PP192—PHARMACOKINETICS OF SELEXIPAG IN SUBJECTS WITH SEVERE RENAL IMPAIRMENT COMPARED WITH HEALTHY SUBJECTS

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Introduction: Selexipag is a new prostacyclin receptor agonist, which is being investigated in Phase III studies for the treatment of pulmonary arterial hypertension (PAH). Renal function impairment can alter the disposition of a large number of drugs and since PAH patients may have impaired renal function, the aim of this study was to assess how severe renal function impairment (SRFI) may affect the pharmacokinetics (PK), safety, and tolerability of selexipag and its active metabolite (ACT-333679).

Patients (or Materials) and Methods: Sixteen subjects were enrolled in this 2-group Phase I study. Groups A and B were composed of 8 subjects with SRFI and 8 healthy subjects, respectively. Subjects in Group B were matching with those in Group A, based on age, sex, race, and body mass index. Subjects received a single oral dose of 400 µg selexipag and were monitored for 144 h (Group A) or 72 h (Group B). PK samples were analyzed by liquid chromatography coupled to tandem mass spectrometry. PK parameters of selexipag and ACT-333679 were explored using ratios of geometric means and their 90% CIs.

Results: PK results (geometric mean (95% CI)) are presented in the table below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax1 [ng/mL]</td>
<td>5.4 (3.9–7.4)</td>
<td>7.3 (6.1–8.7)</td>
</tr>
<tr>
<td>Tmax2 [h]</td>
<td>2.0 (1.0–5.0)</td>
<td>4.0 (1.5–6.0)</td>
</tr>
<tr>
<td>Cmax3/2 [h]</td>
<td>1.0 (0.7–1.5)</td>
<td>13.4 (7.1–25.4)</td>
</tr>
<tr>
<td>AUC0–∞4 [ng*h/mL]</td>
<td>171.3 (13.4–21.6)</td>
<td>70.6 (29.3–170.3)</td>
</tr>
</tbody>
</table>

*peak concentration, 1time to reach Cmax, median (range), 2tertiary half-life, 3exposure from 0 to ↔.

No relevant differences in plasma protein binding of selexipag and ACT-333679 were observed between both groups. Five subjects reported 17 adverse events (AEs): 8 in Group A, 9 in Group B. Headache was the most frequently reported AE in both groups. No deaths or serious adverse events were reported.

Conclusion: Selexipag 400 µg was generally well tolerated in all subjects. Compared with healthy subjects, a 1.7-fold increase in Cmax and AUC to selexipag was observed between subjects with SRFI. Similar results were obtained for ACT-333679, i.e., a 1.4-fold increase in Cmax and an approximately 1.7-fold increase in AUC in subjects with SRFI compared with healthy subjects.

Disclosure of Interest: None declared.

PP193—SIMULTANEOUS LC-MS/MS QUANTIFICATION OF P-GLYCOPROTEIN AND CYTOCHROME P450 PROBE SUBSTANCES AND THEIR METABOLITES IN DRIED BLOOD SPOTS

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Introduction: Modifications in cytochrome P450 (CYP) and/or transporter activities (such as P-glycoprotein [P-gp]) can result in important pharmacokinetic variability and are the underlying mechanism of many drug–drug interactions. CYP and P-gp activity can be assessed by the in vivo administration of a cocktail of probe drugs each of which is metabolized by 1 specific cytochrome or transported by P-gp.

Patients (or Materials) and Methods: In this study, a single HPLC-MS/MS method has been developed for the simultaneous quantification of P-gp (fexofenadine) and CYP probe substrates (caffeine for CYP1A2, bupropion for CYP2B6, flurbiprofen for CYP2C9, omeprazole for CYP2C19, dextromethorphan for CYP2D6 and midazolam for CYP3A4), and their metabolites in dried blood spots (DBS). Substances were extracted from DBS (10 µL) using methanol. DBS analysis was performed using a LC-MS/MS system consisting of a 5500QTrap® triple quadrupole linear ion trap (QqQLT) mass spectrometer equipped with a Turbolon SprayTM interface and an Ultimate 3000 RS instrument as LC system.

Results: The method was validated according to international criteria. The intermediate precision was <10% and the accuracy was in the interval (92.2%–111.1%) for all substances and all concentrations tested. A linear response was observed for the following concentration ranges: 1 to 200 ng/mL for bupropion, hydroxybupropion, and fexofenadine; 0.1 to 100 ng/mL for midazolam; 0.2 to 200 ng/mL for omeprazole, hydroxyomeprazole, hydroxymidazolam, and dextromethorphan; 0.5 to 500 ng/mL for dextropirazone; 50 to 10,000 ng/mL for caffeine and paraxanthine; 50 to 2500 ng/mL for flurbiprofen and 5 to 1000 ng/mL for hydroxyflurbiprofen. All substances were stable in DBS stored at room temperature for at least 15 days. The method has been successfully applied to a pharmacokinetic study where healthy male volunteers have received a low-dose cocktail of the here described P-gp and CYP probe substances. Metabolic ratios were determined for all CYP probe drugs and a good correlation was observed when drug concentrations in capillary DBS samples were compared with venous plasma samples.

Conclusion: DBS is a suitable sampling method for cytochromes and P-glycoprotein phenotyping.

Disclosure of Interest: None declared.

PP194—PHARMACOKINETICS OF SELEXIPAG IN SUBJECTS WITH MILD, MODERATE, OR SEVERE HEPATIC IMPAIRMENT COMPARED WITH HEALTHY SUBJECTS

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Introduction: Selexipag is a new prostacyclin receptor agonist, which is being investigated in Phase III trials for the treatment of pulmonary arterial hypertension (PAH). Selexipag is eliminated for >90% by the liver and because PAH patients may suffer from liver impairment, the aim of this study was to assess how different degrees of liver impairment may affect the pharmacokinetics (PK), safety, and tolerability of selexipag and its active metabolite (ACT-333679).

Patients (or Materials) and Methods: Twenty-six subjects were enrolled in this 4-group Phase I study. Group A, B, C, and D were composed of 8 subjects with mild liver impairment, 8 subjects with moderate liver impairment, 2 subjects with severe liver impairment, and 8 healthy subjects, respectively. Subjects of Group D were matching with those of Group B, based on age, sex, body weight, and height. Subjects received a single oral dose of selexipag (400 µg for