Background and Aims

- Non-alcoholic fatty liver disease (NAFLD) is a broad, heterogeneous disease characterized by excessive hepatic fat accumulation and associated inflammation and fibrosis.
- NAFLD is commonly associated with obesity, diabetes, and hypertension, and it is the most common chronic liver disease in developed countries.
- NASH is often accompanied by liver fibrosis, which can cause a range of adverse clinical outcomes, including cirrhosis, hepatocellular carcinoma, and death.
- Effective treatments are desperately needed to prevent progression to advanced liver disease in NAFLD.
- Cenicriviroc (CVC) is a CCR2/CCR5 inhibitor that has been shown to reduce inflammation and fibrosis in preclinical models.
- The primary endpoint of the CENTAUR study was a reduction in chronic liver inflammation and fibrosis stage (≤2 or >2).
- The CENTAUR study evaluated the efficacy and safety of CVC in adult subjects with liver fibrosis.

Figures and Tables

Figure 1: Summary of Study Design and Timeline

Figure 2: Primary Efficacy Endpoints

Figure 3: Secondary Efficacy Endpoints

Figure 4: Liver Histology

Methods

- Study Design: Randomized, double-blind, placebo-controlled, multicenter, parallel-group, double-dummy, 2:1:1 treatment allocation.
- Treatment arms: Placebo, CVC 150 mg once-daily (QD), Placebo QD.
- Study duration: 2 years (baseline, months 0.5, 3, 6, 12, 15, 18, 24).
- Efficacy endpoints: Change in hepatic stellate cell activation marker (α-smooth muscle actin), Change in collagen morphometry (CPA) on liver biopsy.
- Safety evaluation: Fasting metatbolite tests (for liver and fasting metabolic parameters), physical examination, laboratory tests (hematology, biochemistry).
- Adverse events (AEs), clinical laboratory test abnormalities, vital signs, patient complaints.

Statistical Methods

- **Efficacy analysis**: The primary (Arm A versus Arms B and C at Year 1) and key secondary (Arm A versus Arms B and C at Year 2) efficacy endpoints of the CENTAUR study will be analyzed using a mixed-effects model to compare treatment groups.
- **Population PK analysis**: PK parameters will be evaluated in a mixed-effects model to compare treatment groups.

Results

- **Outcome measures**: Primary efficacy endpoints at 1 year were significantly different between treatment groups.
- **Secondary efficacy endpoints**: Additional efficacy endpoints were also significant between treatment groups.
- **Safety evaluation**: The safety profiles of CVC and placebo were comparable.

Discussion

- **Comparison with previous studies**: The CENTAUR study results are consistent with previous studies demonstrating the efficacy and safety of CVC.
- **Limitations**: The study was limited to age, sex, weight, body mass index (BMI), race, and baseline hepatic fibrosis stage.
- **Future directions**: Further studies with larger sample sizes and longer follow-up are needed to confirm the results of the CENTAUR study.

**CENTAUR, a Phase 2b Efficacy and Safety Study of Cenicriviroc in Adults with Non-alcoholic Steatohepatitis and Liver Fibrosis at Increased Risk of Progression to Cirrhosis**

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**Study endpoints**

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- **Secondary efficacy endpoints**: Change in collagen morphometry (CPA) on liver biopsy.
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