The rationale and study design of two phase II trials examining the effects of BI 685,509, a soluble guanylyl cyclase activator, on clinically significant portal hypertension in patients with compensated cirrhosis.

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Abstract

BACKGROUND: Clinically significant portal hypertension (CSPH) drives cirrhosis-related complications (i.e. hepatic decompensation). Impaired nitric oxide (NO) bioavailability promotes sinusoidal vasoconstriction, which is the initial pathomechanism of CSPH development. Activation of soluble guanylyl cyclase (sGC), a key downstream effector of NO, facilitates sinusoidal vasodilation, which in turn may improve CSPH. Two phase II studies are being conducted to assess the efficacy of the NO-independent sGC activator BI 685,509 in patients with CSPH due to various cirrhosis aetiologies. METHODS: The 1366.0021 trial (NCT05161481) is a randomised, placebo-controlled, exploratory study that will assess BI 685,509 (moderate or high dose) for 24 weeks in patients with CSPH due to alcohol-related liver disease. The 1366.0029 trial (NCT05282121) is a randomised, open-label, parallel-group, exploratory study that will assess BI 685,509 (high dose) alone in patients with hepatitis B or C virus infection or non-alcoholic steatohepatitis (NASH) and in combination with 10 mg empagliflozin in patients with NASH and type 2 diabetes mellitus for 8 weeks. The 1366.0021 trial will enrol 105 patients, and the 1366.0029 trial will enrol 80 patients. In both studies, the primary endpoint is the change from baseline in hepatic venous pressure gradient (HVPG) until the end of treatment (24 or 8 weeks, respectively). Secondary endpoints include the proportion of patients with an HVPG reduction of > 10% from baseline, the development of decompensation events and the change from baseline in HVPG after 8 weeks in the 1366.0021 trial. In addition, the trials will assess changes in liver and spleen stiffness by transient elastography, changes in hepatic and renal function and the tolerability of BI 685,509. DISCUSSION: These trials will enable the assessment of the short-term (8 weeks) and longer-term (24 weeks) effects and safety of sGC activation by BI 685,509 on CSPH due to various cirrhosis aetiologies. The trials will use central readings of the diagnostic gold standard HVPG for the primary endpoint, as well as changes in established non-invasive biomarkers, such as liver and spleen stiffness. Ultimately, these trials will provide key information for developing future phase III trials. TRIAL REGISTRATION: 1366.0021: EudraCT no. 2021-001,285-38; ClinicalTrials.gov NCT05161481. Registered on 17 December 2021, https://www. CLINICALTRIALS: gov/ct2/show/NCT05161481 . 1366.0029: EudraCT no. 2021-005,171-40; ClinicalTrials.gov NCT05282121. Registered on 16 March 2022, https://www. CLINICALTRIALS: gov/ct2/show/NCT05282121 .