Received: 12 April 2023 | Accepted: 28 September 2023

DOI: 10.1097/HC9.0000000000000335

ORIGINAL ARTICLE

OPEN

Phase 2, open-label, rollover study of cenicriviroc for liver fibrosis associated with metabolic dysfunction–associated steatohepatitis

Sven M. Francque[1,2] | **Alexander Hodge**[3] | **Jerome Boursier**[4,5] | **Ziad H. Younes**[6] | **Gerardo Rodriguez-Araujo**[7] | **Grace S. Park**[7] | **Naim Alkhouri**[8] | **Manal F. Abdelmalek**[9]

[1]Department of Gastroenterology and Hepatology, Antwerp University Hospital, Antwerp, Belgium

[2]InflaMed Centre of Excellence, Laboratory for Experimental Medicine and Paediatrics, Translational Sciences in Inflammation and Immunology, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

[3]Department of Gastroenterology Eastern Health, Monash University, Melbourne, Victoria, Australia

[4]HIFIH Laboratory UPRES EA3859, SFR ICAT 4208, Angers University, Angers, France

[5]Hepato-Gastroenterology and Oncology Department, Angers University Hospital, Angers, France

[6]Gastro One, Germantown, Tennessee, USA

[7]AbbVie Inc., North Chicago, Illinois, USA

[8]Arizona Liver Health, Chandler, Arizona, USA

[9]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA

Correspondence
Sven M. Francque, Department of Gastroenterology and Hepatology, Antwerp University Hospital, Drie Eikenstraat 655, Edegem B-2650, Belgium.
Email: sven.francque@uza.be

Abstract

Background: Cenicriviroc (CVC) is a novel, orally administered antagonist of chemokine receptor types 2/5 that has demonstrated antifibrotic activity in a phase 2b study of patients with NASH. This phase 2, open-label, rollover study investigated the long-term safety and tolerability of CVC in patients with NASH and stage 0–4 liver fibrosis.

Methods: Eligible patients who completed the phase 2 CENTAUR study or reached a predefined endpoint in the phase 3 AURORA study were rolled over and received open-label CVC 150 mg once daily. Safety assessments were conducted at the start of the study, and patients were seen in the clinic every 3 months until the study sponsor terminated CVC development. Safety endpoints included treatment-emergent adverse events (TEAEs), treatment-related TEAEs, adverse event severity, and clinical laboratory assessments.

Results: A total of 167 patients were enrolled, with a median treatment duration of 33.6 months. Before study termination, 36 patients (21.6%) prematurely discontinued the study. Treatment-related TEAEs were reported in 28 patients (16.8%). The most common treatment-related TEAEs were 4 cases of diarrhea (2.4%) and 2 cases each (1.2%) of abdominal pain, nausea, alanine aminotransferase increased, aspartate aminotransferase increased, hypertriglyceridemia, myalgia, pruritus, and rash. The majority of these treatment-related events were mild in intensity, and none were life-threatening. There were no clinically meaningful changes in hepatic function, chemistry, or liver parameters from baseline to the end of the study.

Abbreviations: CCL2/CCL3–5, C–C chemokine receptor ligands 2/3–5; CCR2/5, C–C chemokine receptors 2/5; CVC, cenicriviroc; TEAE, treatment-emergent adverse event.

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.hepcommjournal.com.

Conclusions: In this rollover study, CVC 150 mg once daily was well tolerated in patients with NASH and stage 0–4 liver fibrosis. No new safety signals were reported, and these data further support the safety and tolerability of CVC.

INTRODUCTION

NAFLD, now known as metabolic dysfunction–associated steatotic liver disease,[1] is a common liver disease associated with metabolic disorders including type 2 diabetes mellitus and metabolic syndrome.[2–5] NAFLD is characterized by lipid accumulation in the liver (steatosis) that is unrelated to the excessive consumption of alcohol.[3,6–8] In an estimated 10%–25% of cases, NAFLD progresses to NASH, now known as metabolic dysfunction–associated steatohepatitis[1]; however, in populations at risk (eg, patients with diabetes), this can increase to almost half of the cases.[9] NASH, which is characterized by steatosis, lobular inflammation, and hepatocellular ballooning,[10] has become more common as a result of the increasing prevalence of obesity-related disorders[11] and can lead to cirrhosis and HCC.[10] Treatment options are limited and focus on lifestyle modification through diet and exercise. At present, no approved disease-modifying therapeutics are available.[11–13]

The pathogenesis of liver inflammation and fibrosis involves the C–C chemokine receptors 2 (CCR2) and 5 (CCR5), as well as their ligands (CCL2 and CCL3–5, respectively), which contribute to the development of NAFLD and NASH.[14–17] CCR2/CCL2 and CCR5/CCL5 are involved in liver inflammation, fibrosis, and steatosis,[14,15] leading to promising therapeutic targets for the treatment of NASH.

Cenicriviroc (CVC) is a novel, orally administered, potent CCR2 and CCR5 receptor antagonist that has demonstrated antifibrotic effects in animal models.[18–22] CVC has also been shown to block CCR2 and CCR5 in phase 2 studies in patients with HIV.[23,24] In adults with NASH and stage F2 or F3 liver fibrosis in the phase 2b CENTAUR study,[25] CVC significantly improved fibrosis compared with placebo ($p < 0.05$), which is linked to improved clinical outcomes in NAFLD.[26–29] An improvement in liver fibrosis by ≥ 1 stage without worsening of NASH was achieved by 20% of CVC-treated patients versus 10% of placebo-treated patients at year 1 ($p = 0.02$),[29] and efficacy was maintained in most patients at year 2.[30]

The efficacy and safety of CVC were also assessed in a phase 3, multicenter, randomized, double-blind, placebo-controlled study (AURORA).[31] This study did not reach its primary efficacy endpoint of the superiority of CVC compared with placebo in the improvement of liver fibrosis by ≥ 1 stage and no worsening of steatohepatitis; thus, the further development of CVC was terminated by the study sponsor.

Herein, we report the long-term safety results of CVC from the rollover study.

METHODS

Study design

This was an open-label, multicenter study to provide continued access to CVC and to evaluate the long-term safety and efficacy of CVC in patients with liver fibrosis associated with NASH (NCT03059446). This rollover

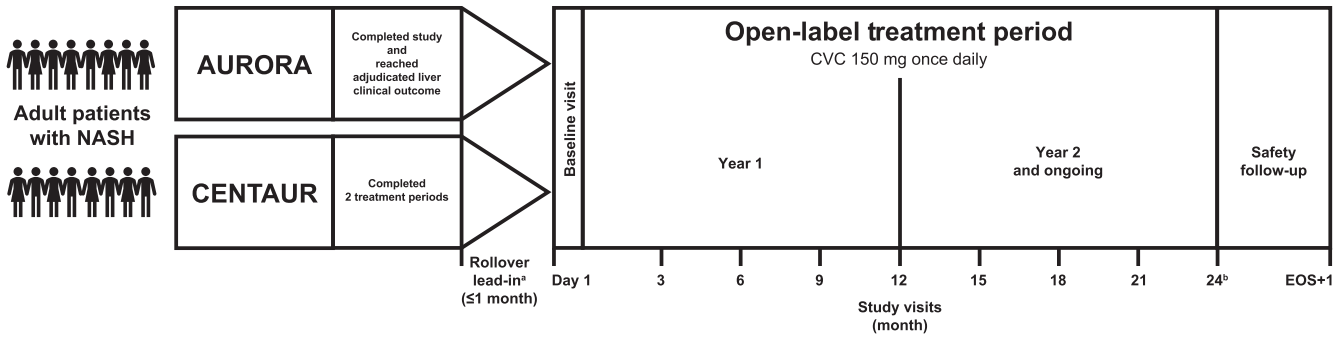

FIGURE 1 Study design. [a]Participants completing treatment periods 1 and 2 of the CENTAUR study or completing the AURORA study as a result of progression to cirrhosis or reaching an adjudicated liver-associated clinical outcome in either part 1 or part 2 of the study, regardless of their treatment assignment (CVC or placebo), provided informed consent to this rollover study (study 3152-201-002) before receiving open-label CVC. Participants were required to roll over within 1 month of completing their final visit assessments in either CENTAUR or AURORA. Participants who completed the CENTAUR or the AURORA study, before the initiation of this protocol at their study center, were allowed to participate in this rollover study. [b]Participants continued to be seen every 3 months until CVC became commercially available or if development was terminated, as applicable. Abbreviations: CVC, cenicriviroc; EOS, end of study.

study was initiated in February 2017 and was terminated early (based on the aforementioned decision of the sponsor to terminate further development of CVC in NASH) on February 7, 2021, with a database lock on April 21, 2021. All patients received oral CVC 150 mg, administered once daily with food. Adult patients with NASH who completed treatment periods 1 and 2 in the CENTAUR study,[29,30] or who completed or reached a predefined endpoint in the AURORA study (progression to cirrhosis or an adjudicated liver-associated clinical outcome) in either part 1 or part 2 of the study,[32] were eligible to roll over to this continued access study within 1 month of completing their final visit assessments in either the CENTAUR or AURORA study (Figure 1).

The study was conducted at up to 480 study centers and in accordance with the Declaration of Helsinki, International Conference on Harmonisation E6 Good Clinical Practice guidelines, and all local and national regulations, and was approved by the relevant institutional review board or independent ethics committee. Written, informed consent was obtained from all patients before study participation.

Patient population

Patients who successfully completed treatment periods 1 and 2 of the CENTAUR study, and patients who completed the AURORA study as a result of reaching an adjudicated liver-associated clinical outcome [histopathological progression to cirrhosis, model for end-stage liver disease score of ≥ 15, ascites requiring intervention, and hospitalization for ≥ 24 h for onset of variceal bleed, hepatic encephalopathy (defined by a West Haven Stage of ≥ 2), or spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis with positive ascitic fluid bacterial culture)] in part 1 or part 2 of the study, were eligible to participate in this rollover study regardless of their treatment assignment (CVC or placebo). A detailed list of the inclusion and exclusion criteria for the CENTAUR and AURORA studies has been described.[25,32] In brief, adult patients (aged ≥ 18 y) with histopathological evidence of NASH and the presence of fibrosis stage 1–3 (CENTAUR F1–3; AURORA F2–3), as defined by the NASH Clinical Research Network scoring system and determined by a central pathologist, were included. Patients with a history of presence of cirrhosis (fibrosis stage 4), prior or planned liver transplantation, other known causes of liver disease, or a known history of HCC were excluded from participating in the CENTAUR and AURORA studies.

Safety assessments

Baseline visit assessments of patients for this rollover study took place within 1 month of completing their final visit assessments in either the CENTAUR or AURORA study (except in the case of eligible patients who completed these studies before the initiation of this protocol at their study center, who were allowed to participate in this rollover study). Patients were seen in the clinic every 3 months for general safety assessments. Safety endpoints, which were analyzed by total treatment duration, included clinical laboratory assessments of interest, treatment-emergent adverse events (TEAEs) coded using the Medical Dictionary for Regulatory Activities version 23.1, treatment-relatedness of TEAEs as assessed by the investigator, and adverse event severity, graded as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening (grade 4), and death (grade 5). TEAEs were defined as events that worsened on or after the treatment start date and within 30 days of the treatment end date. Treatment-related TEAEs were defined as TEAEs that were found to be related to treatment per investigator assessment. Clinical laboratory assessments of interest were elevations in serum biochemistry parameters associated with suspected DILI, that is, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, or bilirubin.

Statistical analysis

The safety analysis was performed using the safety population, consisting of all patients who received ≥ 1 dose of CVC. No inferential statistical testing was conducted. Summaries of demographics, baseline characteristics, treatment exposure, and safety parameters are presented using descriptive statistics for continuous variables and frequency counts with incidence rates for dichotomous or categorical variables.

RESULTS

Patients and treatment

A total of 167 patients were enrolled and received ≥ 1 dose of CVC 150 mg once daily. The majority of patients were rolled over from the CENTAUR study [n = 141 (84.4%); 67 (40.1%) from the CVC group, 74 (44.3%) from the placebo group]. A total of 26 patients (15.6%) came from the AURORA study [17 (10.2%) from the CVC group, 9 (5.4%) from the placebo group]. The median treatment duration was 33.6 months (range, 1–47 mo), and the majority of patients (71.2%) received CVC for 24 to <48 months (Figure 2). The total cumulative CVC treatment given across 167 patients was 411.2 person-years. Before study termination by the sponsor, 36 patients (21.6%) prematurely discontinued the study: 16 (9.6%) due to withdrawal of consent, 11 (6.6%) due to adverse events, 3 (1.8%) were lost to follow-up, 1 (0.6%) due to

protocol violation, and 5 (3.0%) due to other reasons. The study sponsor terminated participation for the remaining 131 patients.

Baseline patient demographics and characteristics are shown in Table 1 and were similar between the CENTAUR and AURORA subgroups, except for the fibrosis stage. All patients who rolled over from the AURORA study exhibited cirrhosis (stage 4; n = 26, 100%), while patients who rolled over from the CENTAUR study had fibrosis stage 0–4; the majority had stage 1–3 (n = 123, 87.2%). The mean (SD) age of the combined total population was 56.8 (10.4) years, and more than half of the patients (52.7%) were female. The majority of patients were white (89.8%), and mean body mass index (SD) was 33.9 (6.8) kg/m^2.

Medical history was reported for 158 (94.6%) of 167 patients. The most frequently reported medical histories by preferred term occurring in ≥40 patients were hypertension (103 patients, 61.7%), type 2 diabetes mellitus (74 patients, 42.5%), and gastroesophageal reflux disease (48 patients, 28.7%).

Safety

TEAEs were reported in 140 of 167 patients (83.8%) (Table 2). The most common TEAEs reported in ≥10% of patients were arthralgia (13.2%), diarrhea (12.0%), and nasopharyngitis (10.2%). The majority of TEAEs were mild or moderate in intensity (56.9%). Grade 3 (severe) TEAEs were reported in 40 patients (24.0%). Life-threatening TEAEs were reported in 4 patients (2.4%) and included gastroenteritis, lipase increased, hypertriglyceridemia, and HCC, each in 1 patient (0.6%). No events were considered treatment-related by the sponsor.

Treatment-related TEAEs, as determined by the investigator, were reported in 28 patients (16.8%) (Table 2). The majority of these events were mild in intensity, and none were life-threatening. The most common treatment-related TEAEs by System Organ Class reported in ≥5 patients were gastrointestinal disorders in 9 patients (5.4%) and skin and subcutaneous tissue disorders in 8 patients (4.8%). The most common treatment-related TEAEs were diarrhea in 4 patients (2.4%) and abdominal pain, nausea, alanine aminotransferase increase, aspartate aminotransferase increase, hypertriglyceridemia, myalgia, pruritus, and rash in 2 patients each (1.2%).

Serious TEAEs were reported in 40 patients (24.0%) (Table 2). The most commonly reported serious TEAEs were angina pectoris, cellulitis, dehydration, and acute kidney injury, each occurring in 3 patients, and legionella pneumonia, acute cholecystitis, sepsis, basal cell carcinoma, and Bowen disease, each occurring in 2 patients. All other serious adverse events were reported in 1 patient. No serious TEAEs were assessed to be treatment-related by the study sponsor. There was 1 death during the study, as a result of a road traffic accident, unrelated to the study treatment. HCC and decompensation may take longer to develop than the duration of this study, so these data were not available to assess.

TEAEs led to permanent discontinuation of CVC in 11 patients (6.6%) (Table 3). Each TEAE occurred in 1 patient. No clinically meaningful mean changes in

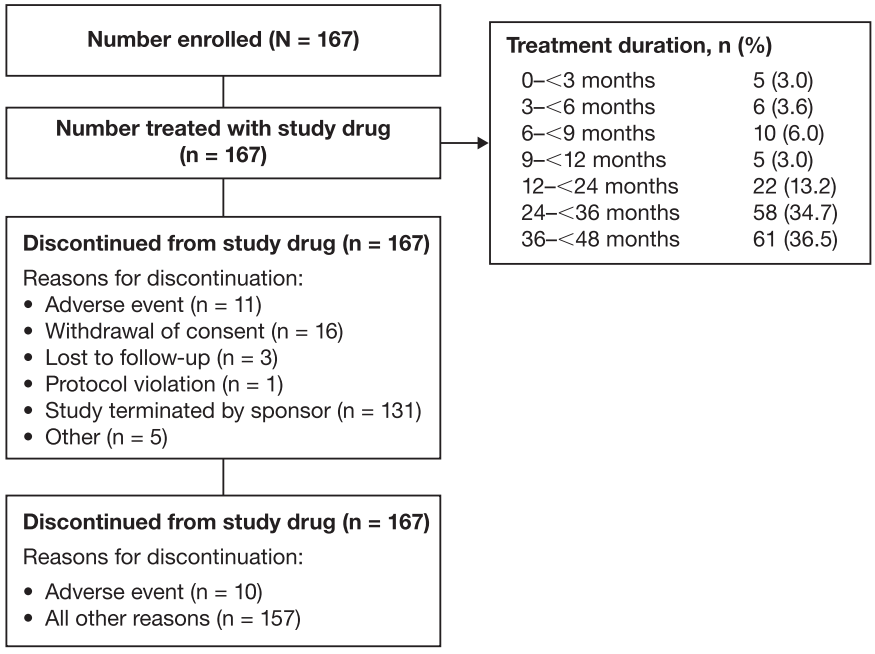

FIGURE 2 Study disposition: safety population. Safety population: patients who received ≥1 dose of the study drug. Patients who discontinued from the study were also discontinued from the study drug.

TABLE 1 Baseline patient demographics and characteristics

Parameter	Total population (N = 167)	CENTAUR subgroup (n = 141)	AURORA subgroup (n = 26)
Age, mean (SD), y	56.8 (10.4)	56.6 (10.4)	58.0 (10.3)
Female, n (%)	88 (52.7)	70 (49.7)	18 (69.2)
Race, n (%)			
White	150 (89.8)	124 (87.9)	26 (100)
Black or African American	4 (2.4)	4 (2.8)	0
Asian	9 (5.4)	9 (6.4)	0
American Indian or Alaska Native	1 (0.6)	1 (0.7)	0
Native Hawaiian or Other Pacific Islander	2 (1.2)	2 (1.4)	0
Other	1 (0.6)	1 (0.7)	0
Ethnicity, n (%)			
Hispanic or Latino	24 (14.4)	18 (12.8)	6 (23.1)
Not Hispanic or Latino	143 (85.6)	123 (87.2)	20 (76.9)
Body weight, mean (SD), kg	96.8 (22.4)	96.1 (22.8)	100.6 (19.7)
BMI, mean (SD), kg/m^2	33.9 (6.8)	33.8 (6.9)	34.9 (6.1)
Type 2 diabetes, n (%)[a]	87 (52.1)	74 (52.5)	13 (50.0)
Serum biochemistry			
Albumin, mean (SD), g/L	45.1 (3.0)	45.1 (2.8)	44.7 (3.8)
ALT, mean (SD), U/L	54.8 (35.3)	54.0 (35.2)	60.6 (35.9)
AST, mean (SD), U/L	44.4 (27.5)	42.5 (26.7)	55.2 (29.5)
ALP, mean (SD), U/L	81.9 (29.4)	78.8 (21.4)	99.9 (52.5)
Bilirubin, mean (SD), mg/dL	0.529 (0.3)	0.531 (0.326)	0.527 (0.331)
Platelet count, mean (SD), 10^9/L	230.8 (67.8)	233.4 (68.9)	217.2 (60.9)
Fibrosis stage, n (%)[a]			
0	6 (3.6)	6 (4.3)	0
1	39 (23.3)	39 (27.7)	0
2	47 (28.1)	47 (33.3)	0
3	37 (22.2)	37 (26.2)	0
4	34 (20.4)	8 (5.7)	26 (100)

[a]Data from 4 patients in the CENTAUR study were not captured.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index.

hepatic function (Supplemental Table S1, http://links.lww.com/HC9/A757), chemistry, or liver parameters were observed from baseline to the end of the study.

DISCUSSION

Overall, CVC 150 mg once daily was well tolerated and exhibited a favorable safety profile in patients in this phase 2, open-label, rollover study, with a median treatment duration of 33.6 months. There were no safety concerns before the early study termination by the sponsor. The majority of TEAEs were mild to moderate in severity, and the most commonly reported TEAEs were arthralgia, diarrhea, and nasopharyngitis. Similarly, the majority of treatment-related TEAEs were mild in severity, and none were life-threatening. The most common treatment-related TEAE was diarrhea. There were no clinically meaningful mean changes in hepatic function, chemistry, or liver parameters from baseline to the end of the study.

In a phase 3 trial of the farnesoid X receptor agonist obeticholic acid (25 mg) in patients with NASH, TEAEs led to treatment drug discontinuation in 83 patients [13% (n = 658)], whereas in this study, TEAEs led to treatment drug discontinuation in 10 patients (6.0%).[33] In another phase 3 trial of pioglitazone (30 mg) in patients with NASH, no cases of serious hepatotoxicity requiring permanent discontinuation of the study drug were reported.[34]

The results of this study are similar to the safety results observed in the previous phase 2 CENTAUR[29,30] and phase 3 AURORA[31] studies of CVC 150 mg once daily for the treatment of liver fibrosis associated with NASH, and confirm the favorable safety profile of CVC. In the primary 1-year analysis of the CENTAUR study, the safety and tolerability of CVC were comparable with those of placebo, with a similar

TABLE 2 Incidence of TEAEs

n (%)	Total population CVC 150 mg once daily (N = 167)
Any TEAE	140 (83.8)
Treatment-related TEAE	28 (16.8)
Serious TEAEs	40 (24.0)
Deaths	1 (0.6)
TEAEs by severity	
Mild (grade 1)	28 (16.8)
Moderate (grade 2)	67 (40.1)
Severe (grade 3)	40 (24.0)
Life-threatening (grade 4)	4 (2.4)
TEAEs reported in ≥5% of patients	
Arthralgia	22 (13.2)
Diarrhea	20 (12.0)
Nasopharyngitis	17 (10.2)
Influenza	14 (8.4)
Nausea	13 (7.8)
Rash	13 (7.8)
Abdominal pain	12 (7.2)
Abdominal pain upper	12 (7.2)
Constipation	12 (7.2)
Bronchitis	12 (7.2)
Diabetes mellitus	12 (7.2)
Fatigue	10 (6.0)
ALT increased	10 (6.0)
Sinusitis	9 (5.4)
Upper respiratory tract infection	9 (5.4)
Headache	9 (5.4)
Cough	9 (5.4)
Hypertension	9 (5.4)
Treatment-related TEAEs reported in ≥5% of patients	
Gastrointestinal disorders	9 (5.4)
Skin and subcutaneous tissue disorders	8 (4.8)

Abbreviations: ALT, alanine aminotransferase; CVC, cenicriviroc; TEAE, treatment-emergent adverse event.

TABLE 3 TEAEs leading to permanent discontinuation of CVC

n (%)	Total population CVC 150 mg once daily (N = 167)	Time from treatment day 1 to AE onset date (median months) (n = 13)
Any TEAE leading to permanent discontinuation	11 (6.6)	Median (25th, 75th percentile): 14.77 (5.39, 24.06)
ALT increase[a]	1 (0.6)	2.86
Arthralgia	1 (0.6)	0.20
AST increase[a]	1 (0.6)	2.86
Blood bilirubin increase[a]	1 (0.6)	2.86
COVID-19 pneumonia	1 (0.6)	18.45
Diabetes mellitus	1 (0.6)	27.40
Fatigue	1 (0.6)	5.39
HCC	1 (0.6)	35.00
Hypertriglyceridemia	1 (0.6)	14.77
Invasive lobular breast carcinoma	1 (0.6)	21.68
Ovarian cancer	1 (0.6)	12.40
Procedural pain[b]	1 (0.6)	24.04
Renal cancer	1 (0.6)	9.87

Patients are counted only once within each preferred term.
[a]The same patient had all 3 TEAEs.
[b]Led to the patient discontinuing the drug, not the study.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CVC, cenicriviroc; TEAE, treatment-emergent adverse event.

incidence of TEAEs, which were generally grade 1 or grade 2 in severity.[29] The most common treatment-related grade ≥2 TEAEs in the CVC group were fatigue, diarrhea, and headache.[29] Similar results were reported in the final 2-year analysis, with a comparable incidence of TEAEs in the CVC and placebo groups, the majority of which were grade 1 or grade 2 in severity.[30]

The AURORA study included 1185 patients treated with CVC and 593 patients treated with a placebo in the safety population of the full study cohort.[31] CVC 150 mg was generally well tolerated, with a similar profile to placebo except for a higher incidence of nausea, sinusitis, increased alanine aminotransferase, increased aspartate aminotransferase, and nephrolithiasis. There were no fatal or life-threatening TEAEs. TEAEs considered by the investigator to be treatment-related were numerically similar between CVC and the placebo group. CVC has also demonstrated a favorable safety and tolerability profile in more than 1200 patients, including those with HIV-1 and hepatic impairment.[35]

CONCLUSIONS

The safety results from this rollover study demonstrated that CVC 150 mg once daily is well tolerated in patients with stage 0–4 liver fibrosis associated with NASH and has a favorable safety profile, consistent with the previous phase 2 CENTAUR and phase 3 AURORA studies that assessed the safety and efficacy of CVC in adults with NASH and liver fibrosis. No new safety signals were reported.

DATA AVAILABILITY STATEMENT

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual-level and trial-level data (analysis data sets), as well as other information

(eg, protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

AUTHOR CONTRIBUTIONS

All authors had access to relevant data and participated in the drafting, review, and approval of this publication.

ACKNOWLEDGMENTS

No honoraria or payments were made for authorship. Medical writing and editorial support were provided by Karlien Kallmeyer, PhD, Anjeza Petersen, PhD, and Jade Moores, MSc, of Complete HealthVizion, IPG Health Medical Communications, and funded by AbbVie Inc.

FUNDING INFORMATION

This study was funded by Allergan plc, Dublin, Ireland (before acquisition by AbbVie Inc.). Allergan plc, Dublin, Ireland participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication.

CONFLICTS OF INTEREST

Financial arrangements of the authors with companies whose products may be related to the present report are listed below, as declared by the authors. Sven M. Francque holds a senior clinical investigator fellowship from the Research Foundation Flanders (FWO; 1802154N); his institution has received grants from Astellas, Falk Pharma, Genfit, Gilead Sciences, Glympse Bio, Janssen Pharmaceuticals, Inventiva, Merck Sharp & Dohme, Pfizer, and Roche; he has acted as a consultant for AbbVie, Actelion, Aelin Therapeutics, AgomAb, Aligos Therapeutics, Allergan, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CSL Behring, Coherus, Echosens, Eisai, Enyo, Galapagos, Galmed, Genentech, Genfit, Gilead Sciences, Intercept, Inventiva, Janssen Pharmaceuticals, Julius Clinical, Madrigal, MedImmune, Merck Sharp & Dohme, NGM Bio, Novartis, Novo Nordisk, Promethera, and Roche; and has acted as a lecturer for AbbVie, Allergan, Bayer, Eisai, Genfit, Gilead Sciences, Intercept, Inventiva, Janssen-Cilag, Merck Sharp & Dohme, Novo Nordisk, and Promethera. Alexander Hodge has acted as a consultant for Novotech and Medical Developments International. Jerome Boursier has acted as a consultant for Diafir, Echosens, Intercept, and Siemens; has attended speaker bureaus for Echosens, Gilead, Intercept, and Siemens; has served on advisory boards for Bristol Myers Squibb, Gilead, Intercept, MSD, Novo Nordisk, and Pfizer; and has received research support from Echosens, Intercept, Inventiva, and Siemens. Ziad H. Younes has received research support from AbbVie, Axcella, Bristol Myers Squibb, CymaBay, Galectin, Intercept, Inventiva, Madrigal, NGM, Novo Nordisk, NST, Poxel, and Sagimet; has acted as a speaker for AbbVie, Intercept, and Bristol Myers Squibb; and as a consultant for Intercept and Madrigal. Gerardo Rodriguez-Araujo and Grace S. Park are employees of AbbVie Inc. and may own company stock and/or stock options. Naim Alkhouri has received research funding from 89Bio, Akero, AbbVie/Allergan, Better Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Corcept, Galectin, Genentech, Genfit, Gilead, Healio, Hepagene, Intercept, Inventiva, Ionis, Madrigal, Merck, NGM, Noom, NorthSea, Novo Nordisk, Perspectum, Pfizer, Poxel, Viking, and Zydus; has attended speaker bureaus for AbbVie/Allergan, Alexion, Echosens, Eisai, Exelixis, Gilead, Intercept, Perspectum, Salix, and Theratechnologies; and has acted as a consultant for AbbVie/Allergan, Echosens, Gilead, Intercept, Madrigal, Novo Nordisk, Perspectum, Pfizer, and Zydus. Manal F. Abdelmalek has received a research grant from Allergan/Tobira for her institution.

ORCID

Sven M. Francque https://orcid.org/0000–0002–7527–4714
Alexander Hodge https://orcid.org/0000–0001–6680–2303
Jerome Boursier https://orcid.org/0000–0002–7282–1436
Ziad H. Younes https://orcid.org/0000–0001–7382–3698

REFERENCES

1. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. Hepatology. 2023;78:1966–86.
2. Abenavoli L, Milic N, Di Renzo L, Preveden T, Medić-Stojanoska M, De Lorenzo A. Metabolic aspects of adult patients with nonalcoholic fatty liver disease. World J Gastroenterol. 2016;22:7006–16.
3. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67:328–57.
4. Rhee EJ. Nonalcoholic fatty liver disease and diabetes: An epidemiological perspective. Endocrinol Metab (Seoul). 2019;34:226–33.

5. Gastaldelli A, Cusi K. From NASH to diabetes and from diabetes to NASH: Mechanisms and treatment options. JHEP Rep. 2019; 1:312–28.
6. McCullough AJ. The clinical features, diagnosis and natural history of nonalcoholic fatty liver disease. Clin Liver Dis. 2004;8: 521–33.
7. Nasr P, Ignatova S, Kechagias S, Ekstedt M. Natural history of nonalcoholic fatty liver disease: A prospective follow-up study with serial biopsies. Hepatol Commun. 2018;2:199–210.
8. Francque SM, Marchesini G, Kautz A, Walmsley M, Dorner R, Lazarus JV, et al. Non-alcoholic fatty liver disease: A patient guideline. JHEP Rep. 2021;3:100322.
9. McPherson S, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: Implications for prognosis and clinical management. J Hepatol. 2015;62:1148–55.
10. Rinella ME, Tacke F, Sanyal AJ, Anstee QM. participants of the AASLD/EASL Workshop. Report on the AASLD/EASL Joint Workshop on Clinical Trial Endpoints in NAFLD. Hepatology. 2019;70:1424–36.
11. Sarwar R, Pierce N, Koppe S. Obesity and nonalcoholic fatty liver disease: Current perspectives. Diabetes Metab Syndr Obes. 2018;11:533–42.
12. Rotman Y, Sanyal AJ. Current and upcoming pharmacotherapy for non-alcoholic fatty liver disease. Gut. 2017;66:180–90.
13. Ratziu V, Francque S, Sanyal A. Breakthroughs in therapies for NASH and remaining challenges. J Hepatol. 2022;76:1263–78.
14. Kim BM, Abdelfattah AM, Vasan R, Fuchs BC, Choi MY. Hepatic stellate cells secrete Ccl5 to induce hepatocyte steatosis. Sci Rep. 2018;8:7499.
15. Marra F, Tacke F. Roles for chemokines in liver disease. Gastroenterology. 2014;147:577–94.
16. Pan X, Chiwanda Kaminga A, Liu A, Wen SW, Chen J, Luo J. Chemokines in non-alcoholic fatty liver disease: A systematic review and network meta-analysis. Front Immunol. 2020;11:1802.
17. Roh YS, Seki E. Chemokines and chemokine receptors in the development of NAFLD. Adv Exp Med Biol. 2018;1061:45–53.
18. Guicciardi ME, Trussoni CE, Krishnan A, Bronk SF, Lorenzo Pisarello MJ, O'Hara SP, et al. Macrophages contribute to the pathogenesis of sclerosing cholangitis in mice. J Hepatol. 2018; 69:676–86.
19. Krenkel O, Puengel T, Govaere O, Abdallah AT, Mossanen JC, Kohlhepp M, et al. Therapeutic inhibition of inflammatory monocyte recruitment reduces steatohepatitis and liver fibrosis. Hepatology. 2018;67:1270–83.
20. Kruger AJ, Fuchs BC, Masia R, Holmes JA, Salloum S, Sojoodi M, et al. Prolonged cenicriviroc therapy reduces hepatic fibrosis despite steatohepatitis in a diet-induced mouse model of nonalcoholic steatohepatitis. Hepatol Commun. 2018;2:529–45.
21. 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:e0158156.
22. Yu D, Cai SY, Mennone A, Vig P, Boyer JL. Cenicriviroc, a cytokine receptor antagonist, potentiates all-trans retinoic acid in reducing liver injury in cholestatic rodents. Liver Int. 2018;38:1128–38.
23. Marier JF, Trinh M, Pheng LH, Palleja SM, Martin DE. Pharmacokinetics and pharmacodynamics of TBR-652, a novel CCR5 antagonist, in HIV-1-infected, antiretroviral treatment-experienced, CCR5 antagonist-naive patients. Antimicrob Agents Chemother. 2011;55:2768–74.
24. Thompson M, Saag M, DeJesus E, Gathe J, Lalezari J, Landay AL, et al. A 48-week randomized phase 2b study evaluating cenicriviroc versus efavirenz in treatment-naive HIV-infected adults with C-C chemokine receptor type 5-tropic virus. AIDS. 2016;30:869–78.
25. Friedman S, 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;47:356–65.
26. 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;149:389–97.
27. Dulai PS, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology. 2017;65:1557–65.
28. 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;61:1547–54.
29. Friedman SL, Ratziu V, Harrison SA, Abdelmalek MF, Aithal GP, Caballeria J, et al. A randomized, placebo-controlled trial of cenicriviroc for treatment of nonalcoholic steatohepatitis with fibrosis. Hepatology. 2018;67:1754–67.
30. Ratziu V, Sanyal A, Harrison SA, Wong VW, Francque S, Goodman Z, et al. Cenicriviroc treatment for adults with nonalcoholic steatohepatitis and fibrosis: Final analysis of the Phase 2b CENTAUR study. Hepatology. 2020;72:892–905.
31. Anstee QM, Neuschwander-Tetri BA, Wai-Sun Wong V, Abdelmalek MF, Rodriguez-Araujo G, Landgren H, et al. Cenicriviroc lacked efficacy to treat liver fibrosis in nonalcoholic steatohepatitis: AURORA phase III randomized study. Clin Gastroenterol Hepatol. 2024;22:124–134.e1.
32. Anstee QM, Neuschwander-Tetri BA, Wong VW, Abdelmalek MF, Younossi ZM, Yuan J, et al. Cenicriviroc for the treatment of liver fibrosis in adults with nonalcoholic steatohepatitis: AURORA phase 3 study design. Contemp Clin Trials. 2020;89:105922.
33. Younossi ZM, Ratziu V, Loomba R, Rinella M, Anstee QM, Goodman Z, et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: Interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. Lancet. 2019;394:2184–96.
34. 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;362:1675–85.
35. Abdelmalek MF, Charlton RW III, Martins EB, Tan B, Coviello AD, Alkhouri N. Cenicriviroc safety in over 1, 200 subjects [Abstract]. Diabetes. 2019;68(suppl 1):1148-P.

How to cite this article: Francque SM, Hodge A, Boursier J, Younes ZH, Rodriguez-Araujo G, Park GS, et al. Phase 2, open-label, rollover study of cenicriviroc for liver fibrosis associated with metabolic dysfunction–associated steatohepatitis. Hepatol Commun. 2024;8:e0335. https://doi.org/10.1097/HC9.0000000000000335