ABSTRACT

BACKGROUND: Obeticholic acid (OCA), a potent Farnesoid X receptor (FXR) agonist, has demonstrated biochemical and clinical improvement in patients with primary biliary cirrhosis (PBC) in short-term and extension studies. This 2-year study evaluated the long-term safety and tolerability of OCA in patients with PBC. METHODS: Patients were randomized to 10 mg OCA daily (n=106), 20 mg OCA daily (n=100) or placebo (n=79). The primary endpoint was mean change in alkaline phosphatase (AP) from baseline at 12 months. RESULTS: The most common AE was pruritus: 22% of patients in the placebo group, 44% in 10 mg OCA group and 60% in 20 mg OCA group. Pruritus was transient in most patients. Although pruritus occurred in most patients, it was manageable in the majority of patients. Significant improvements in AP, GGT, AST, ALT were observed following 8 weeks of treatment. The mean change in ALP from baseline in the 10 mg (19%), 20 mg (23%) OCA groups were less than once daily dose allowed, if appropriate (pruritus). Study 202 LT: UDCA could be added, if appropriate. Safety assessments: 3 monthly and after dose titration. CONCLUSIONS: OCA: safe and tolerable in PBC patients. Significant improvements in AP, GGT, AST, ALT were observed following 8 weeks of therapy and >1 year of therapy. Although pruritus occurred in most patients, it was manageable in the majority of patients. Titration from 10 mg to 25 mg in selected patients is appropriate.

METHODS

• After 2 Phase II, double-blind, placebo-controlled, studies patients were enrolled in long-term (LT) extension trials.
• Most patients started at a dose of 10 mg daily
• Dose titration: up to 50 mg in 8 weeks based on safety and tolerability of OCA (AEs). Titration to less than once daily dose allowed, if appropriate (pruritus).
• Study 201 LT: UDCA could be added, if appropriate.
• Safety assessments: 3 monthly and after dose titration.
• Study 202 LT (addition to UDCA): discontinued after patients had completed ≥1 yr.
• Study 201 LT (monotherapy): ongoing data cut-off January 2012.
• Change from baseline evaluations: Wilcoxon signed rank test.

DISPOSITION

• 106 patients enrolled, female: x%.
• LT 202: n=78
• LT 201: n=28
• 84 (79%) patients completed 1 year dosing
• LT 202: n=61
• LT 201: n=23
• Doses: 3 - 60 mg daily equivalent
• LT 202 Mean Final Dose: 20 mg
• LT 201: 14 patients (60%) titrated to ≥ 20mg
• Discontinuations: 24 patients (23%) prematurely
• Pruritus: 13 patients, 12%
• Other AEs: 6 patients, 6%
• Other: 5 patients, 5%

SAFETY

• Pruritus, was the most common AE:
  - LT 202: x%
  - LT 201: y%
• Headache occurred in 32% of patients (LT 201) and all other AEs occurred in ≥21% of patients.
• 10 patients experienced 13 SAEs, all unlikely related to study drug: cystocele, atelectasis, uterine leiomyoma, vaginal prolapse, rib fracture, pneumonia, peripheral ischaemia, abdominal pain, bradycardia, uterine prolapse surgery, hip fracture vertigo, left pelvic fracture.

RESULTS

• Pruritus, was the most common AE:
  - LT 202: x%
  - LT 201: y%
• Headache occurred in 32% of patients (LT 201) and all other AEs occurred in ≥21% of patients.
• 10 patients experienced 13 SAEs, all unlikely related to study drug: cystocele, atelectasis, uterine leiomyoma, vaginal prolapse, rib fracture, pneumonia, peripheral ischaemia, abdominal pain, bradycardia, uterine prolapse surgery, hip fracture vertigo, left pelvic fracture.

REFERENCES

• Mason, A et al. Hepatology. 2010;52;No 4 (Abstract 75).

OBJECTIVES

Primary: Safety of OCA during long-term administration in PBC
Secondary: Efficacy of OCA on AP, and other liver enzymes during long-term administration
Effect of increasing doses of OCA on AP

CONCLUSIONS

• Long-term therapy with OCA appears to be safe and tolerable in PBC patients.
• Significant improvements in ALP, GGT, AST, and ALT were observed following 8 weeks of therapy and >1 year of therapy.
• Although pruritus occurred in most patients, it was manageable in the majority of patients.
• Titration from 10 mg to 25 mg in selected patients is appropriate.