Introduction

- Homozygous familial hypercholesterolemia (HoFH) is a rare inherited disorder characterized by elevated low-density lipoprotein cholesterol (LDL-C) levels and a high risk of early onset cardiovascular disease.

- Lomitapide is a novel, selective inhibitor of microsomal triglyceride transfer protein, indicated as an adjunct to a low-fat diet and other lipid-lowering treatments (with or without statins) to reduce LDL-C, total cholesterol, apolipoprotein B, and non-high-density lipoprotein cholesterol in patients with HoFH.

- Lomitapide metabolism is mainly hepatic with a mean terminal half-life of 20-23 hours.

- Lomitapide is a selective substrate of cytochrome P450 3A4 (CYP3A).

- Strong CYP3A4 inhibitors increase lomitapide exposure by approximately 22-fold.

- Concomitant use of lomitapide with strong or moderate CYP3A4 inhibitors is contraindicated.

- The extent of interaction between lomitapide and weak CYP3A4 inhibitors was investigated.

- Two Phase I studies were conducted to assess the potential impact on lomitapide exposure of weak CYP3A4 inhibitors coadministered alongside lomitapide.

- Both studies were designed to evaluate the effects of the weak CYP3A4 inhibitors atorvastatin and ethinyl estradiol/norgestimate on lomitapide pharmacokinetics in healthy subjects.

Objectives

- To assess the effect of atorvastatin (study 733-024) and the oral contraceptive EE/NGM (study 733-029), both weak CYP3A4 inhibitors, on the pharmacokinetics (PK) of lomitapide and its 2 primary metabolites, M1 and M3.

- To compare the effects of atorvastatin or EE/NGM on the PK of lomitapide and its 2 primary metabolites, M1 and M3, when administered simultaneously versus administered 12 hours apart.

Methods

Study Design

- Both studies were open-label, randomized, 2-arm, 2-period drug interaction studies that followed the same design (Figure 1).

- In Arm 1, administration of the weak CYP3A4 inhibitor and lomitapide was simultaneous.

- In Arm 2, administration of the weak CYP3A4 inhibitor and lomitapide was staggered (separated by an interval of 12 hours).

- Atorvastatin study (733-024):

- Subjects were healthy, male or female adults (18-50 years old), body mass index (BMI) range of 18.5 to 32.0 kg/m².

- Subjects were confined to the Clinical Research Unit from Day -1 until study completion on Day 22.

- EE/NGM study (733-029): Subjects were healthy, female, non-smoking adults (18-40 years old), BMI range of 18.5 to 32.0 kg/m².

- Subjects were confined to the Clinical Research Unit from Day 1 through Day 8 and from Day 21 to study completion.

Results

- In both studies, subjects received a low-fat diet, supplying <10% of calories from fat, on the day prior to lomitapide dosing, on the day of lomitapide dosing and for 2 days after each lomitapide dose.

- Treatment sequence:

  - Lomitapide: 20 mg per dose (4 hours after the evening meal followed by a 2-hour fast from food).

  - Atorvastatin: 80 mg per dose.

  - EE/NGM: 0.35 mg per dose.

- Pharmacokinetic Analysis:

  - Plasma concentrations of lomitapide and its metabolites (M1 and M3) were determined using validated liquid chromatography/mass spectrometry (LC/MS).

  - Pharmacokinetic parameters determined from plasma concentrations-timecourse data were calculated, including:

    - Area under the plasma concentration-time curve extrapolated to infinity (AUC∞).

    - Maximum observed plasma concentration (Cmax).

    - Time of maximum observed plasma concentration (tmax).

    - Terminal elimination half-life (t½).

- Pharmacokinetic parameters were calculated from plasma concentrations-timecurve data using a mixed effects analysis of variance (ANOVA) model.

- The incidence of AEs was increased following simultaneous coadministration of lomitapide with atorvastatin.

- The incidence of AEs was increased following simultaneous coadministration of lomitapide with EE/NGM.

Safety

- The proportion of subjects experiencing gastrointestinal AEs was lower with lomitapide alone (9 [56.3%] subjects vs 2 [12.5%] subjects).

- The incidence of all AEs was increased following simultaneous coadministration of lomitapide with atorvastatin compared with lomitapide alone (9 [56.3%] subjects vs 2 [12.5%] subjects).

- All AEs were mild.

- No clinically significant findings in laboratory assessments, ECGs, or physical examinations were observed.

- No apparent skeletal muscle effects such as rhabdomyolysis were observed.

Conclusions

- Simultaneous dosing of the weak CYP3A4 inhibitors atorvastatin with lomitapide approximately doubled lomitapide exposure and increased the incidence of AEs.

- Staggered dosing of atorvastatin with lomitapide resulted in only modest (1.3-6 fold) increased lomitapide levels and no increase in AEs.

- No clinically relevant lomitapide exposure change was seen with EE/NGM.

- The incidence of AEs was increased following simultaneous coadministration of lomitapide with EE/NGM.

- Gastrointestinal AEs, mostly diarrhea, were the most common AEs.

- The incidence of all AEs was increased following simultaneous coadministration of lomitapide with atorvastatin compared with lomitapide alone (9 [56.3%] subjects vs 2 [12.5%] subjects).

- All AEs were mild.

- No clinically significant findings in laboratory assessments, ECGs, or physical examinations were observed.

- No apparent skeletal muscle effects such as rhabdomyolysis were observed.

References


