OBJECTIVES

• To present the supporting preclinical rationale for evaluating bexotegrast in PSC and provide an overview of the INTEGRIS-PSC study

• To present an update on the randomized study population

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a rare, idiopathic, cholestatic liver disease characterized by biliary inflammation and progressive fibrosis, which over time can lead to serious and often fatal liver complications. Transforming growth factor-beta (TGF-β), a key driver of fibrosis in the liver, is inhibited by bexotegrast. In PSC, αTGF-β, transforming growth factor-beta, COL1A1, collagen type I alpha 1 chain; αvβ6, integrin αvβ6; SMAD2/3, SMAD2/3; αvβ1, integrin αvβ1

PRECLINICAL RESEARCH

• Bexotegrast or vehicle was administered orally for 6 weeks in BALB/c Mdr2-/- mice with established biliary fibrosis

• Hepatic collagen and cholestasis were quantified by collagen proportionate area (CPA) and serum alkaline phosphatase (ALP) respectively

• Bexotegrast dose-dependently reduced CPA (up to ~50%; p<0.05) and serum ALP (46%, p<0.01) vs. vehicle in the BALB/c Mdr2-/- mouse model

INTEGRIS-PSC CLINICAL STUDY

Methods

• INTEGRIS-PSC is an ongoing, multinational, randomized, double-blind, dose-ranging, placebo-controlled Phase 2a study evaluating safety, tolerability, pharmacokinetics (PK), and markers of fibrosis following multiple doses of bexotegrast administered 2Q in participants with PSC

• Following review of safety data from the 40 mg, 80 mg, and 160 mg cohorts (Figure 4A), an additional 320 mg cohort was initiated with a longer treatment duration of at least 24 and up to 48 weeks

CONCLUSIONS

• The INTEGRIS-PSC Phase 2a study evaluating the safety, tolerability, and pharmacokinetics of bexotegrast in participants with PSC continues without modification by an independent data safety monitoring board

• Twelve-week results from this study (60 mg, 80 mg, and 160 mg vs. placebo) are expected in Q3 2023

Figure 1

Examples

COL1A1
COL4A1
TIMP1
ATX
LTA4H

COL1A1, collagen type I alpha 1 chain; COL4A1, collagen type IV alpha 1 chain; ATX, alkaline phosphatase; LTA4H, leukotriene A4 hydrolase

Figure 2

Effect of dual αvβ6 and αvβ1 inhibition with bexotegrast on collagen deposition and cholestasis in the BALB/c Mdr2-/- mouse model

Figure 4b

Examples

Beotegrast (100 µM)

Vehicle

DCOT

COL4A1

TIMP1

ATX

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Figure 4b

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