Cenicriviroc for the treatment of liver fibrosis in adults with nonalcoholic steatohepatitis: AURORA Phase 3 study design

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A B S T R A C T

Introduction: Nonalcoholic steatohepatitis (NASH) is a sub-classification of nonalcoholic fatty liver disease (NAFLD) characterized by increased risk of progressive liver fibrosis. Cenicriviroc (CVC) is a novel, orally administered, potent chemokine 2 and 5 receptor antagonist currently in development for the treatment of liver fibrosis in adults with NASH.

Methods and analysis: Efficacy and safety of CVC will be comprehensively evaluated in a global, Phase 3, multicenter, randomized, double-blind, placebo-controlled study (AURORA, NCT03028740) of subjects with NASH and Stage F2 or F3 fibrosis. Approximately 2000 adults (Part 1, 1200 subjects; Part 2, 800 additional subjects) aged 18–75 years with histological evidence of NASH with Stage F2 or F3 fibrosis (NASH Clinical Research Network classification system) will be randomized 2:1 to CVC 150 mg or placebo orally once daily. Primary efficacy endpoints will include the proportion of subjects with ≥1-stage improvement in liver fibrosis and no worsening of steatohepatitis at Month 12 relative to screening (Part 1), and time to first occurrence of any adjudicated event: death; histopathologic progression to cirrhosis; liver transplant; Model of End-Stage Liver Disease score ≥15; ascites; hospitalization due to liver decompensation (Part 2). Patient-reported outcomes will assess changes in health outcomes from baseline (Chronic Liver Disease Questionnaire - NAFLD; Work Productivity and Activity Impairment in NASH; 36-Item Short Form Health Survey version 2). Adverse events will be assessed throughout the study. As there are currently no approved treatments indicated for NASH, the AURORA CVC Phase 3 study addresses an unmet medical need.

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ABSTRACT

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Abbreviations: AE, adverse event; ALT, alanine aminotransferase; APRI, AST to platelets ratio index; AST, aspartate aminotransferase; CCR, C-C chemokine receptor; CI, confidence interval; CLDQ-NAFLD-NASH, Chronic Liver Disease Questionnaire – Nonalcoholic Fatty Liver Disease; CVC, cenicriviroc; FIB-4, fibrosis-4 index; HIV, human immunodeficiency virus; ITT, intent-to-treat; MELD, Model of End-Stage Liver Disease; mITT, modified intent-to-treat; NASH CRN, Nonalcoholic steatohepatitis Clinical Research Network; NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NCI, National Cancer Institute; SF-36, 36-Item Short Form Health Survey; T2DM, type 2 diabetes mellitus; ULN, upper limit of normal; WPAI-NASH, Work Productivity and Activity Impairment in NASH

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1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a common, often “silent” liver disease associated with metabolic disorders [1]. It is characterized by accumulation of fat in the liver (steatosis), unrelated to excessive alcohol consumption [2–5]. Up to 44% of individuals with NAFLD will progress to nonalcoholic steatohepatitis (NASH) [6–8], which is characterized by steatosis, hepatocellular ballooning, and lobular inflammation, and can progress to cirrhosis and hepatocellular carcinoma [9–11]. The increasing prevalence of obesity-related disorders has contributed to a rapid increase in the prevalence of NASH (3–5% in the US) [12], now the most common indication for liver transplantation in women in the US and second most common in men [13]. The increasing burden of NASH on patients and healthcare providers [14], combined with an absence of approved therapies, represents an unmet medical need.

Liver inflammation is regulated by chemokines that control the activities and migration of various hepatic and immune cells [15]. The C–C chemokine receptor types 2 (CCR2) and 5 (CCR5) and their respective ligands (CCL2 and CCL3-5) are involved in the pathogenesis of liver inflammation and fibrosis, contributing to the development of NAFLD and NASH [15–17]. CCL2 and its receptor CCR2 become up-regulated in the liver, promoting macrophage accumulation, inflammation, fibrosis, and steatosis [15], while CCL5 exhibits profibrotic activity and also induces steatosis and pro-inflammatory factors in hepatocytes via the CCR5 receptor [16]. In mouse models, CCR2 [18,19] or CCR5 [20,21] inhibition resulted in a reduction in liver fibrosis and de-activation of immune cells. Therefore, CCR2 and CCR5 have been established as promising therapeutic targets for NASH.

Cenicriviroc (CVC) is a novel, orally administered, and potent CCR2 and CCR5 receptor antagonist which is currently in clinical development for the treatment of liver fibrosis in adults with NASH, having received Fast Track designation by the US Food and Drug Administration. CVC demonstrated antifibrotic effects in animal models [22–26], and also blocked CCR2 and CCR5 in Phase 2 studies in subjects with human immunodeficiency virus (HIV) [27,28]. In the Phase 2b CENTAUR study in adults with NASH and liver fibrosis [29], CVC treatment improved fibrosis, the histological feature consistently linked with clinical outcomes in NAFLD [30–32], and was twice as likely to provide an antifibrotic benefit compared with placebo [33]. Among the Phase 3 target population in the Phase 2b study, subjects with NAS and Stage F2 or F3 liver fibrosis, 28% of CVC-treated subjects achieved ≥1 stage improvement in liver fibrosis without worsening of NASH compared to 16% on placebo (odds ratio 2.2; 95% confidence interval [CI] 1.00–4.69; p = .049) [33]; most maintained efficacy at Year 2, with a greater effect observed in those with more advanced fibrosis [33]. Overall, CVC has shown a favorable safety and tolerability profile in > 1200 subjects [34], including those with cirrhosis and hepatic impairment [33,35].

Following these promising Phase 2 results, the AURORA Phase 3 study aims to evaluate and confirm the efficacy and safety of CVC for the treatment of liver fibrosis in adults with NASH.

2. Study design

2.1. Structure

AURORA (NCT03028740) is a global, Phase 3, multicenter, randomized, double-blind, placebo-controlled study, which will be conducted in two parts (Fig. 1). In Part 1, approximately 1200 subjects with histological evidence of NASH and Stage F2 or F3 fibrosis will be randomized 2:1 to CVC 150 mg orally or placebo once daily to evaluate a surrogate histology endpoint at Year 1. There will be approximately 2000 subjects in Part 2, including approximately 1200 subjects from Part 1 and 800 newly randomized subjects, also with histological evidence of NASH and Stage F3 fibrosis. A target of at least 60% of subjects with Stage F3 fibrosis will be enrolled in the study overall. Part 2 will assess clinical outcomes and will end when adjudicated events have been accrued in approximately 367 individual subjects across both parts of the study. The treatment duration is estimated to be 60 months for subjects participating in the study and will vary depending on the time taken to accrue the necessary number of adjudicated events.

2.2. Study endpoints

The objective of Part 1 is to demonstrate the superiority of CVC compared to placebo on liver histology at Month 12 relative to screening. The primary endpoint is the proportion of subjects with improvement in liver fibrosis by ≥1 stage AND no worsening of steatohepatitis, defined as no worsening of lobular inflammation or hepatocellular ballooning grade. The key and other secondary endpoints are shown in Table 1, with exploratory objectives including the proportion of subjects with resolution of steatohepatitis AND no worsening of fibrosis, the proportion of subjects with improvement in fibrosis by ≥1 stage (using a modified Ishak system), the proportion of subjects with histopathologic progression to cirrhosis, the proportion of subjects with hepatic decompensation, and the change from baseline in non-invasive assessments of liver fibrosis.

The objective of Part 2 is to demonstrate the superiority of CVC compared to placebo on the composite endpoint of histopathologic progression to cirrhosis (NASH Clinical Research Network [CRN] classification system, Stage F4), liver-related clinical outcomes, and all-cause mortality. The primary and secondary endpoints are shown in Table 1, with exploratory objectives including: the time to first occurrence of ascites (requiring intervention) or hospitalization for onset of variceal bleeding, hepatic encephalopathy (West Haven Stage ≥2), or spontaneous bacterial peritonitis; the proportion of subjects with histopathologic progression to cirrhosis (NASH CRN Stage F4); and the effect of CVC compared to placebo on liver histology.

2.3. Sample size

The planned sample size for Part 1 (800 subjects in the CVC arm and 400 in the placebo arm) is based on the primary binary endpoint at Month 12, and is expected to provide 84% power to demonstrate strong evidence with a single study (two-sided significance level of 0.0012), assuming a 15% response rate for the placebo arm and a 25% response rate for CVC (based on the effect observed in the Phase 2b CENTAUR study results).

The sample size for the Part 2 primary endpoint analysis is based on an estimated event-free survival rate of 80% for the placebo group (based on observed cumulative survival free of transplants in patients with NASH and any stage of fibrosis, and taking into account that subjects enrolled in AURORA will have Stages F2 or F3 fibrosis), and a hazard ratio of 0.62 by the end of the study, corresponding to a median event-free survival time of approximately 15 years for placebo and 25 years for CVC [30]. A total of 2000 subjects enrolled for an overall study duration of 8 years, with dropout rate estimated at 20%, is expected to lead to approximately 367 events. This calculation gives 85% power to demonstrate strong evidence of superiority of CVC over placebo (two-sided 0.00125 significance level), and 99% power to test the superiority of CVC over placebo (two-sided 0.05 significance level). East* 6.4 software (Cytel, Cambridge, MA, USA) was used for the calculation.

3. Study procedures

3.1. Recruitment and screening processes

Centers in North, Central, and South America, Europe, and Asia Pacific will participate in the AURORA study. The study will be conducted in accordance with the Declaration of Helsinki, International
3. Eligibility

Key inclusion criteria are: adults aged 18–75 years with histopathological evidence of NASH based on central reading of biopsy slides, with Stages F2 or F3 liver fibrosis for subjects in Part 1 (defined using NASH CRN system) and Stage F3 liver fibrosis for subjects newly enrolled in Part 2 (NASH CRN), at screening or based on historical evidence (if the following conditions are met: historical biopsy obtained no > 6 months prior to the first day of screening; hepatic tissue available for central histological evaluation; no new pharmacological intervention for NASH made during the period between the biopsy and screening; and subjects have been metabolically stable since the biopsy); females of child-bearing potential and males must use at least two approved methods of contraception throughout the study and for 30 days after stopping the study drug; females who are postmenopausal must have documentation of cessation of menses for ≥12 months without an alternative medical cause.

Key exclusion criteria include: a history or presence of cirrhosis (NASH CRN Stage F4) and/or hepatic decompensation including ascites, hepatic encephalopathy, or variceal bleeding; other known causes of chronic liver disease; prior or planned liver transplantation; HIV-1 or HIV-2 infection; inability to undergo a liver biopsy; hepatitis B surface antigen-positive; alcohol consumption > 21 units/week for males or 14 units/week for females (one unit of alcohol is defined in this study as a half pint of beer [285 mL; 9.64 oz], one glass of wine [125 mL; 4.23 oz], or one glass of spirits [25 mL; 0.85 oz]); > 5 × upper limit of normal (ULN) aspartate aminotransferase (AST) [ULN range: 31–43 U/L] or alanine aminotransferase (ALT) [ULN range: 32–43 U/L] and glycated hemoglobin > 9% (> 75 mmol/mol) at screening; total bilirubin > 1.3 mg/dL (> 22.2 μmol/L); international normalized ratio > 1.3; and Model for End-Stage Liver Disease (MELD) score > 12.

Concomitant medications will be allowed unless they are investigational or if they are CYP3A4 substrates with a narrow therapeutic index, or strong inducers or inhibitors of CYP3A4 or CYP2C8. The use of pioglitazone or vitamin E (> 400 IU/day) will be disallowed based on the potential for confounding effect on the study efficacy endpoints [36].

3.3. AURORA Toolbox

A major challenge encountered in previous clinical trials, including CENTAUR, was the high screening failure rate observed in NASH patients. This may be up to 80% of screened cases, the majority of which fail due to insufficiently meeting the required histological criteria for study entry. To mitigate this, a non-invasive testing strategy was
developed using a number of readily available and cost-effective screening tools.

As a result, the AURORA Toolbox, a novel online portal, will be made available to investigators as a non-mandatory pre-screening tool. The Toolbox aids assessment of subjects for clinically significant NAFLD based on clinical characteristics, non-invasive serum fibrosis measures (fibrosis-4 index [FIB-4]; NAFLD fibrosis score; AST to platelets ratio index [APRI]) and other laboratory values, as well as liver stiffness measure and controlled attenuation parameter via transient elastography (FibroScan®, Echosens, Paris, France). The Toolbox will leverage the high negative predictive value of these non-invasive tests to assess individual risk of fibrotic NASH [37–39]. For each test, the Toolbox classifies risk as low, intermediate, or high. These outputs help inform pre-screening at sites, indicating patients at a low probability of passing the histological threshold for trial inclusion, and therefore helping investigators select appropriate patients and minimize the number of “low inclusion probability” patients undergoing liver biopsies during screening.

3.4. Randomization

Randomization will be performed centrally using an interactive response system. In Part 1, at baseline (Day 1), eligible subjects will be assigned to treatment arms (2:1 CVC or placebo) using permuted block randomization stratified by NASH CRN fibrosis stage (F2 or F3) and the presence or absence of documented T2DM (“yes” or “no”). Additional subjects in Part 2 will be randomized at Part 2 baseline (Day 1) using the same method, and stratified only based on presence or absence of documented T2DM.

3.5. Study drug administration

Subjects will take one 150 mg tablet of study drug (double-blinded CVC or placebo) daily with food. Subjects, investigators, and all site personnel will be blinded to CVC and placebo individual treatment assignment until Part 2 is complete and the database has been locked. Blinding will be accomplished by the sponsor providing the study drug, and packaging for active and placebo products will be identical apart from a unique bottle identification number on the label. Data will be unblinded at the end of Part 1 to allow for data analysis, although individual subject treatment assignments will not be provided to sites or subjects until the analysis of Part 2 is completed. Emergency unblinding may take place where immediate knowledge of the treatment received (CVC versus placebo) is necessary for the management of the subject and may be requested via the interactive response system.

4. Study assessments

4.1. Efficacy assessments

Liver biopsies will be performed at screening, and at Months 12 and 60, to evaluate the histological features of NASH, including fibrosis stage (using both NASH CRN and modified Ishak systems). The liver biopsy for each subject will be evaluated by an independent central pathologist that is blinded to treatment arm designation and without regard to history assessments performed at any previous timepoints; if possible, the same pathologist will evaluate all biopsies from an individual subject.

The NASH CRN uses a defined and validated semiquantitative scoring system [40], the NAFLD activity score (NAS), which is used to assess overall histological change based on an unweighted sum of grades of steatosis (0–3), lobular inflammation (0–3), and hepatocellular ballooning (0–2). Histopathological diagnosis of NASH requires the presence of steatosis, lobular inflammation, and ballooning in a characteristic pattern, and will be determined by the central pathologist. The NASH CRN fibrosis staging system will be used to score fibrosis stage as follows: none (Stage F0); perisinusoidal or periportal (Stage F1); mild, zone 3, perisinusoidal (Stage F1a); moderate, zone 3, perisinusoidal (Stage F1b); portal/periportal only (Stage F1c); perisinusoidal and portal/periportal (Stage F2); bridging fibrosis (Stage F3); and cirrhosis (Stage F4) [40].

As the original Ishak staging system was designed for chronic viral hepatitis [41], a modified Ishak system will be used to classify NASH fibrosis stage, as it provides additional granularity at higher fibrosis stages. Stages F0–F2 will use the same histologic definitions as the NASH CRN system (without further classification of Stage F1 into F1a, F1b, or F1c), and Stages F3–F6 will be defined as follows: occasional bridging fibrosis (< 50% linkage of portal and/or central zones) [Stage F3]; marked bridging fibrosis (> 50% linkage of portal and/or central zones but not yet cirrhosis) [Stage F4]; early or incomplete cirrhosis (Stage F5); and established or advanced cirrhosis (Stage F6) [42].

4.2. Patient-reported outcomes

Three patient-reported outcomes measures will assess change in health outcomes from baseline: the Chronic Liver Disease Questionnaire – Nonalcoholic Fatty Liver Disease (CLDQ-NAFLD-NASH) [43], Work Productivity and Activity Impairment in NASH (WPAI-NASH) [44], and 36-Item Short Form Health Survey (SF-36) version 2 (health-related quality of life index) [45,46]. Data will be collected at baseline, Months 6 and 12 for Part 1; at baseline and Month 12 for newly randomized subjects in Part 2; and annually thereafter for all study subjects.

4.3. Safety assessments

Adverse events (AEs) will be assessed at each study visit and classified as shown in Table 2. AEs of special interest include elevations in biochemistry associated with liver injury. Various laboratory tests will be performed periodically throughout the study, and confirmation of compliance with eligibility criteria regarding concomitant medications and alcohol consumption will be obtained at each study visit. Population pharmacokinetics of CVC will also be assessed: pre-dose and 1 h post-dosing plasma samples will be collected at Months 3 and 12 of Part 1; at Month 6, plasma samples will be collected pre-dose and 2–6 h post-dosing.

An independent data and safety monitoring board will review the safety data from the study. An independent adjudication committee will review all events which may potentially contribute to the Part 2 primary endpoint; only events confirmed by the adjudication committee will be included in this analysis.

4.4. Study discontinuation

The study drug will be discontinued in the following instances: suspected drug-induced liver injury (criteria based on ALT and AST elevations); unacceptable toxicity; acute viral hepatitis (hepatitis A, B, C, D, or E); autoimmune or alcoholic hepatitis, hypoxic/ischemic hepapthopathy, or biliary tract disease during the study; hepatocellular carcinoma; liver transplant; pregnancy; a subject requests to discontinue participation; liver transplant; pregnancy; a subject requests to discontinue treatment for any reason; and discontinuation of the study at the request of the sponsor, a regulatory agency, institutional review board, independent ethics committee, or data and safety monitoring board.

The drug will be permanently discontinued if a confirmed Grade 4 (life-threatening) laboratory abnormality or clinical event is considered related to study drug, or if AST or ALT elevations meet the following criteria upon repeat testing within 48–72 h: > 3 × ULN and > 5 × baseline measure, if baseline value < 2 × ULN; > 3 × baseline measure, if baseline value ≥ ULN < 5; or > 2 × baseline measure, if baseline value ≥ 5 × ULN (ULN range: 31–37 U/L for AST; 32–43 U/L for ALT). Dosing should be interrupted if a confirmed Grade 3 laboratory abnormality or clinical event is considered related to study...
drug. For laboratory abnormalities or clinical events considered unrelated to study drug, the drug may be continued at the discretion of the investigator, with appropriate follow up and management. For subjects who discontinue study participation, every effort will be made to ensure that they return for early discontinuation procedures within 48 h. These subjects will also be required to return to the clinic 30 days after the last dose of study drug for a follow-up visit. If feasible, within 48 h. These subjects will also be required to return to the clinic for early discontinuation procedures with the investigator, with appropriate follow up and management. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions of the drug. If the dose is reduced or drug withdrawn, the AE abates or resolves, and reappears upon rechallenge.

### 4.5. Statistical analyses

For Part 1, two-sided 95% CI for the proportion who meet the primary efficacy endpoint will be calculated using Wilson's method for CI. The key secondary endpoint will be tested only when the primary endpoint result is significant (Table 1). The surrogate endpoint will be tested at 0.0012 (two-sided) level to manifest strong evidence from a single confirmatory study, and 0.048 (two-sided) level for study success. Cochran–Mantel–Haenszel tests will be used, stratified by fibrosis stage (F2 or F3) and presence or absence of T2DM at baseline, to compare the rates in the two randomized treatment arms. The primary efficacy endpoint will be evaluated in the modified intent-to-treat (mITT) population (all subjects in the intent-to-treat [ITT] analysis set who received at least one dose of the study drug), and sensitivity analyses will be performed using the ITT and per-protocol populations. Exploratory efficacy endpoints will be summarized by randomized treatment group using descriptive statistics (mITT analysis set).

#### 4.6. Missing data

For the Part 1 primary efficacy analysis, any available liver biopsy obtained after receipt of at least 6 months of assigned study drug but before 15 months of follow up may be used for the Month 12 biopsy. For subjects with multiple liver biopsies, the evaluable biopsy closest to the Month 12 visit will be used. Subjects without an evaluable biopsy at both screening and Month 12 will be included as non-responders. Sensitivity analyses will account for both “missing at random” and “missing not at random” scenarios.

For the Part 2 primary efficacy analysis, any available liver biopsy after baseline may be used. If a subject has any biopsy that meets the primary endpoint definition (determined by the adjudication committee), this will be included as an event. Subjects without evaluable biopsies at screening and post baseline will be included as non-events, unless they meet criteria for a primary endpoint component unrelated to the biopsy. A sensitivity analysis assuming data are “missing not at random” will be reported [47].

### 5. Discussion

As there are currently no approved treatments specifically for NASH, the AURORA CVC Phase 3 study is an important clinical trial in this disease area. The AURORA population consists of subjects shown to be more likely to benefit from treatment – those with Stage F2 or F3 fibrosis – following results from the Phase 2b CENTAUR study which demonstrated significant improvements in fibrosis in this group after 1 year of treatment [29].

This design has a number of advantages. The primary endpoint (the proportion of subjects with improvement in fibrosis by ≥ 1 stage [NASH CRN system] and no worsening of steatohepatitis) is measurable, sensitive to change and the effects of treatment, and is consistently quantifiable [48,49]. Although there are currently no validated surrogate endpoints for NASH, published evidence already supports the assertion that fibrosis stage is an independent predictor of mortality [32,50]; in this context, it is plausible that any sustained improvement in fibrosis observed in this trial has important implications regarding improved hard outcomes such as liver-related mortality. The histological surrogate endpoints used in this trial may therefore predict clinical benefit in preventing cirrhosis and death.
Use of histological methods to assess clinical benefit also serves as a limitation of the design, as liver biopsies are invasive, can be painful, are associated with risk of complications and may be subject to sampling error [48,51]. However, liver biopsy is currently the only reliable and generally accepted method for assessing the severity of NASH [52]. With this in mind, non-invasive markers may prove useful for supporting evidence of efficacy [48,49], which is reflected in the choice of secondary endpoints [53]. They may also be useful in optimizing subject selection, as per the AURORA Toolbox, which provides a novel and innovative method for classifying subjects’ prior risk for clinically significant fibrotic NASH, aiding pre-screening efforts by investigators and potentially reducing the need for screening biopsies.

While there are currently no approved treatments for NASH, obeticholic acid, resmetirom, and elafibranor are also undergoing clinical investigations in Phase 3 trials in the setting of non-cirrhotic NASH, with similar development timelines (NCT02548351 [REGENERATE]; NCT03900429 [MAESTRO-NASH]; NCT02704403 [RESOLVE-FT], respectively). However, to date, comprehensive study designs have only been published for REGENERATE [54].

In conclusion, the AURORA Phase 3 study has been carefully designed based on the clinically meaningful results of the well-powered Phase 2b CENTAUR study to ensure a comprehensive assessment of the efficacy and safety of CVC treatment compared to placebo in adult subjects with NASH and Stage F2 or F3 liver fibrosis. This assessment is consistent with the recently recommended baseline assessments of patients in NASH trials for harmonizing clinical trial data across trials [3].

Disclosures


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