Cenicriviroc for the treatment of non-alcoholic steatohepatitis and liver fibrosis

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Cenicriviroc for the treatment of non-alcoholic steatohepatitis and liver fibrosis

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Running title: Cenicriviroc for NASH and liver fibrosis

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Abstract

Introduction: Nonalcoholic fatty liver disease (NAFLD) has an increasing prevalence worldwide. At present, no specific pharmacotherapy is approved for NAFLD. Simple steatosis and nonalcoholic steatohepatitis (NASH) can progress to liver fibrosis that is associated with mortality in NAFLD. The recruitment of inflammatory monocytes and macrophages via chemokine receptor CCR2 as well as of lymphocytes and hepatic stellate cells via CCR5 promote the progression of NASH to fibrosis.

Areas covered: I summarize preclinical and clinical data on the efficacy and safety of the dual CCR2/CCR5 inhibitor cenicriviroc (CVC, also TBR-652 or TAK-652) for the treatment of NASH and fibrosis. In animal models of liver diseases, CVC potently inhibits macrophage accumulation in the liver and ameliorates fibrosis. In a phase 2b clinical trial (CENTAUR) on 289 patients with NASH and fibrosis, CVC consistently demonstrated liver fibrosis improvement after 1 year of therapy and had an excellent safety profile, leading to the implementation of a phase 3 trial (AURORA).

Expert opinion: Preclinical and clinical data support the development of CVC as a safe and potent antifibrotic agent. However, open questions around CVC are the durability of antifibrotic responses, divergent effects on NASH versus fibrosis, potential long-term concerns and the expected path to approval.
1. Introduction

Nonalcoholic fatty liver disease (NAFLD) has become the most prevalent liver disease in Western countries, affecting between 20-30% of the adult population. Due to demographic changes (i.e. an ageing population) and the dramatic increase of associated conditions like obesity, metabolic syndrome and type 2 diabetes, the prevalence of NAFLD is expected to increase even further within the next decade [1]. At present, no specific pharmacotherapy is approved for the treatment of NAFLD [2]. Some experts have suggested to consider PPAR-γ agonists, such as pioglitazone, or statins in NAFLD patients with high cardiovascular risk, until specific pharmacological interventions become available [3, 4, 5]. However, the scientific evidence for beneficial effects of any drugs in NAFLD is currently considered low, supporting the pressing need of larger clinical trials, especially on novel innovative drug candidates [6, 7].

Among the large group of individuals affected by NAFLD, about 10% suffer from the progressive inflammatory form, termed nonalcoholic steatohepatitis (NASH), which are at the highest risk to progress to the life-threatening complications liver cirrhosis and hepatocellular carcinoma (HCC) [8]. However, it has become evident that low-grade inflammatory processes are also present in “simple steatosis” and that both simple steatosis and NASH can progress, though at a variable pace [9, 10]. On a histological level, the presence and stage of liver fibrosis, i.e. scarring of the liver tissue as a response to chronic injury and inflammation, is the strongest and most reliable predictor of liver-related but also overall morbidity and mortality [11]. Due to the immense clinical and economic burden of the disease, current efforts to develop new pharmacotherapies focus on these high-risk groups of NAFLD patients that show NASH and either fibrosis or cirrhosis [8].

The better understanding of the pathogenesis of NAFLD and NASH resulted in a variety of novel interventional approaches that are currently being evaluated in clinical trials. Many of these approaches target hepatic fat accumulation, alteration of metabolic pathways or resultant hepatocyte cell death, including farnesoid X receptor (FXR) agonists (obeticholic acid or non-steroidal FXR agonists), peroxisome proliferator-activator receptor agonists (e.g., elafibranor, lanifibranor, saroglitazar), acetyl-CoA carboxylase inhibitors (e.g., GS-0976), caspase inhibitors (e.g., emricasan) and fibroblast growth factor (FGF)-21 or FGF-19 analogues [12]. Cenicriviroc (CVC) differs conceptually from these compounds, as it targets “downstream” pathogenic events at the interface between inflammation and fibrosis, giving rise to the expectation that a key step from translating hepatocyte stress and injury into devastating tissue scarring can be pharmacologically attenuated.
2. Pharmaceutical properties of cenicriviroc

Cenicriviroc mesylate (CVC, also referred to as TBR-652 and formerly known as TAK-652) is an orally active, potent inhibitor of ligand binding to C-C chemokine receptor type 2 (CCR2) and C-C chemokine receptor type 5 (CCR5). In vitro, CVC reaches a >95% receptor occupation for CCR2 on human monocytes at 6 nM and >90% of CCR5 on human CD4+ T-cells at 3.1 nM. CVC does not inhibit ligand binding to CCR1 (an alternative target of CCR5 ligands). The mean half-life in healthy volunteers is 35 to 40 hours, which allows daily dosing of the drug [13]. Due to its CCR5 blocking activity, CVC has initially been tested as a drug against CCR5-tropic HIV infection. In a double-blind placebo controlled trial involving 54 HIV-infected participants, CVC monotherapy at different doses (25, 50, 75, 100, or 150 mg) led to a dose-dependent reduction in HIV-1 RNA levels and concomitant increases in circulating levels of the CCR2 ligand monocyte chemoattractant protein 1 (MCP-1, or CCL2), suggesting potent CCR2 and CCR5 inhibition in vivo [14]. Already in these early clinical trials, CVC was found to be a very safe drug with a wide therapeutic range and fairly low pharmacokinetic variability [14]. CVC is a substrate of CYP3A4, CYP2C8, and P-glycoprotein, and also a weak inhibitor of CYP3A4. It is bound to plasma proteins at >98%, metabolized in the liver and is excreted via the bile and feces [15].

3. Chemokines and immune cells in NASH and fibrosis

The concept of evaluating CCR2/CCR5 inhibitors in NASH and liver fibrosis is founded on a solid basis of experimental evidence emphasizing the key role of chemokines and chemokine-directed immune cell subset infiltration during the progression from steatosis to steatohepatitis and fibrosis [16]. Roughly, CCR2 is primarily expressed on monocytes, the circulating precursor cell for tissue macrophages and dendritic cells, while CCR5 is found on a variety of lymphocytes (T cells, NK cells) as well as on hepatic stellate cells, the main precursor for liver myofibroblasts [17]. Distinct chemokine pathways, including the CCR2 and CCR5 ligands, orchestrate the hepatic recruitment, migration and/or activation of immune cells as well as hepatic stellate cells, thereby linking hepatocyte stress and injury with subsequent inflammation and fibrosis in NAFLD [18]. Moreover, chemokines such as CCL2 are systemically upregulated in NASH, contributing to the close link between hepatic and extrahepatic (e.g., adipose tissue) inflammation [16].

Macrophages in the liver represent a main cellular component for disease progression in NAFLD [19]. The understanding of their roles in health and disease has been greatly advanced by recognizing different macrophage subsets. In principle, tissue-resident Kupffer cells that originate from embryogenic precursors and proliferate locally can be distinguished from monocyte-derived macrophages that infiltrate the liver upon specific signals in NASH
Kupffer cells, but also stressed hepatocytes, stressed adipocytes or activated stellate cells, can release CCL2, which provides a strong signal for the mobilization of CCR2+ monocytes into the circulation and subsequently for their recruitment into the tissue [21, 22, 23, 24, 25]. In mouse models of obesity, steatohepatitis or liver fibrosis, the CCR2-dependent recruitment of inflammatory monocytes has been unequivocally linked to the aggravation of inflammation and fibrogenesis [24, 26, 27, 28, 29, 30]. These functional data from mouse models are in full agreement with translational data from patients. Elevated CCL2 serum levels and increased numbers of CCR2 expressing cells have been reported for patients with chronic liver diseases and fibrosis [31, 32]. Elevated numbers of CCR2+ macrophages in adipose tissue are found in patients with NASH and correlate with disease activity in the liver [33]. Moreover, we have reported that the density of CCR2+ macrophages is significantly higher in patients with NASH and fibrosis (or cirrhosis) as compared to simple steatosis or non-fibrotic NASH (Figure 1A) [34]. Overall, the prominent role of macrophages in the progression of NAFLD and the functional diversification with distinct liver macrophage subsets fueled the concept of therapeutically targeting hepatic macrophages [35]. The CCR2 inhibitory component of CVC is expected to reduce the numbers of inflammatory infiltrating monocytes, thereby abrogating fibrogenic signals in the liver (Figure 1B).

In comparison to CCR2, CCR5 has a wider expression among non-parenchymal cells in the liver and shares many of its main ligands (CCL3, CCL4, CCL5) with the chemokine receptor CCR1 [16, 17]. In mouse models of obesity, NAFLD or liver fibrosis, genetic deletion of CCR5 or CCL5 were associated with reduced inflammation and fibrosis progression [36, 37, 38]. On a functional level, CCR5 signaling has been associated with the recruitment and positioning of lymphocytes in the liver [16], but also to migratory as well as proliferative responses of hepatic stellate cells, indicating that this chemokine receptor directly mediates profibrogenic stellate cell activities [39]. Patients with chronic liver diseases have elevated expression levels of CCR5 in the liver and higher circulating levels of potential CCR5 ligands in the serum [31, 37, 40]. Therefore, the CCR5 inhibitory component of CVC can be expected to dampen lymphocyte-mediated inflammation and fibrogenic activation of hepatic stellate cells.

4. Preclinical evidence on cenicriviroc in liver disease models

Based on the critical role of CCR2 for monocyte recruitment upon liver injury and the involvement of CCR5 in lymphocyte recruitment and stellate cell activation, pharmacological treatment with the dual CCR2/CCR5 inhibitor CVC represents a promising novel strategy for liver diseases, in particular for NASH and fibrosis [35]. Consequently, this strategy has been evaluated in a variety of experimental liver disease models in rodents. CVC can be used in
mice and rats, but has a substantially lower half-life and a lower (and partially different) CCR2/CCR5 receptor occupancy in rodents compared for humans [41], which needs to be accounted for in animal models (e.g., frequency of application and dosing).

The principal ability of CVC to inhibit monocyte migration in vivo was demonstrated in a mouse model of thioglycollate-induced peritonitis, in which the simultaneous application of CVC by gavage reduced monocyte infiltration into the peritoneal cavity in a dose-dependent manner [41]. Similarly, if an acute liver injury was induced by a single intraperitoneal injection of the hepatotoxic agent carbon tetrachloride (CCl₄) in mice, the simultaneous oral application of CVC specifically prevented the accumulation of CD11b⁺ F4/80⁺ monocyte-derived macrophages in injured livers [42]. CCl₄ induces massive hepatic necrosis with ALT levels reaching 10,000 U/L after 24h, provoking a strong inflammatory reaction that is dominated by macrophages (and inhibited by CVC). However, CVC treatment did not change the composition of hepatic lymphoid cell populations in vivo, although it has significant inhibitory effects on splenic lymphocytes (NK cells, T cells) in vitro [42]. A potential explanation is that CVC blocks CCR5 less potently than CCR2 in mice (other than in humans) [41, 42], which might explain that CCR2- and monocyte-dependent effects prevail in all mouse models studied with CVC to date.

A comprehensive analysis on functional consequences of inhibiting monocyte infiltration into acutely injured livers has been reported from the acetaminophen (APAP, paracetamol) model in mice. APAP injection provokes an acute liver injury, similar to APAP-induced liver failure in humans. CCL2 levels rapidly increase in this model (as early as 6 hours after injury induction), followed by the CCR2-dependent accumulation of monocyte-derived macrophages in the liver, which peaks at 12-24h after APAP [43]. In contrast to resident Kupffer cells or patrolling monocytes, these monocyte-derived macrophages express many markers related to inflammation, pattern recognition, but also tissue repair. Consequently, if CVC is administered before or very early after APAP injury, it effectively blocks monocyte infiltration and ameliorates liver damage following APAP poisoning [43]. However, if it is blocked at a later stage (when damage is already initiated), CVC did not provide beneficial effects in the APAP mouse model [43]. These data emphasize that chemokine responses and immune cell recruitment are quite tightly regulated in acute inflammatory settings, making chronic diseases a much easier target for therapeutic interventions.

The chronic administration of CVC was thus tested in a mouse model of NASH ("stellic model"), based on streptozotocin injection 2 days post-birth (causing pancreatic beta cell islet destruction) plus a high-fat diet feeding, and in a rat model of liver fibrosis, induced by repetitive injections of thioacetamine (TAA). In both models, CVC was associated with reduced collagen deposition in the liver, as assessed by fiber staining [41]. The NASH model also revealed reduced ALT levels and a lower histological NAS score in CVC-treated animals.
Surprisingly, the number of hepatic macrophages by immunohistochemical staining for F4/80 did not change upon CVC treatment in the NASH or the TAA model [41]. This seeming paradoxon could be partially resolved by a systematic immunological analysis of CVC treatment in two dietary models of steatohepatitis in mice, the methionine-choline-deficient (MCD) diet and the Western diet [34]. CVC or vehicle was given PO during the last 4 weeks of an 8 weeks MCD diet or 8 weeks of a 16 weeks Western diet, respectively. CVC specifically inhibited the subset of CCR2-dependent monocyte-derived macrophages, characterized by CD11b, F4/80 and Ly6C expression in mice, while the number of Kupffer cells remained unaffected [34]. RNA-sequencing analyses from sorted macrophage populations revealed functional differences (and partial redundancies) between both macrophage populations. Monocyte-derived macrophages specifically up-regulated growth factors and cytokines associated with fibrogenesis and angiogenesis, while Kupffer cells activated pathways related to inflammation initiation and lipid metabolism [34]. In the Western diet model of steatohepatitis and obesity, CVC treatment improved insulin resistance and hepatic triglyceride levels. In the MCD diet model, therapeutic CVC application reduced histological NASH activity and hepatic fibrosis [34].

While monocyte-derived macrophages promote inflammation and fibrosis during liver disease progression, they have been shown to switch their phenotype towards a restorative profile during regression from injury [44, 45, 46]. Thus, there is a principle concern that pharmacological CCR2 inhibition might delay resolution of injury. The effect of CVC administration during liver fibrosis regression has been tested in the rat model of TAA-induced fibrosis [41] as well as in resolution from APAP toxicity [41, 43] and MCD diet induced fibrosis [34]. In these three independent settings in rodent models, CVC did not delay fibrosis regression or tissue repair [34, 41, 43].

Taken together, CVC has been widely studied in preclinical rodent models of liver disease, demonstrating an effective inhibition of monocyte infiltration into injured liver with subsequent beneficial effects, especially a consistent finding of reduced liver fibrosis progression. These data are in line with reports of similar pharmacological interventions, e.g., using the CCR2 inhibitor propagermanium [47, 48] or the CCL2-aptamer antagonist mNOX-E36 [30, 49]. Thus, the preclinical data overall support favorable consequences of CVC on key pathways at the interface between liver injury and inflammation or fibrosis.

5. **Clinical experiences with cenicriviroc in HIV-infected individuals**

As stated above, CVC has initially been tested for treatment of HIV-1 infection. In a prospective, randomized controlled multicenter phase 2b study, 143 HIV-1 infected, treatment-naïve patients (HIV-1 RNA ≥1000 copies/ml, CD4 cell count ≥200 cells/μl, CCR5-
tropic HIV) were randomized 2:2:1 to CVC 100mg (n=59), CVC 200mg (n=56), or efavirenz 600mg (EFV, n=28), each drug together with emtricitabine/tenofovir disoproxil fumarate. CVC demonstrated a similar antiviral efficacy against HIV as EFV, but had a more favorable safety profile with less treatment-related adverse events and reduced total and LDL cholesterol levels [50]. In this study, circulating CCL2 (MCP-1) levels increased in a dose-dependent manner in CVC treated individuals, supporting an effective CCR2 inhibition in conjunction with the CCR5 blockade that mediated the antiviral efficacy. This was further supported by reduced levels of soluble CD14, a monocyte-related activation marker, below baseline values in CVC-exposed individuals throughout the study [50]. Moreover, the investigators assessed several non-invasive biomarkers and scores of liver fibrosis, such as the aminotransferase-to-platelet count ratio index (APRI), the hepatic fibrosis risk (FIB-4) score and the enhanced liver fibrosis (ELF) score [51]. Although these scores have been developed and validated in patients with chronic liver diseases, especially viral hepatitis [51], it was a striking observation that APRI, FIB-4 and ELF scores significantly improved in the CVC-treated HIV-infected patients over the course of 48 weeks [50, 52]. However, HIV-infected patients with elevated bilirubin (above the upper limit of normal [ULN]) or AST levels >2.6 fold ULN had been excluded from the trial, and no sufficient liver imaging or histology were available to support antifibrotic effects in this study [50].

6. Clinical efficacy of cenicriviroc in patients with NASH and liver fibrosis

The efficacy and safety of using CVC in patients with NASH and hepatic fibrosis has been tested in a multicenter phase 2b clinical trial, the CENTAUR trial (NCT02217475), over a period of two years, of which the primary and secondary end-point analyses after 1 year have been published [52, 53]. The inclusion criteria of this study attempted to enrich the study population for NASH patients at highest risk for disease progression. On the one hand, patients had histological evidence of NASH (defined by a NAS ≥4 with ≥1 in each component) and fibrosis (stage 1-3, according to NASH CRN criteria). On the other hand, participants had either type 2 diabetes, overweight/obesity (with a body mass index >25 kg/m²) with ≥1 criteria of the metabolic syndrome, or bridging fibrosis (stage 3) and/or high disease activity (NAS ≥5) [52]. Among 812 screened individuals, of which 610 underwent liver biopsy, 289 participated in the study. Patients were randomized 2:1:1 into arm 1 (CVC 150 mg for two years), arm 2 (placebo for year 1, then CVC 150 mg for year 2) and arm 3 (placebo for 2 years) (Fig.2A). Patients underwent liver biopsy at baseline, end of year 1 and end of year 2. The primary outcome was defined as a ≥2-point improvement in NAS and no worsening of fibrosis at year 1, in line with endpoints used in prior trials [12]. Among several secondary outcomes assessed in the CENTAUR trial, the histological resolution of steatohepatitis without worsening of fibrosis as well as improvement in fibrosis by ≥1 stage
and no worsening of steatohepatitis were obtained at year 1 [52]. In the end, n=145 patients were treated with CVC for 1 year (arm A), while n=144 received placebo (arms B and C) for year 1. Overall, their mean age was 55 year, 47% were male, 52% were diabetics, the mean BMI was 34 kg/m², and all three fibrosis stages were well represented (F1 33%, F2 29%, F3 38%); the patient characteristics did not differ between CVC and placebo [53]. In each group, n=126 patients had sufficiently evaluable paired liver biopsies (baseline – year 1).

Treatment with CVC for 1 year did not significantly change the number of patients achieving a ≥2-point improvement in NAS or achieving NASH resolution (Fig.2B), so the primary endpoint was not met [53]. However, twice as many of the CVC treated patients (20%) as compared to placebo treated patients (10%, p=0.023) achieved an improvement in fibrosis by ≥1 stage without worsening of NASH (odds ratio 2.20, 95% confidence interval 1.11–4.35) (Fig.2B). The improvement of fibrosis was seen across all stages of fibrosis, with significant benefit in the pooled data for stage 2 and 3 fibrosis (Fig.2C), as well as for the Ishak and the NASH-CRN fibrosis scoring system [53]. On the other hand, CVC treatment did not change body weight, ALT or AST levels, liver function test or insulin resistance [53], supporting the conclusion that CVC does not affect metabolic alterations or steatohepatitis per se in NASH patients. In multiple subgroups analyses, patients with higher degree of NAS and higher degree of ballooning demonstrated more pronounced fibrosis improvement as compared to patients with less active disease, while other parameters (diabetes, weight, PNPLA3 genotype, gender, age) appeared non-predictive regarding the response to CVC [53].

When comparing these clinical efficacy data after one year of CVC treatment with the preclinical evidence, it is striking that the significant reduction on fibrosis progression in animal models [34, 41] could be translated into significant fibrosis improvement in patients. In addition, most animal NASH models also showed either no or mild effects of CVC on hepatocyte ballooning, hepatic inflammation or liver injury markers such as ALT [34, 41], which is in line with the neutral effects of CVC on these parameters in patients. The mode of antifibrotic action in patients, however, requires further studies. In the CENTAUR trial, systemic inflammatory markers such as high sensitive C-reactive protein, fibrinogen, soluble CD14, interleukin (IL) 1β or IL-6 were decreased and circulating CCL2 was increased [53], supporting beneficial effects of CVC on monocyte- or macrophage-driven inflammation and fibrogenesis [35]. On the other hand, the histological assessment of “inflammation” did not reveal differences between CVC and placebo-treated patients, which is at least unexpected given the proposed mode of action on the CCR2-dependent recruitment of monocytes into the injured liver. A possible explanation might be the very distinct effect of CVC on the hepatic monocyte/macrophage composition [34, 42, 43], which cannot be accurately captured without very granular analyses (e.g., using multicolor-FACS or multiparametric immunostaining).
Although the primary and key secondary analyses of the CENTAUR trial were conducted after year 1 (and guided the design of the phase 3 clinical development), it will be interesting to see if the fibrosis improvement by CVC is sustained during the whole 2 year duration of the study (Fig.2A). The liver biopsies at the end of year 2 have been performed, and the study is terminated. However, the final results from the CENTAUR trials have not been published yet. In a press release, the company disclosed that patients that were switched from placebo to CVC for the second year displayed a similar benefit regarding fibrosis improvement as reported for the first year, while patients treated for two years with CVC did not demonstrate a difference in fibrosis improvement as compared to patients treated for two years with placebo (https://www.allergan.com/news/news/thomson-reuters/new-data-from-centaur-phase-2b-clinical-study-sup). It is currently impossible to meaningfully comment on the data before they have been formally presented and published.

7. Cumulative safety profile of cenicriviroc

Tolerability and safety are major concerns in developing NASH medication, because a long-term exposure to the drug is currently anticipated for the novel treatment strategies in NASH [12]. CVC has now been administered to >1000 participants in the phase 1 and 2 clinical studies, including single- and multiple-dose phase 1 studies in healthy volunteers and participants with hepatic impairment [15], phase 2 studies in HIV-infected patients [14, 50], phase 2 studies in participants with NASH with fibrosis [53], and with prediabetes or type 2 diabetes and suspected NAFLD (table 1). Overall, CVC has been well tolerated, and no major safety signals were noted. In the phase 2b trial with HIV-infected patients, adverse events were less often reported in CVC- (86%) compared to EFV-treated (96%) patients [50]. One patient discontinued CVC due to a new-onset depression. The incidence of grade 3 adverse events was numerically higher in EFV (10.7%) than in CVC (4.3%) exposed individuals. No life-threatening adverse events or deaths occurred in CVC-treated HIV-infected patients [50]. In the CENTAUR trial, 93% of CVC- and 92% of placebo-treated patients reported adverse events [53]. The majority of adverse events were mild, such as fatigue (2.8%) and diarrhea (2.1%) in CVC- and headache (3.5%) in placebo-exposed patients. No life-threatening adverse events (grade 4) and no deaths were reported. During the first year of treatment, one serious adverse event of grade 2 arrhythmia was assessed as drug related, but this patient remained blinded, and the event resolved on treatment [53]. Ten patients on CVC (7%) and twelve patients on placebo (8.3%) discontinued the study drug due to adverse events [53].

While the body of safety data in non-cirrhotic patients is solid, there is a paucity of data on CVC in cirrhotic individuals. Patients with liver cirrhosis were excluded from the CENTAUR
trial. However, a small phase 1 trial exposed patients with either Child A (n=7) or Child B (n=8) cirrhosis to 150 mg CVC daily, in comparison to matched healthy controls (n=15), for 14 days. CVC exposures were increased in patients with Child B cirrhosis (over the time dosing +55%, maximal plasma concentration 29% higher), but not in Child A cirrhosis [15]. Again, CVC was well tolerated; only one Child A cirrhosis patients discontinued CVC due to vomiting. Two participants with Child B cirrhosis due to chronic hepatitis C experienced transient liver enzyme elevations of >5-times ULN; however, these patients completed the study without dosing interruption [15].

A principal concern regarding chemokine and monocyte inhibition in patients with chronic liver diseases might be the potential risk of infectious complications. However, preclinical data provided experimental evidence that bacterial clearance and responses to infectious threats are primarily mediated by Kupffer cells [19, 54, 55], the resident macrophage population of the liver that is not affected by CVC treatment [34]. In line, neither the HIV- nor the NASH-trials have reported increased susceptibility to infections in CVC-exposed participants up to now [50, 53]. Moreover, the few patients with Child A or B exposed to CVC for 14 days did not display significant increases in biomarkers of bacterial translocation such as flagellin, lipopolysaccharide-binding protein (LBP) or intestinal fatty acid binding protein (I-FABP) [15].

8. Outlook on the further development of cenicriviroc in NASH and liver fibrosis

Based on the efficacy and safety data presented above, Tobira Therapeutics, a subsidiary of Allergan plc, has initiated the large phase 3 trial AURORA (NCT03028740) that evaluates CVC for the treatment of liver fibrosis in adults with NASH. In the AURORA trial, about 2000 patients will be randomized 2:1 to receive either CVC 150mg or placebo. Patients will undergo three consecutive biopsies at baseline (screening), after 12 months and after 60 months; clinical events will be recorded throughout the duration of the study that is anticipated to last for at least 5 years. The study will have two main outcome measures, which are either assessed after 1 or after 5 years of treatment (https://clinicaltrials.gov/ct2/show/NCT03028740):

- Superiority of CVC compared to placebo on liver histology at Month 12 relative to the Screening biopsy [Time Frame: measurements at Baseline and 12 months]: Proportion of subjects with improvement in fibrosis by at least 1 stage (NASH CRN system) and no worsening of steatohepatitis
- Superiority of CVC compared to placebo on the composite endpoint of histopathologic progression to cirrhosis, liver-related clinical outcomes, and all-cause
mortality [Time Frame: Time to accrue a pre-specified number of adjudicated events, End of Study, estimated to be 5 years]

The first endpoint (improvement in fibrosis after 1 year) will be assessed on the first 1000 patients and was accepted as a surrogate for interim approval by the FDA. Compared to the CENTAUR trial, the focus of this study is clearly to demonstrate a benefit on liver fibrosis. Therefore, only patients with stage 2 or 3 fibrosis due to NASH will be included in the trial. Besides the AURORA phase 3 trial, patients from the CENTAUR phase 2b trial are being offered to enroll in an open-label continuation trial (“CENTAUR roll-over study”) to receive CVC. Tobira/Allergan also collaborates with Novartis to test the combination therapy of CVC with their FXR agonist and will very likely test the combination of CVC with the FXR agonist AGN-242266 that has been recently acquired by Allergan.

9. **Expert Opinion**

Two key observations favor the future development of CVC in patients with NASH and liver fibrosis: the consistent finding of fibrosis improvement after 1 year of therapy and the excellent safety profile (with a tolerability and safety comparable to placebo). Moreover, a broad set of experimental evidence from preclinical models supports that inhibiting CCR2- and CCR5-mediated immune mechanisms ameliorates the progression of liver fibrosis. At the same time, several findings from the currently available clinical data challenge the use of CVC in this indication. I will address these concerns by the following questions.

*How efficient and how durable is the antifibrotic activity of CVC as a monotherapy?*

The absolute number of patients showing a clear fibrosis benefit after one year of therapy (20% in the CENTAUR trial vs. 10% on placebo) is low [53]. To my opinion, this challenge is not unique to CVC, but was also observed in other trials evaluating obeticholic acid [56] or elafibranor [57]. The current trials in the field are limited by non-drug-specific randomization (potentially, patients with high numbers of CCR2+ macrophages in their biopsies might benefit most from CVC?) and a histological read-out (that is limited by the small area of liver tissue examined and by the considerable variability in the disease over time). From a clinical perspective, not the absolute number of patients achieving a ≥1 stage improvement in fibrosis and no worsening of steatohepatitis is most relevant, but the number of patients not progressing with their disease to clinical endpoints such as liver cirrhosis, decompensation, cardiovascular events or hepatocellular carcinoma. In addition, inhibiting fibrosis might also reduce the likelihood of extrahepatic complications of NAFLD such as cardiovascular events...
Thus, only the long-term studies such as AURORA that focus on these endpoints will be able to reveal the true number of patients benefiting from the CVC treatment.

Although the year 2 data of the CENTAUR trial have not been published yet, first reports from this trial indicate that CVC treatment beyond one year does not further increase antifibrotic effects and/or may not sustain the difference in fibrosis improvement compared to placebo in all patients. This may be partly related to the large variability of histological changes in the natural history of the disease, which explains the favorable “placebo responses” observed in many trials [2]. On the other hand, a serious challenge in targeting CCR2/CCR5 is the high level of redundancy within the chemokine network [16]. For instance, not only CCR2-CCL2, but also CCR8-CCL1 [59], CCR1-CCL3/4/5 [37], CX3CR1-CX3CL1 [60] or CXCR3-CXCL10 [61, 62] have been implicated in the recruitment or differentiation of monocyte-derived macrophages in experimental fibrosis. The multitude of pathways, in addition to CCR5, leading to hepatic stellate cell activation [63] or to lymphocyte recruitment [64] is even much higher. Thus, it is conceivable that either alternative chemokine pathways compensate for CVC-inhibited monocyte recruitment or that alternative sources of macrophages exert fibrogenic activities during progression of NASH in the long run.

Can you treat fibrosis without treating NASH?

There is a clear indication from several observational cohorts that the presence and stage of fibrosis is associated with liver-related and overall morbidity and mortality in NAFLD [11, 65, 66]. This nurtures the assumption that any NASH therapy not affecting fibrosis might not be efficacious regarding patient-relevant endpoints [12]. However, it is not clear, if the opposite holds true as well. In case of CVC, the current data suggest rather neutral effects on metabolism and steatohepatitis [53]. In fact, part of the above discussed compensatory fibrogenic mechanisms might be driven by the continuous presence of NASH and related pathomechanisms (hepatocyte stress & cell death, gluco- and lipotoxicity, inflammation). Thus, it appears logical to combine CVC, using its antifibrotic potency, with drugs targeting liver metabolism and steatohepatitis. Among many candidates, FXR agonists, PPAR agonists or FGF-21 could represent examples for potentially useful and mechanistically complementary combination partners. Due to the excellent safety profile of CVC, this appears realistic, and the right combination of drugs might even demonstrate synergistic effects.

Could there be long-term risks associated with CCR2/CCR5 inhibition?
As outlined above, there is currently no signal from the clinical trials that inhibiting CCR2 and/or CCR5 would confer an increased susceptibility to infectious complications. The likely mechanistic explanation is that the heterogeneity of hepatic macrophages and their functional diversification ensures sufficient bacterial clearance and defense by Kupffer cells, while the target of CCR2 inhibition, monocyte-derived macrophages, appear dispensable for this task [19]. This is, however, not so clear for viral infections. Especially CCR5-dependent pathways have been frequently linked to adaptive immune responses against viral infections, especially T cell responses in viral hepatitis [16]. However, there is a high redundancy of the chemokine system on lymphocytes, reflected by the fact that the CCR5-activating ligands also activate CCR1 that shows co-expression with CCR5 on many cell types [17]. Moreover, the CCR5 inhibitor maraviroc is in clinical use for one decade now, without serious safety signals regarding specific infectious complications.

Another potential concern is the development of hepatocellular carcinoma (HCC). HCCs usually arise in chronically inflamed and fibrotic/cirrhotic livers, as a consequence of persistent cell death, aberrant regeneration and progressive inflammation [67]. NASH represents a particular high-risk situation for HCC, and HCC can even arise in non-cirrhotic livers [68, 69]. The optimal surveillance measures for HCC in NASH patients are controversial [2, 70]. While it is undisputed that inflammation drives the progression of liver cancer, there is increasing evidence that immune mechanisms are also important for cancer surveillance [71]. In experimental models of primary liver cancer, CD4 T cells recognized senescent, pre-malignant hepatocytes and activate macrophages for the clearance of these tumor precursors [72, 73, 74]. This effect of macrophage-mediated tumor clearance in very early HCC stages is dependent on CCR2 [72]. On the other hand, suppression of CCR2-CCL2 dependent monocyte-derived macrophages in experimental models of established HCC are beneficial regarding tumor progression [72, 75]. CCR2-expressing, monocyte-derived macrophages further have angiogenic functions, even in the absence of HCC, thereby likely promoting a tumor-prone microenvironment [49]. Thus, it is currently more likely that long-term CCR2/CCR5 inhibition will suppress hepatocarcinogenesis, but the effects of CVC on the occurrence of HCC (and extrahepatic malignancies) requires careful monitoring in clinical trials.

Will CVC be approved for the treatment of NASH and liver fibrosis in the near future?

The outcome of the phase 3 AURORA trial will determine, if CVC is granted (provisional) approval by the FDA. The primary endpoint used in the AURORA trial is “improvement in fibrosis and no worsening of steatohepatitis” after 1 year of treatment. From the current picture of phase 2 data, one can anticipate that there is a high likelihood that this endpoint
will be reached for the provisional approval of CVC. However, the final approval will depend on long-term benefits including clinical events, death, rate of liver transplantations and progression to cirrhosis in a liver biopsy at 60 months. To my opinion, it is much more uncertain if this long-term benefit can be demonstrated with the current number of patients anticipated in the CVC and placebo arm. Various other compounds have similar targets as CVC, such as investigational CCR2 (CCX140-b, JNJ-41443532) or CCR2/5 (BMS-813160, PF-04634817) antagonists. If CVC reaches FDA / EMA approval, several other compounds may follow. In addition, the proposed mechanisms of antifibrotic activities of CVC are not specific to NASH, making it likely that patients with other chronic liver diseases with fibrosis would also benefit from this strategy.

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Declaration of Interest

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Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.


• a current overview on the global burden of NAFLD


• multidisciplinary international guideline on the management of NAFLD


• important meta-analysis that established the association between fibrosis and clinical endpoints in NAFLD


• this study established the role of infiltrating CCR2+ monocytes for the progression of liver fibrosis


37. Li BH, He FP, Yang X, et al. Steatosis induced CCL5 contributes to early-stage liver fibrosis in nonalcoholic fatty liver disease progress. Translational research : the...

• experimental evidence for the anti-fibrotic role of CVC in animal models of liver and kidney fibrosis


• experimental evidence for the effect of CVC on monocyte migration into injured livers in vivo


• phase II clinical evaluation of CVC in HIV-infected individuals, supporting the excellent safety profile of the drug


- study design of the phase II trials on CVC in NASH and fibrosis


- report of antifibrotic activity of CVC from year 1 biopsies of the large phase 2 trial


• experimental evidence for a dual role of CCR2+ macrophages in liver cancer development


Table 1. Selected clinical trials with cenicriviroc (CVC).
The trials listed below reported tolerability and safety data. Not all of the studies are yet available as full reports.

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Population</th>
<th>N</th>
<th>N exposed to CVC (dose)</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>652-1-121</td>
<td>1</td>
<td>Participants with mild or moderate (Child-Pugh A or B) hepatic impairment (n=16) and matched healthy volunteers (n=15)</td>
<td>31</td>
<td>31 (150 mg)</td>
<td>14 days</td>
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<tr>
<td>(NCT02120547)</td>
<td></td>
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<tr>
<td>652-2-201</td>
<td>2a</td>
<td>Treatment-experienced participants with CCR5-tropic HIV-1 infection</td>
<td>54</td>
<td>(CVC or placebo)</td>
<td>10 days</td>
</tr>
<tr>
<td>(NCT01092104)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>652-2-202</td>
<td>2b</td>
<td>Treatment-naïve participants with CCR5-tropic HIV-1 infection</td>
<td>143</td>
<td>(CVC or EFV)</td>
<td>48 weeks</td>
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<tr>
<td>(NCT01338883)</td>
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<tr>
<td>652-2-203;</td>
<td>2b</td>
<td>Participants with NASH with liver fibrosis</td>
<td>289</td>
<td>(CVC or placebo)</td>
<td>2 years</td>
</tr>
<tr>
<td>CENTAUR (NCT02217475)</td>
<td></td>
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<tr>
<td>652-2-204;</td>
<td>2a</td>
<td>Obese participants with prediabetes or T2DM and suspected NAFLD</td>
<td>45</td>
<td>(CVC or placebo)</td>
<td>24 weeks</td>
</tr>
<tr>
<td>ORION (NCT02330549)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>652-205;</td>
<td>2a</td>
<td>Participants with primary sclerosing cholangitis (still ongoing)</td>
<td>22</td>
<td>(CVC open label)</td>
<td>24 weeks</td>
</tr>
<tr>
<td>PERSEUS (NCT02653625)</td>
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<td></td>
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<tr>
<td>652-2-801</td>
<td>2a</td>
<td>Participants with HIV-associated neurocognitive disorder</td>
<td>20</td>
<td>(CVC open label)</td>
<td>24 weeks</td>
</tr>
<tr>
<td>(NCT02128828)</td>
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</table>
Fig. 1. Role of CCR2 in NASH and fibrosis. (A) Representative staining for CCR2 (brown) in human liver biopsies of NASH patients with either early fibrosis (stage F1) or advanced fibrosis / cirrhosis (stage F4). Please note the massive increase of CCR2+ monocyte-derived macrophages in the periportal fibrotic areas. (B) Functional role of CCR2 signaling in NASH and fibrosis, based on mouse models (scheme). In case of NAFLD, stress hepatocytes, Kupffer cells (= resident liver macrophages) and hepatic stellate cells release the chemokine CCL2 (MCP-1), which promotes the recruitment of monocytes into the liver that have an inflammatory phenotype. These monocyte-derived macrophages activate hepatic stellate cells to become myofibroblasts, the main extracellular matrix producing cells in the liver. Photographs from human liver are a courtesy of Olivier Govaere and Quentin Anstee (Newcastle University, Newcastle-upon-Tyne, UK).
Fig. 2. Phase 2b clinical data on cenicriviroc in patients with NASH and liver fibrosis.
(A) Design of the Centaur phase 2b trial. Patients were randomized 2:1:1 into arm 1 (CVC 150 mg for two years), arm 2 (placebo for year 1, then CVC 150 mg for year 2) and arm 3 (placebo for 2 years). Patients underwent liver biopsy at baseline, end of year 1 and end of year 2. (B) Year 1 efficacy data as intention-to-treat analysis. The primary end-point (≥2 points improvement in NAS score without worsening of fibrosis) and the first secondary end-point (complete resolution of NASH and no worsening of fibrosis) were not met. The other secondary endpoint (improvement of fibrosis by ≥1 stage and no worsening of steatohepatitis) was significantly more often reached in the CVC group. (C) There was a consistent trend for fibrosis improvement and no worsening of NASH across all stages of fibrosis, and patients with a baseline F2 and F3 fibrosis more often achieved improvement in CVC treated groups after 1 year. Placebo responses are depicted in blue columns, CVC in red.
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