A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, Efficacy, and Pharmacokinetics of INT-787 in Subjects With Severe Alcohol-Associated Hepatitis: Study Design, Objectives, and Novel Assessments

Poster #3503-C

Thomas Capozza[1]; Steven Lauder[1]; Sam Madison[1]; Jennifer Callahan[1]

[1]Intercept Pharmaceuticals Inc., Morristown, NJ, USA

Introduction

- Severe alcohol-associated hepatitis (sAH) is the most acute and serious form of alcohol-associated liver disease, identified clinically by the presence of jaundice, hepatitis, and systemic inflammatory response, and correlated with significant morbidity and mortality rates[1-3]
- Therapeutic options for sAH are limited; guideline-recommended corticosteroid treatment lacks survival benefit beyond 28 days[1,2,4]
- INT-787 is a hydrophilic, semisynthetic bile acid farnesoid X receptor (FXR) agonist derived from chenodeoxycholic acid with significant intestinal FXR activity and has potential as a treatment option for sAH[5]
- FXR agonism regulates a variety of target genes involved in bile acid, lipid, and glucose homeostasis, as well as fibrotic and immune responses[3,5]
- Preclinical studies of FXR agonists, including INT-787, have demonstrated improvements in hepatic steatosis, inflammation, fibrosis, and intestinal mucosal integrity, as well as reductions in plasma endotoxin and bile acids in various liver-related disorders[3,6-9]
- The goal of this study is to evaluate the safety, tolerability, early efficacy, and pharmacokinetics (PK) of INT-787 in patients with sAH

Methods

PATIENTS AND DESIGN

- This is a phase 2a, randomized, double-blind, placebo-controlled, multicenter, dose-escalation, proof-of-concept study (FRESH; NCT05639543)
- Patients admitted to participating hospitals who satisfy all inclusion and exclusion criteria (**Table 1**) will have up to a 7-day screening period, followed by a 28-day treatment period and 56-day follow-up period
- Oral INT-787 will be administered once daily to patients with a diagnosis of AH, a Modified Maddrey's Discriminant Function (mDF) ≥32 and ≤70, and a Model for End-Stage Liver Disease (MELD) score of 18-25
- Up to 5 dose cohorts are planned, starting with 5 mg/day (**Figure 1**)
  - Each cohort will include 10 randomized patients (4:1) to receive INT-787 capsules or matching placebo for 28 days
  - Barring clinically significant safety or tolerability concerns at a dose cohort, and after review and approval by the Sponsor's Global Safety Committee, a decision will be made to progress the study to the next dose cohort
  - Dose escalations will not exceed a 3-fold increase from cohort to cohort and a maximum dose level of 120 mg
  - Primary efficacy analysis will be conducted using a modified intention-to-treat population, which includes all intention-to-treat participants who took at least 1 dose of the investigational product with Lille score response data at day 7 and who did not receive systemic corticosteroids within the first 7 days of the treatment period

Methods (continued)

ENDPOINTS AND ASSESSMENTS (TABLE 2)

- The primary endpoint is the assessment of sAH disease response by Lille score at day 7
- Secondary endpoints include changes in MELD score and total bilirubin, occurrence of infectious complications, clinical outcomes (short- and intermediate-term mortality or liver transplantation), and PK
- Safety and tolerability will be evaluated by incidence of treatment-emergent adverse events, serious adverse events, adverse events of special interest, and adjudicated events
  - Any potential drug-induced liver injury (DILI) or acute kidney injury (AKI) events will be independently reviewed by a third-party expert Hepatic Safety Adjudication Committee or Renal Adjudication Committee
- Other assessments include PK and pharmacodynamic (PD) analyses, stool microbiome analysis, and markers of bacterial translocation (lipopolysaccharide-binding protein and 16S ribosomal deoxyribonucleic acid)

Table 1. Key study inclusion and exclusion criteria

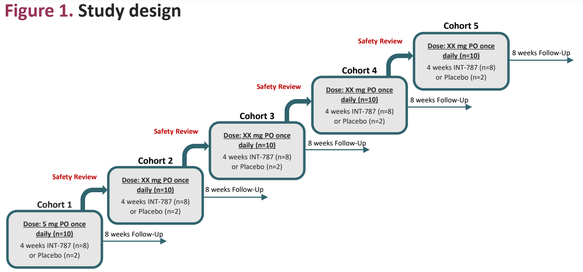
Inclusion criteria

• Males or females aged 18 to 65 years (inclusive)
• Clinical diagnosis of sAH based on *all the following*:
  ▪ History of excessive alcohol (>60 g/day [male] or >40 g/day [female]) use for ≥6 months, with <60 days of abstinence prior to the onset of jaundice
  ▪ Serum total bilirubin >3.0 mg/dL
  ▪ AST ≥50 U/L
  ▪ AST/ALT ratio ≥1.5
  ▪ Onset of jaundice within prior 8 weeks
  ▪ mDF score ≥32 and ≤70
• MELD score 18 to 25 (inclusive)
• Patients must agree to participate in an alcohol use disorder program during the study period, as recommended by the local institution's addiction medicine specialists, including posthospitalization

Exclusion criteria
• Patients taking products containing obeticholic acid within 30 days prior to randomization • Patients taking >2 doses of systemic corticosteroids within 30 days prior to randomization • Patients who have been inpatient at a referral hospital for >7 days prior to transfer • Abstinence from alcohol consumption for >2 months before day 1 • AST or ALT >400 U/L; mDF <32 or >70 at screening; MELD score <18 or >25 at screening • Other causes of liver disease, including chronic hepatitis B (hepatitis B surface antigen positive); chronic hepatitis C virus RNA positive; DILI, biliary obstruction, and autoimmune liver disease • Kidney injury (SCr >1.5 mg/dL) or requirement for renal replacement therapy • History of hepatocellular carcinoma, liver transplantation, or human immunodeficiency virus • Malignancy <2 years prior to screening • Portal vein thrombosis • Acute pancreatitis or gallbladder disease • Positive urine drug screen

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; mDF, Modified Maddrey's Discriminant Function; MELD, Model for End-Stage Liver Disease; sAH, severe alcohol-associated hepatitis; SCr, serum creatinine.

Figure 1. Study design



Abbreviation: PO, by mouth.

Table 2. Study objectives and endpoints

Primary objective	Primary endpoint
Treatment efficacy as assessed by sAH disease response	Lille score at day 7
Secondary objectives	**Secondary endpoints**
Treatment efficacy	MELD score at day 28; change from baseline in TB at days 7, 14, 21, 28
Clinical outcomes	28-day (short-term), 56-day, and 84-day (intermediate-term) mortality or liver transplantation
Safety and tolerability	TEAEs, SAEs, AESIs (pruritus and DILI), physical examinations, vital signs, ECGs, and clinical laboratory results
Infectious complications	Occurrence of infection by system organ class
Urine biomarkers	NGAL, KIM-1, IL-18, L-FABP
INT-787 PK	INT-787, tauro-INT-787, glyco-INT-787 and other metabolites as applicable, total INT-787
PD parameters of FXR activation	C4, FGF-19, and endogenous bile acids
Exploratory objectives	**Exploratory endpoints**
Clinical outcomes	Hospital readmission due to AH during the study period
Measures of healthcare utilization	Hospitalization length of stay, ICU days, major medical procedures, and emergency room visits
Health-related quality of life	Change from baseline in EQ-5D-5L
Measures of serum liver biochemistries, markers of inflammation, and lipid metabolism	Change from baseline in ALP, ALT, AST, GGT, TB, and DB; IL-6, hs-CRP, CK-18, and TNF-α; LDL, HDL, TC, VLDL, and TG
Markers of bacterial translocation and stool microbiome analysis	Change from baseline in LBP, 16S rDNA, and stool alpha-1-antitrypsin and microbiome/metabolome analysis

Abbreviations: AESI, adverse events of special interest; AH, alcohol-associated hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; C4, 7α-hydroxy-4-cholesten-3-one; CK-18, cytokeratin 18; DB, direct bilirubin; DILI, drug-induced liver injury; ECG, electrocardiogram; EQ-5D-5L, 5-level EQ-5D version; FGF-19, fibroblast growth factor 19; FXR, farnesoid X receptor; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; ICU, intensive care unit; IL, interleukin; KIM-1, kidney injury molecule-1; L-FABP, liver-type fatty acid-binding protein; LBP, lipopolysaccharide binding protein; LDL, low-density lipoprotein; MELD-Na, Model for End-Stage Liver Disease-Sodium; NGAL, neutrophil gelatinase-associated lipocalin; PD, pharmacodynamic; PK, pharmacokinetic; rDNA, ribosomal deoxyribonucleic acid; SAE, serious adverse event; sAH, severe alcohol-associated hepatitis; TB, total bilirubin; TC, total cholesterol; TEAE, treatment-emergent adverse event; TG, triglyceride; TNF-α, tumor necrosis factor-alpha; VLDL, very low-density lipoprotein.

Results

- Up to 50 patients are targeted for enrollment across the 5 dose cohorts at up to approximately 30 investigational sites globally

Conclusions

- INT-787 is a promising and distinct FXR agonist with preclinical data supporting exploration in the treatment of alcohol-associated hepatitis
- The FRESH study includes novel clinical trial assessments in sAH, including DILI and AKI expert adjudication

References

1. Karakike E, Moreno C, Gustot T. Infections in severe alcoholic hepatitis. *Ann Gastroenterol*. 2017;30(2):152-160. doi:10.20524/aog.2016.0101
2. Pimienta M, Tien C, Terrault NA. Prospective clinical trials and novel therapies in the medical management of severe alcohol-associated hepatitis. *Clin Liver Dis (Hoboken)*. 2022;20(6):202-208. doi:10.1002/cld.1265
3. Wu W, Zhu B, Peng X, Zhou M, Jia D, Gu J. Activation of farnesoid X receptor attenuates hepatic injury in a murine model of alcoholic liver disease. *Biochem Biophys Res Commun*. 2014;443(1):68-73. doi:10.1016/j.bbrc.2013.11.057
4. Bataller R, Arab JP, Shah VH. Alcohol-associated hepatitis. *N Engl J Med*. 2022;387(26):2436-2448. doi:10.1056/NEJMra2207599
5. Pellicciari R, Passeri D, De Franco F, et al. Discovery of 3α,7α,11β-trihydroxy-6α-ethyl-5β-cholan-24-oic acid (TC-100), a novel bile acid as potent and highly selective FXR agonist for enterohepatic disorders. *J Med Chem*. 2016;59(19):9201-9214. doi:10.1021/acs.jmedchem.6b01126
6. Hartmann P, Hochrath K, Horvath A, et al. Modulation of the intestinal bile acid/farnesoid X receptor/fibroblast growth factor 15 axis improves alcoholic liver disease in mice. *Hepatology*. 2018;67(6):2150-2166. doi:10.1002/hep.29676
7. Verbeke L, Mannaerts I, Schierwagen R, et al. FXR agonist obeticholic acid reduces hepatic inflammation and fibrosis in a rat model of toxic cirrhosis. *Sci Rep*. 2016;6:33453. doi:10.1038/srep33453
8. Baghdasaryan A, Claudel T, Gumhold J, et al. Dual farnesoid X receptor/TGR5 agonist INT-767 reduces liver injury in the Mdr2-/- (Abcb4-/-) mouse cholangiopathy model by promoting biliary HCO^-_3 output. *Hepatology*. 2011;54(4):1303-1312. doi:10.1002/hep.24537
9. Adorini, L, Rigbolt K, Voldum-Clausen, K, et al. The novel FXR agonist INT-787 shows higher efficacy as well as greater hepatic and ileal gene modulation than obeticholic acid in the gubra-amln mouse model of diet-induced and biopsy-confirmed nonalcoholic steatohepatitis. Poster presented at: American Association for the Study of Liver Diseases; November 3-8, 2022; Washington, D.C.

Acknowledgments

This study was funded by Intercept Pharmaceuticals, Inc. Medical writing and editorial support were provided by Lori Ellezian, PharmD, and funded by Intercept Pharmaceuticals, Inc.

Disclosures

TC, **SL**, **SM**, and **JC** are employees of Intercept Pharmaceuticals, Inc.

Corresponding Author

Sam Madison
sam.madison@interceptpharma.com