A Comparison of Safety and Pharmacokinetics of Esuberaprost (BPS-314*d*-MR) in Subjects with Normal, Mild and Moderate Hepatic Impairment

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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-314*d*) exerts its pharmacologic actions by specifically binding to PGI2 receptors on smooth muscle, vascular endothelium, and platelets. This leads to vasodilatation, inhibition of platelet aggregation, and antiproliferation. Esuberaprost is undergoing clinical evaluation in an ongoing Phase 3 study in USA and Israel.

To date, no clinical investigations have been conducted with BPS in subjects with hepatic impairment. This study investigated the PK and safety of BPS-314*d*-MR tablets in subjects with Child-Pugh Class A or B hepatic impairment, in comparison to subjects with normal hepatic function. Evaluating the effect of different degrees of hepatic impairment on BPS-314*d* pharmacokinetics (PK) is important to be able to establish dosing parameters for BPS-314*d*-MR in patients with pulmonary hypertension, who may have compromised hepatic function.

Methods

This was an open-label, nonrandomized, multi-center, multiple-dose, parallel-group, safety, tolerability, and PK study in subjects with normal, Child-Pugh Class A (mild), and B (moderate) hepatic impairment. Subjects in Child-Pugh Class C (severe) were not enrolled after an interim PK and safety analysis of the other groups. Demographics of subjects with moderate impairment were matched with normal subjects for age (± 10 years), body weight (± 20%), smoking status, and gender. One 15-µg tablet of esuberaprost was administered orally 4 times daily (QID) during waking hours on Days 1 through 4. Standard safety and PK parameters were analyzed.

Results

A total of 30 subjects were enrolled in the study. All enrolled patients completed the study and no serious adverse events (SAEs) were reported. Patient demographics are shown in Table 1.

Safety

- BPS-314*d*-MR was well tolerated when administered as QID doses of 15 µg for 4 days to subjects with normal hepatic function and subjects with mild or moderate hepatic impairment.
- There were no SAEs or withdrawals due to TEAEs.
- Overall, 14 subjects (46.7%) reported a total of 27 TEAEs. The majority (43.3%) of TEAEs were mild and 3 were moderate TEAEs (muscle spasms, headache, and nausea).
- The type and incidence of TEAEs was similar in subjects across all groups: normal hepatic function (4 subjects: 3 with mild TEAEs, 1 with moderate TEAE), mild hepatic impairment (5 subjects: 5 with mild TEAEs) and moderate hepatic impairment (5 subjects: 5 with mild TEAEs, 1 with moderate TEAE).
- Overall, 13 subjects (43.3%) reported 25 TEAEs that were considered by the Investigator to be related or possibly related to study drug.
- No clinically significant changes or findings were noted in clinical laboratory evaluations, vital sign measurements, ECGs or physical examinations.

Pharmacokinetics

- The arithmetic mean plasma concentration profiles are shown in Figure 1.
- In comparison to subjects with normal hepatic function, BPS-314*d* had an approximately 2.2-fold increase in $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, and maximum C_{max} in subjects with moderate hepatic impairment and an approximately 1.1-fold increase in $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, and maximum C_{max} in subjects with mild hepatic impairment.
- In comparison to subjects with normal hepatic function, BPS-314d had an approximately 7% and 54% decrease in CL/F for subjects with mild and moderate hepatic impairment.
- In comparison to subjects with normal hepatic function, BPS-314*d* had an approximately 58% shorter $t_{1/2}$ for subjects with mild and moderate hepatic impairment, respectively.
- AUCs over the 4 intervals (0 to 4, 4 to 8, 8 to 12 and 12 to 24 hours) had approximately 1.8-, 2.2-, 1.6- and 2.4-fold increases, respectively, in subjects with moderate hepatic impairment compared to subjects with normal hepatic function. In subjects with mild hepatic impairment, there was an approximately 13% decrease and approximately 1.2-, 1.0- and 1.1-fold increase, respectively, compared to subjects with normal hepatic function (data not shown).
- The C_{max} values over the 4 intervals (0 to 4, 4 to 8, 8 to 12 and 12 to 24 hours) had approximately 2.0-, 2.0-, 1.5- and 2.7-fold increases, respectively, in subjects with moderate hepatic impairment compared to subjects with normal hepatic function. In subjects with mild hepatic impairment, there was an approximately 1.0- and 1.1-fold increase, 8% decrease and 1.4-fold increase, respectively, compared to subjects with normal hepatic function (data not shown).
- BPS-314*d* concentrations decreased to the lower limit of quantitation by approximately 24 hours after the first dose on Day 4 in the subjects with normal hepatic function and subjects with mild hepatic impairment and approximately 36 hours after the first dose on Day 4 in subjects with moderate hepatic impairment (data not shown).

Conclusions

Based on the PK and safety results of this study, esuberaprost should be titrated upwards with caution in subjects with hepatic impairment under the careful supervision of a qualified physician.

Disclosure

This Phase 1 study was sponsored by Lung Biotechnology and was performed under Contract. Authors are either employees of Contract organizations or Lung Biotechnology.

Table 1. Patient Demographics

		Normal (Control)[a] (N = 10)	Mild (N = 10)	Moderate (N = 10)	Overall (N = 30)
Age (years)	Mean (SD)	56 (7.7)	54 (4.8)	56 (6.0)	55 (6.1)
Sex (n [%])	Male	6 (60.0%)	7 (70.0%)	6 (60.0%)	19 (63.3%)
	Female	4 (40.0%)	3 (30.0%)	4 (40.0%)	11 (36.7%)
Race (n [%])	White	8 (80.0%)	7 (70.0%)	9 (90.0%)	24 (80.0%)
	Black or African American	2 (20.0%)	2 (20.0%)	1 (10.0%)	5 (16.7%)
	Asian	---	1 (10.0%)	---	1 (3.3%)
Weight (kg)	Mean (SD)	79.6 (18.91)	86.7 (20.41)	80.8 (20.14)	82.3 (19.39)
BMI (kg/m²)	Mean (SD)	28.3 (4.09)	28.6 (5.22)	29.9 (6.06)	28.9 (5.05)

BMI = body mass index; **n** = number of observations; **N** = number of subjects; **SD** = standard deviation;

HEPATIC GROUPS: Normal (control) = subjects with normal hepatic function (control) matched to subjects with moderate hepatic impairment; **Mild** = subjects with mild hepatic impairment (Child-Pugh A); **Moderate** = subjects with moderate hepatic impairment (Child-Pugh B).

[a] The demographics of the subjects with normal hepatic function were matched with those of the subjects with moderate hepatic impairment with respect to age (± 10 years), body weight (± 20%), smoking status, and sex.

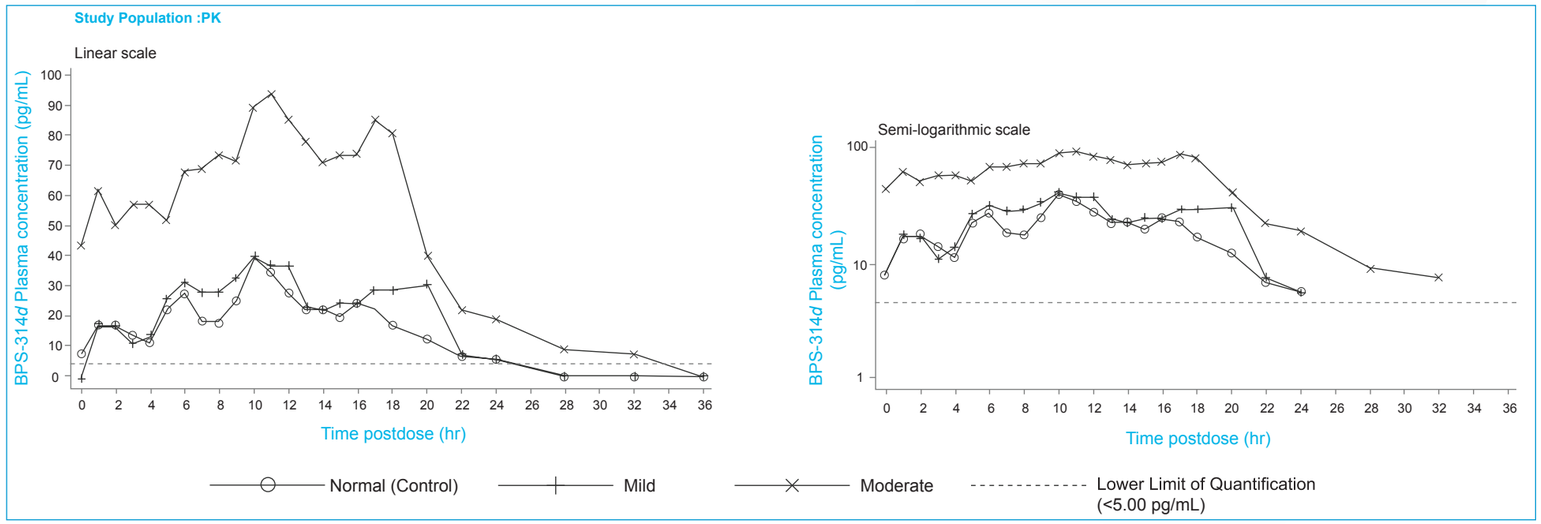

Figure 1. Arithmetic mean plasma concentration profiles of BPS-314d.

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