Seladelpar’s Mechanism of Action as a Potential Treatment for Primary Biliary Cholangitis and Non-Alcoholic Steatohepatitis

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INTRODUCTION

Seladelpar, a potent and selective agonist of the peroxisome-proliferator activated receptor (PPAR)-delta, is being developed for primary biliary cholangitis (PBC) and non-alcoholic steatohepatitis (NASH). PPARs are intra-nuclear receptors that form dimers with the retinoic X receptor (RXR) and regulate transcription of specific genes. PPAR-delta is activated by lipids and controls metabolic and inflammatory pathways in the liver, inflammatory cells, muscle, fat and intestinal tissues. PPAR-delta differs from PPAR-alpha and gamma because of its broad tissue distribution and its unique set of target genes. In the liver, the delta receptor differs from the other isotopes by its broad activity in hepatocytes, cholangiocytes, Kupffer cells and stellate cells. We present data supporting the mechanism of action of seladelpar for PBC and NASH.

METHODS

Seladelpar was evaluated in a multiple ascending dose study in healthy volunteers; in two Phase 2 studies in dyslipidemia (NCT03919835 and 02472355) and in two Phase 2 studies in PBC (NCT02699044 and 02559662). Supportive data were obtained from preclinical in vivo models of metabolic diseases and from culture studies with hepatocytes, intestinal cells and macrophages.

PRECLINICAL STUDIES

1. Human primary hepatocytes in sandwich culture: CYP7A1 gene expression and total bile acid content.
2. Cholesterol absorption study in mice using the fecal dual isotope ratio method: Cholesterol absorption measurement and intraductal NPC1l1 gene expression using zeludem as a comparator.
4. High fat, high cholesterol fed guinea pig study: Total cholesterol, LDL-C and HDL-C.
5. Mitochondrial fatty acid oxidation (FAO) in mouse liver: Givens involved in FAO.

CLINICAL STUDIES

1. PBC low dose study:
   - Phase 2, 52 weeks, open-label, randomized, dose-ranging
   - PBC subjects with inadequate response under UDCA or intolerant to UDCA
   - AP ± 1.67 x ULN, ALT or AST ≥ 3 x ULN. Total bilirubin ≥ 2 mg/dL
   - UDCA treatment maintained at the pre-study dose
   - Seladelpar 2 mg, 5 mg or 10 mg
   - Ongoing study with interim analysis data (71 subjects)
2. PBC high dose study:
   - Phase 2, 12 weeks, double-blind, randomized, placebo-controlled, dose ranging
   - PBC subjects with inadequate response to UDCA or intolerant to UDCA
   - AP ± 1.67 x ULN, ALT or AST ≥ 3 x ULN. Total bilirubin ≥ 2 mg/dL
   - UDCA treatment maintained at the pre-study dose
   - Placebo, seladelpar 50 mg or 200 mg (n=41).
3. Dyslipidemia study: Lipid, metabolic and anti-inflammatory benefits:
   - Phase 2, double-blind, randomized placebo-controlled parallel group study
   - Non-diabetic obese/overweight subjects with hyperlipidemia
   - Placebo, seladelpar 50 mg, 100 mg each t.a. oral; 20 mg treated for 8 weeks (n=181)
4. Multiple Ascending Dose study
   - Phase 1, single center, double-blind, randomized, placebo-controlled study
   - Healthy male subjects
   - Placebo, seladelpar 50 mg, 100 mg or 200 mg treated for 3 weeks (n=36)

CONCLUSION

Seladelpar results in profound anti-cholestatic and anti-inflammatory effects in PBC subjects with no drug-induced pruritus. Seladelpar targets key mechanisms at play in NASH and may constitute a backbone therapy. In both mice and humans, seladelpar was found to lower transaminases, reduce triglycerides and cholesterol, and to have favorable effects on glucose homeostasis. The anti-cholestatic activity was mediated by the decrease in bile acid synthesis as well as decreases in the absorption and synthesis of cholesterol, the precursor of bile acids. Evidence of regulation of fatty acid oxidation was also observed both preclinically (mitochondrial fatty acid oxidation genes) and clinically (metabolic analysis of acyl-carnitines). Reduction in hepatic and circulating lipids appeared associated with improvements seen preclinically in NASH pathology, fibrosis and features of dyslipidemic and diabetic inflammatory fatty liver disease. Specific evidence for effects on inflammation and fibrosis was obtained preclinically and is currently being confirmed in the clinic.

REFERENCES


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