CRN)			
1 — no. (%)	47 (32.4)	48 (33.3)	95 (32.9)
2 — no. (%)	42 (29.0)	40 (27.8)	82 (28.4)
3 — no. (%)	56 (38.6)	55 (38.2)	111 (38.4)

HEP-17-0693

Table 2. Change from Baseline to Year 1 in Biomarkers of Systemic Inflammation, Monocyte/Macrophage Activation, CCR2 and CCR5 Blockade and Hepatocellular Apoptosis (PP population)

	CVC 150 mg (N = 144)			Placebo (N = 143)		
	Baseline	Year 1	Change	Baseline	Year 1	Change
hs-CRP						
no.	110	110	110	110	110	110
Median (min, max), mg/L	2.35 (0.2, 24.0)	1.70 (0.2, 35.1)	–0.40 (–16.4, 29.1)	2.45 (0.2, 31.7)	2.55 (0.3, 34.8)	0.30 (–10.8, 28.2)
95% CI for difference in change from baseline (CVC 150 mg – placebo)			(–1.3, –0.4)			
Fibrinogen						
no.	94	94	94	102	102	102
Median (min, max), mg/dL	376.5 (145, 607)	355.5 (20, 536)	–36.5 (–439, 154)	382.5 (20, 724)	392.5 (235, 760)	7.0 (–272, 569)
95% CI for difference in change from baseline (CVC 150 mg – placebo)			(–58, –14)			

HEP-17-0693

IL-1β						
no.	95	95	95	102	102	102
Median (min, max), pg/mL	0.090 (0.00, 2.69)	0.050 (0.00, 0.92)	–0.020 (–2.65, 0.76)	0.030 (0.00, 0.83)	0.050 (0.00, 1.05)	0.005 (–0.81, 1.02)
95% CI for difference in change from baseline (CVC 150 mg – placebo)			(–0.06, 0)			
IL-6						
no.	95	95	95	102	102	102
Median (min, max), pg/mL	4.30 (1.4, 475.6)	2.60 (0.9, 521.6)	–1.50 (–13.1, 46.0)	4.50 (1.5, 22.7)	3.65 (1.0, 24.4)	–0.55 (–8.8, 12.0)
95% CI for difference in change from baseline (CVC 150 mg – placebo)			(–1.5, –0.2)			
sCD14						
no.	97	97	97	103	103	103
Median (min, max), µg/L	1731.0 (138, 3601)	1628.0 (768, 2635)	–115.0 (–1306, 1337)	1808.0 (1030, 3137)	1803.0 (927, 3562)	–45.0 (–1199, 1646)

HEP-17-0693

95% CI for difference in change from baseline (CVC 150 mg – placebo)			(–204, 19)			
sCD163						
no.	97	97	97	103	103	103
Median (min, max), µg/L	615.0 (263, 1486)	615.0 (189, 1410)	3.0 (–736, 532)	679.0 (278, 1738)	642.0 (237, 1927)	–41.0 (–527, 624)
95% CI for difference in change from baseline (CVC 150 mg – placebo)			(–18, 88)			
CCL2						
no.	95	95	95	102	102	102
Median (min, max), pg/mL	499.00 (166.1, 1497.4)	2115.20 (305.9, 6725.5)	1674.90 (–49.8, 6351.4)	464.50 (264.3, 763.6)	445.40 (240.3, 1023.4)	–6.20 (–320.7, 452.3)
95% CI for difference in change from baseline (CVC 150 mg – placebo)			(1454, 1878)			
CCL4						
no.	95	95	95	102	102	102

HEP-17-0693

Median (min, max), pg/mL	90.80 (2.6, 2432.9)	241.30 (2.5, 36238.8)	126.00 (–227.2, 36190.0)	92.85 (31.9, 881.0)	102.70 (5.4, 2746.4)	5.00 (–118.0, 2697.8)
95% CI for difference in change from baseline (CVC 150 mg – placebo)			(103.9, 140.9)			
CK-18 (caspase-cleaved [M30])						
no.	97	97	97	103	103	103
Median (min, max)	624.0 (125, 2353)	433.0 (107, 2562)	–77.0 (–1600, 1365)	704.0 (98, 3564)	472.0 (37, 2426)	–155.0 (–2240, 1368)
95% CI for difference in change from baseline (CVC 150 mg – placebo)			(–25, 228)			
CK-18 (total [M65])						
no.	97	97	97	103	103	103
Median (min, max)	421.0 (104, 3673)	438.0 (84, 7031)	1.0 (–1273, 6296)	448.0 (113, 2149)	415.0 (100, 6023)	–22.0 (–1156, 5119)
95% CI for difference in change from baseline (CVC 150 mg – placebo)			(–45, 151)			