Effect of Steady-State Esuberaprost (BPS-314*d*-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-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.

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 therpeutic index, other concomitant therapies can cause an increased risk of bleeding or clotting by potentiating the anticoagulation properties of warfarin. Notably, drugs that inhibit platelet activation, such as prostacylins can amplify the bleeding risks associated with warfarin. Therefore, a drug-drug interaction study was conducted to determine the potential effects of BPS-314*d*-MR tablets on warfarin pharmacokinetics.

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 BPS-314*d*-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/m^2, 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 through 168 hours after each dose of warfarin. Blood samples for the determination of BPS-314*d* 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 rashes) 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-314*d*-MR at steady state compared with 25 mg warfarin administered alone (Tables 2-5, Figures 1-2).
- The PD parameters AUC_{aPTT}, AUC_{INR}, AUC_{PT}, and $aPTT_{max}$ were similar following administration of 25 mg warfarin alone or coadministered with 30 µg QID BPS-314*d*-MR at steady state (Table 6).
- A statistically significant interaction effect of steady-state BPS-314*d*-MR on the PT_{max} and INR_{max} was observed when warfarin was coadministered with BPS-314*d*-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 PT_{max} and INR_{max} values following coadministration of warfarin with BPS-314*d*-MR were within the range of individual values observed following administration of warfarin alone (Table 7).
- Following multiple doses of 15 µg QID BPS-314*d*-MR for 4 days followed by 30 µg QID BPS-314*d*-MR, steady state had been reached by the fourth day of 30 µg BPS-314*d*-MR administration (data not shown).

Safety

- Overall, 77.8% of subjects reported TEAEs of any causality during the study, with 55.6% of subjects reporting TEAEs that were considered by the investigator to be related or possibly related to BPS-314*d*-MR alone or with warfarin.
- No SAEs were reported during the study.
- Most TEAEs (drug-related or all causalities) occurred during dosing with BPS-314*d*-MR alone, most commonly on the first day of dosing at 15 µg QID (Day 9).
- No drug-related TEAEs were reported during the warfarin only treatment period and 2 drug-related TEAEs were reported during the warfarin coadministered with BPS-314*d*-MR treatment period.
- All TEAEs were mild in severity, except for a single moderate-severity TEAE of syncope that was not considered to be related to warfarin with BPS-314*d*-MR.
- The most commonly reported TEAEs (all causalities) were headache and pruritus, while the most commonly reported drug-related TEAEs were headache, pruritus and papular rash.
- Four subjects were withdrawn from the study due to TEAEs that were considered to be related or possibly related to study drug and occurred during dosing with BPS-314*d*-MR alone. All 4 of these subjects were withdrawn before receiving the second dose of warfarin (Day 17).

Conclusions

These study 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 is 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.

Table 1. Schematic of Study Design

		Run-in Period			Period 2			
Screening	Check- in	Period 1 Day 1	Days 9 to 12	Days 13 to 16	Day 17	Day 18 to 23	Day 24	Follow- up
Days -28 to -1	Day -1	single dose of warfarin (25 mg, alone)	BPS-314*d*-MR (15 µg, QID)	BPS-314*d*-MR (30 µg, QID)	coadmin-istration of a single dose of warfarin (25 mg) and BPS-314*d*-MR (30 µg, QID)	BPS-314*d*-MR (30 µg, QID)	discharge[a]	Day 33 ± 2

ABBREVIATIONS: MR = modified release; **QID** = 4 times daily.
[a] Subjects were discharged on Day 24 if international normalized ratio (INR) results were within normal range (or results were outside the normal range but deemed not clinically significant by the Investigator).

Table 2. Summary of PK Parameters of (R)-Warfarin

	GEOMETRIC MEAN (CV%)	
Parameter (Units)	25 mg Warfarin Alone (N=18)	25 mg Warfarin + 30 µg QID BPS-314*d*-MR (N=14*)
C_{max} (ng/mL)	1760 (23.5)	1630 (20.8)
t_{max}[a] (hr)	1.00 (0.500-4.00)	1.00 (0.500-7.83)
AUC_{0-t} (ng·hr/mL)	80900 (20.4)	79700 (26.6)
AUC_{0-168} (ng·hr/mL)	80900 (20.4)	79600 (26.6)
$AUC_{0-\infty}$ (ng·hr/mL)	90000 (25.4)	89500 (32.7)
$t_{½}$ (hr)	48.9 (24.4)	49.8 (25.6)

ABBREVIATIONS: AUC_{0-168} = area under the concentration-time curve (AUC) from Hour 0 to 168 hours postdose; $AUC_{0-\infty}$ = AUC extrapolated to infinity; AUC_{0-t} = AUC from Hour 0 to the last measurable concentration; C_{max} = maximum observed plasma concentration; **CV%** = coefficient of variation; **MR** = modified release; **N** = number of subjects; **QID** = 4 times daily; $t_{½}$ = apparent terminal elimination half-life; t_{max} = time to maximum observed plasma concentration
[a] Median (min-max).
* Note: Subject 0104 was withdrawn by Investigator decision after completing Period 1 and 4 doses of Period 2; therefore, this subject was included in the PK and PD analyses.

Table 3. Statistical Analysis of the PK Parameters of (R)-Warfarin

	25 mg Warfarin + 30 µg QID BPS-314*d*-MR (Test)		25 mg Warfarin Alone (Reference)		Test/Reference[b]	90% CI[c]
Parameter (Units)	n	LS Mean[a]	n	LS Mean[a]	(%)	(%)
C_{max} (ng/mL)	14	1641	18	1760	93.2	(84.8, 102.4)
AUC_{0-t} (ng·hr/mL)	14	81380	18	80914	100.6	(97.1, 104.1)
$AUC_{0-\infty}$ (ng·hr/mL)	14	91182	18	89993	101.3	(97.9, 104.9)

	n	Median	n	Median	Test/Reference[b]	90% CI[c] (%)	p-Value[f]
$t_{½}$ (hr)	14	1.00	14	1.00	0.25	(-0.25, 0.75)	0.3574

ABBREVIATIONS: $AUC_{0-\infty}$ = area under the concentration-time curve (AUC) extrapolated to infinity; AUC_{0-t} = AUC from Hour 0 to the last measurable concentration; **ANOVA** = analysis of variance; **CI** = confidence interval; C_{max} = maximum observed plasma concentration; **LS** = least squares; **MR** = modified release; **n** = number of observations; **QID** = 4 times daily; t_{max} = time to maximum observed plasma concentration
[a] Least squares means for AUCs and C_{max} from ANOVA, calculated by transforming the natural log means back to the linear scale (ie, geometric LS means).
[b] Ratio of LS means for natural log-transformed AUCs and C_{max} (expressed as a percentage), natural log transformed back to the linear scale.
[c] 90% CI for ratio of LS means of natural log-transformed AUCs and C_{max} (expressed as a percentage), natural log transformed back to the linear scale.
[d] Median difference between the test and reference treatments.
[e] 90% CI of median difference between the test and reference treatments.
[f] From Wilcoxon signed-rank test of t_{max}.

Table 4. Summary of PK Parameters of (S)-Warfarin

	GEOMETRIC MEAN (CV%)	
Parameter (Units)	25 mg Warfarin Alone (N=18)	25 mg Warfarin + 30 µg QID BPS-314*d*-MR (N=14*)
C_{max} (ng/mL)	1820 (23.8)	1650 (21.5)
t_{max}[a] (hr)	1.00 (0.500-4.00)	1.00 (0.500-3.83)
AUC_{0-t} (ng·hr/mL)	53200 (23.5)	52500 (31.5)
AUC_{0-168} (ng·hr/mL)	53200 (23.5)	55200 (35.1)
$AUC_{0-\infty}$ (ng·hr/mL)	55600 (26.8)	55200 (35.1)
$t_{½}$ (hr)	37.2 (21.5)	37.2 (25.7)

ABBREVIATIONS: AUC_{0-168} = area under the concentration-time curve (AUC) from Hour 0 to 168 hours postdose; $AUC_{0-\infty}$ = AUC extrapolated to infinity; AUC_{0-t} = AUC from Hour 0 to the last measurable concentration; C_{max} = maximum observed plasma concentration; **CV%** = coefficient of variation; **MR** = modified release; **N** = number of subjects; **QID** = 4 times daily; $t_{½}$ = apparent terminal elimination half-life; t_{max} = time to maximum observed plasma concentration.
[a] Median (min-max).

Table 5. Statistical Analysis of the PK Parameters of (S)-Warfarin

	25 mg Warfarin + 30 µg QID BPS-314*d*-MR (Test)		25 mg Warfarin Alone (Reference)		Test/Reference[b]	90% CI[c]
Parameter (Units)	n	LS Mean[a]	n	LS Mean[a]	(%)	(%)
C_{max} (ng/mL)	14	1653	18	1823	90.7	(81.8, 100.6)
AUC_{0-t} (ng·hr/mL)	14	52698	18	53175	99.1	(94.8, 103.6)
$AUC_{0-\infty}$ (ng·hr/mL)	14	55186	18	55584	99.3	(95.0, 103.8)

	n	Median	n	Median	Test/Reference[b]	90% CI[c] (%)	p-Value[f]
$t_{½}$ (hr)	14	1.00	14	1.00	0.25	(-0.25, 0.75)	0.3789

ABBREVIATIONS: $AUC_{0-\infty}$ = area under the concentration-time curve (AUC) extrapolated to infinity; AUC_{0-t} = AUC from Hour 0 to the last measurable concentration; **ANOVA** = analysis of variance; **CI** = confidence interval; C_{max} = maximum observed plasma concentration; **LS** = least squares; **MR** = modified release; **n** = number of observations; **QID** = 4 times daily; t_{max} = time to maximum observed plasma concentration
[a] Least squares means for AUCs and C_{max} from ANOVA, calculated by transforming the natural log means back to the linear scale (ie, geometric LS means).
[b] Ratio of LS means for natural log-transformed AUCs and C_{max} (expressed as a percentage), natural log transformed back to the linear scale.
[c] 90% CI for ratio of LS means of natural log-transformed AUCs and C_{max} (expressed as a percentage), natural log transformed back to the linear scale.
[d] Median difference between the test and reference treatments.
[e] 90% CI of median difference between the test and reference treatments.
[f] From Wilcoxon signed-rank test of t_{max}.

Table 6. Summary of PK Parameters Following Administration of Warfarin Alone or Coadministered with BPS-314*d*-MR

	GEOMETRIC MEAN (CV%)	
Parameter (Units)	25 mg Warfarin Alone (N=18)	25 mg Warfarin + 30 µg QID BPS-314*d*-MR (N=14)
PT_{max} (s)	20.9 (23.5) [15.4 – 30.8]	16.4 (19.1) [12.7 – 22.5]
AUC_{PT} (s·hr)	2390 (13.0) [2010 – 3080]	2150 (8.8) [1870 – 2530]
$aPTT_{max}$ (s)	32.3 (8.4) [28.0 – 38.7]	31.9 (6.1) [29.3 – 37.1]
$AUCa_{PTT}$ (s·hr)	5000 (7.3) [4340 – 5750]	4840 (5.5) [4320 – 5290]
INR_{max} (1)	1.91 (22.9) [1.40 – 2.80]	1.51 (18.5) [1.20 – 2.10]
AUC_{INR} (hr)	224 (12.5) [188 – 284]	202 (8.7) [175 – 238]

ABBREVIATIONS: **$aPTT_{max}$** = maximum activated partial thromboplastin time (aPTT) observed; **$AUCa_{PTT}$**= area under the aPTT versus time curve from Hour 0 to 168 hours postdose; **AUC_{INR}** = area under the International Normalized Ratio (INR) versus time curve from Hour 0 to 168 hours postdose; **AUC_{PT}** = area under the prothrombin time (PT) versus time curve from Hour 0 to 168 hours postdose; **CV%** = coefficient of variation; **INR_{max}** = maximum INR observed; **MR** = modified release; **N** = number of subjects; **PT_{max}** = maximum PT observed; **QID** = 4 times daily.

Table 7. Statistical Analysis of the PK Parameters Following Administration of Warfarin Alone or Coadministered with BPS-314d-MR

	25 mg Warfarin + 30 µg QID BPS-314*d*-MR (Test)		25 mg Warfarin Alone (Reference)		Test/Reference[b]	90% CI[c]
Parameter (Units)	n	LS Mean[a]	n	LS Mean[a]	(%)	(%)
PT_{max} (s)	14	16.9	18	20.9	80.8	(76.7, 85.1)
AUC_{PT} (s·hr)	14	2182	18	2389	91.3	(89.4, 93.3)
$aPTT_{max}$ (s)	14	32.5	18	32.3	100.6	(99.3, 101.9)
$AUCa_{PTT}$ (s·hr)	14	4905	18	4999	98.1	(97.4, 98.8)
INR_{max} (1)	14	1.55	18	1.91	81.3	(77.1, 85.8)
AUC_{INR} (hr)	14	204	18	224	91.4	(89.5, 93.3)

ABBREVIATIONS: **ANOVA** = analysis of variance; **$aPTT_{max}$** = maximum activated partial thromboplastin time (aPTT) observed; **$AUCa_{PTT}$** = area under the aPTT versus time curve from Hour 0 to 168 hours postdose; **AUC_{INR}** = area under the International Normalized Ratio (INR) versus time curve from Hour 0 to 168 hours postdose; **AUC_{PT}** = area under the prothrombin time (PT) versus time curve from Hour 0 to 168 hours postdose; **CI** = confidence interval; **INR_{max}** = maximum INR observed; **LS** = least squares; **MR** = modified release; **n** = number of observations; **PT_{max}** = maximum PT observed; **QID** = 4 times daily.
[a] Least squares means for pharmacodynamic parameters from ANOVA, calculated by transforming the natural log means back to the linear scale (ie, geometric LS means).
[b] Ratio of LS means for natural log-transformed parameters (expressed as a percentage); natural log transformed back to the linear scale.
[c] 90% CI for ratio of LS means of natural log-transformed parameters (expressed as a percentage); natural log transformed back to the linear scale.

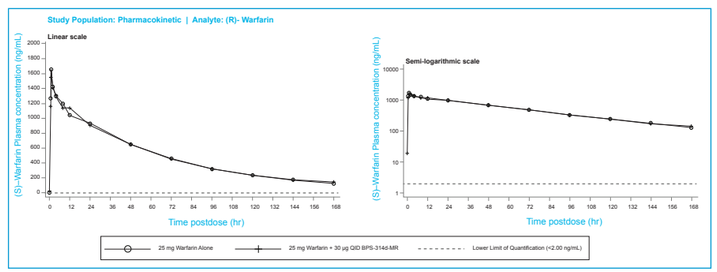

Figure 1. Arithmetic mean plasma concentration profiles of (R)-warfarin.

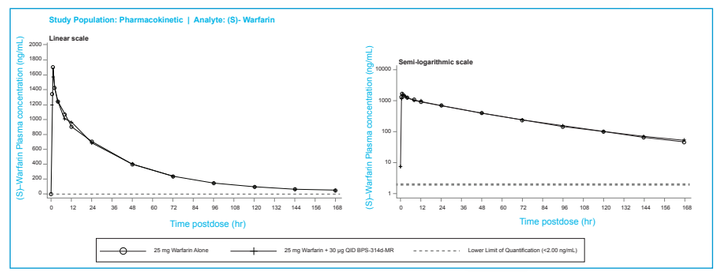

Figure 2. Arithmetic mean plasma concentration profiles of (S)-warfarin.

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