Effect of Steady-State Esuberaprost (BPS-314d-MR) on the Safety, Pharmacokinetics and Pharmacodynamics of Warfarin in Healthy Adult Subjects

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Introduction

The prostacyclin analogue beraprost (BPS) consists of a mixture of 4 stereoisomers and is available for treatment of PAH in Japan and other Asian countries. The pharmacologically active isomer esuberaprost (BPS-314d-MR) exerts its pharmacologic actions by specifically binding to PG2 receptors on smooth muscle, vascular endothelium, and platelets. This leads to vasodilatation, inhibition of platelet aggregation, and anticoagulation. Esuberaprost is undergoing clinical evaluation in an ongoing Phase 3 study in USA and isla.

Warfarin is administered as a racemic mixture of (R)- and (S)-enantiomers and is completely absorbed after oral administration, with peak concentration generally attained within the first 4 hours. The anticoagulant effect of warfarin generally occurs within 24 hours after drug administration. However, the peak anticoagulant effect may be delayed up to 72 to 96 hours. The duration of action of a single dose of racemic warfarin is 2 to 5 days. Since multiple CYP enzymes are involved in the metabolism of warfarin, and also due to its narrow therapeutic index, other concomitant therapies can cause an increased risk of bleeding or clotting by potentiating warfarin’s activity.

Methods

This study was a single-center, open-label, fixed-sequence, PK and PD drug-drug interaction study of the coadministration of 4 times daily (QID) doses of 30 μg QID BPS-314d-MR with a single dose of 25 mg warfarin. Healthy male or female subjects, aged between 18 and 75 years, inclusive, and with a body mass index between 18.5 and 32.0 kg/m², inclusive, were selected for the study.

Serial blood samples for the determination of warfarin PK and PD (prothrombin time [PT], activated partial thromboplastin time [aPTT], and international normalized ratio [INR]) were collected predose and at each postdose blood collection time point through 168 hours after each dose of warfarin. Blood samples for the determination of BPS-314d PK were collected on Days 14, 15, and 16. A schematic of the study design is presented in Table 1 below.

Results

A total of 18 subjects were enrolled into the study, of which 13 subjects completed the study. Four subjects were withdrawn due to drug-related AEs (all of which were skin reactions such as pruritus or rash) and 1 subject had dosing stopped due to physician decision. The withdrawn subjects were not replaced.

The mean subject age was 38, with 8 (44%) males and 10 (56%) females. 11 (61%) subjects were white, 6 (33%) were Black or African American and 1 was Other (6%); the mean weight was 75.5 kg with a BMI of 26.8.

Pharmacokinetics of Warfarin

▶ There were no statistically significant differences in the single-dose PK parameters of (R)- or (S)-warfarin following coadministration of 25 mg warfarin with 30 μg QID BPS-314d-MR at steady state compared with 25 mg warfarin administered alone (Tables 2-5, Figures 1-2).

▶ Systemically available warfarin is slowly absorbed and eliminated with a half-life (t½) of 2 to 5 days. Since multiple CYP enzymes are involved in the metabolism of warfarin, and also due to its narrow therapeutic index, other concomitant therapies can cause an increased risk of bleeding or clotting by potentiating warfarin’s activity.

Safety

▶ Overall, 77.8% of subjects reported TEAEs of any causality during the study, with 55.6% of subjects reporting TEAEs that were considered to be related or possibly related to BPS-314d-MR alone or with warfarin.

▶ There were no statistically significant differences in the single-dose PK parameters of (R)- or (S)-warfarin following coadministration of 25 mg warfarin with 30 μg QID BPS-314d-MR at steady state compared with 25 mg warfarin administered alone (Tables 2-5, Figures 1-2).

▶ The PD parameters AUCPTT, AUCaPT and aPTTmax were similar following administration of 25 mg warfarin alone or coadministered with 30 μg QID BPS-314d-MR at steady state (Table 6).

▶ A statistically significant interaction effect of steady-state BPS-314d-MR on the PTmax and INRmax was observed when warfarin was coadministered with BPS-314d-MR compared with warfarin administered alone, but this difference was not considered to be clinically significant. Despite the apparent difference between treatments, the geometric mean PTmax and INRmax values following coadministration of BPS-314d-MR with warfarin were within the range of individual values observed following administration of warfarin alone (Table 7).

Conclusions

These results demonstrate that PK and PD parameters for warfarin are not adversely affected by co-administration of esuberaprost and that dose adjustments for their concurrent use are not warranted.

Disclosure

This Phase 1 study was sponsored by Lung Biotechnology and was performed under Contract. At the time of publication, authors were either employees of Contract organizations or Lung Biotechnology.