HEPATIC IMPAIRMENT STUDIES IN EARLY DEVELOPMENT SERVICES:
INNOVATIVE PATIENT PHARMACOLOGY MODELS FOR PHASE I-IIa SUPPORT

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EXECUTIVE SUMMARY: Early Phase Hepatic Impairment Trials

PRA Health Sciences’ Early Development Services (EDS) has established a group of experts dedicated to early phase patient studies. Our innovative Patient Pharmacology Services (PPS) features a unique scientific/medical and operational model that enables us to conduct studies in patients with hepatic impairment following the same processes and guidelines that we apply to traditional Phase I or Phase IIa trials. This approach has demonstrated proven advantages compared to the standard monitor-based site management model and results in the delivery of faster and better patient pharmacology data to our clients. Having more than 20 years of experience and over 50 studies performed in this special area, we know how to do the job and, even better, we will do it for you in the shortest possible timeframe. When you select PRA to conduct your hepatic impairment trial, you can expect short timelines, dedicated and experienced staff, and the highest-quality data.
PRA’s Innovative Patient Pharmacology Services

It is recommended to have hepatic impairment trials conducted relatively early in the clinical development process, because the outcome may influence the patient population as well as the inclusion and exclusion criteria of Phase II and III trials. The timing of these trials is generally before or in parallel with Phase II.

BACKGROUND

Most small molecules are eliminated either through renal or hepatic excretion. They are metabolized in the liver and then excreted renally. A renal and/or hepatic impairment trial is generally conducted as part of the clinical development of a drug and requested by the FDA and the EMA.

The hepatic impairment trial’s objectives are to:

• Assess the influence of hepatic impairment on the drug’s pharmacokinetics (PKs) and metabolites
• Allow recommendations for dose adaptations in hepatically impaired patients
• Evaluate the safety and tolerability of the study drug in this vulnerable, special population

All hepatically impaired trial protocols designed by PRA will follow FDA and EMA guidance documents. The FDA and EMA have issued the following guidance on how to perform hepatic impairment trials:


• EMA: “Guideline on the Evaluation on the Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic Function, February 2005”

As noted in the Executive Summary, it is recommended to have hepatic impairment trials conducted relatively early in the clinical development process, because the outcome may influence the patient population as well as the inclusion and exclusion criteria of Phase II and III trials. The timing of these trials is generally before or in parallel with Phase II.
STUDY DESIGN

Both the FDA’s and EMA’s published guidelines are very similar and recommend using the Child-Pugh Score\(^1\) as a basis of categorization of patients with hepatic impairment.

The Child-Pugh Score has been introduced as a tool for predicting mortality of patients with liver cirrhosis following surgery. Since then, the Child-Pugh Score is widely used as a tool for classification of the liver function in patients with liver cirrhosis.

To develop specific dosing recommendations for all hepatically impaired subjects, the full design study should be performed in patients in all three Child-Pugh categories (mild, moderate, and severe, as well as controls). At least six subjects should be evaluated in each arm.

A reduced study design can be used if the investigational medical product is not intended to be used in severe hepatically impaired subjects. In this case moderately hepatically impaired subjects and control subjects would be included. At least eight subjects should be evaluated in each arm. The findings in the moderate hepatically impaired group would then be also applied to subjects with mild hepatic impairment. Treatment of subjects with severe hepatic impairment would generally be contraindicated.

Patients are usually classified as follows (Table 1):

<table>
<thead>
<tr>
<th>Hepatic Group</th>
<th>Description</th>
<th>Score</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal Hepatic Function</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>Mild Hepatic Impairment</td>
<td>Child-Pugh A</td>
<td>5 to 6 points</td>
</tr>
<tr>
<td>3</td>
<td>Moderate Hepatic Impairment</td>
<td>Child-Pugh B</td>
<td>7 to 9 points</td>
</tr>
<tr>
<td>4</td>
<td>Severe Hepatic Impairment</td>
<td>Child-Pugh C</td>
<td>10 to 15 points</td>
</tr>
</tbody>
</table>

Table 1: Patient Classification

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\(^1\) Published by C. G. Child und J. G. Turcotte in 1964 and modified by R. N. Pugh in 1972.
The route of administration should be the same as the intended route of administration for the product. If more than one route of administration is proposed, then the route that provides maximum information regarding the impact of hepatic impairment on the drug’s elimination should be used.

A single-dose study is suggested in all cases where multiple-dose PK can be accurately predicted by single-dose data for both parent drug and active metabolites. This is the case when the PK of the drug and potential active metabolites exhibit linear and time-independence over the anticipated dose range. Otherwise, a multiple dose study should be performed with determination of the PKs at a steady state.

The administered dose is in general the same as the planned clinical dose; however, a reduced dose may be appropriate in hepatically impaired patients if there are concerns about the drug toxicity at higher blood levels.

In any case, simulated plasma levels in hepatically impaired patients shall not exceed the maximum tolerated plasma levels in healthy volunteers. Preferably, the same dose should be administered to all patients.

A discerning selection of inclusion and exclusion criteria for these kinds of trials is essential. Most hepatically impaired subjects suffer from other diseases as well, including diabetes, hypertension and metabolic disorders (increases in urea, lipids, etc); that is why using narrow eligibility criteria could jeopardize patient enrollment and negatively impact timelines as well as the successful conduct of the study. By following the appropriate criteria, PRA’s PPS group usually targets an accelerated recruitment rate of 3 to 6 patients per investigational site, per month.

The Child-Pugh Score (Table 2) is strictly reserved for subjects with liver cirrhosis and cannot be used in subjects without liver cirrhosis.

<table>
<thead>
<tr>
<th></th>
<th>1 Point</th>
<th>2 Points</th>
<th>3 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (µmol/L)</td>
<td>&lt; 34.2</td>
<td>34.2 - 51.3</td>
<td>&gt; 51.3</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>&lt; 2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>&lt; 35</td>
<td>28 - 35</td>
<td>&lt; 28</td>
</tr>
<tr>
<td>(g/dL)</td>
<td>&gt; 3.5</td>
<td>2.8 - 3.5</td>
<td>&lt; 2.8</td>
</tr>
<tr>
<td>Prolongation of</td>
<td>&lt; 4</td>
<td>4 - 6</td>
<td>&gt; 6</td>
</tr>
<tr>
<td>Prothrombin Time (sec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
<td>Slight</td>
<td>Moderate</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Grade 0</td>
<td>Grade 1 or 2</td>
<td>Grade 3 or 4</td>
</tr>
</tbody>
</table>

1) SI units (preferred)  
2) Traditional units  
3) Compared to the MNPT as specified for the laboratory kit used

Table 2: Child-Pugh Score
Patients enrolled into these special population trials are often taking a variety of different concomitant medications needed to treat the multiple concomitant diseases they have. On the other side, concomitant medication might serve as a relevant drug/drug interaction partner with the drug under evaluation. Those interactions should be excluded to the furthest possible extent. Depending on the metabolic pathway and available information on the inhibitory or introductory activity of the compound on various metabolic enzymes and pathways, the selection of allowed and disallowed drugs is recommended.

PPS has implemented a group of medical experts (Medical Affairs group) that reviews every potential drug/drug interaction and potential influences of co-diseases of every patient before and during the trial. In addition, PRA’s experts are always available to discuss relevant medical aspects with study investigators and the sponsors’ medical experts.

In Table 3, we have provided the drugs typically used in subjects with hepatic impairment.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatoprotective Drugs</td>
<td>Silymarin (eg, Legalon™), Mixture of Phospholipids and Vitamins B (eg, Essentiale™)</td>
</tr>
<tr>
<td>Antiviral Agents</td>
<td>Ribavirin, Lamivudine, Interferon-α</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Furosemide, Chlorthalidone, Amicloton, Hydrochlorothiazide</td>
</tr>
<tr>
<td>Corticosteroids (in Case of Autoimmune Hepatitis)</td>
<td>Prednisolone, Prednisone</td>
</tr>
<tr>
<td>Nutritional Supplements</td>
<td>Vitamin K, Vitamin D, Calcium, Potassium, Magnesium, Folic Acid, Ursodeoxycholic Acid</td>
</tr>
<tr>
<td>Non-Selective β-Blockers</td>
<td>Propanolol</td>
</tr>
<tr>
<td>Prokinetic Drugs (in Case of Gastric Hypomotility)</td>
<td>Benzamides (eg, Metoclopramide)</td>
</tr>
<tr>
<td>H2 Receptor Antagonists</td>
<td>Famotidine (Cimetidine and Ranitidine are not allowed)</td>
</tr>
<tr>
<td>Proton Pump Inhibitor</td>
<td>Omeprazole, Esomeprazole, Pantoprazole, Lansoprazole, Rabeprazole</td>
</tr>
<tr>
<td>Antihypertensive Drugs</td>
<td>ACE Inhibitors, Ca Channel Blockers (eg, Dihydropyridines (Nifedipine), Central Alpha 2-Adrenergic Agonists, eg, Guanfacine, Peripheral Alpha 1-, β-Adrenergic Antagonists)</td>
</tr>
<tr>
<td>Antidiabetic Drugs</td>
<td>Insulin, Acarbose, Metformin, Sulfonyl Ureas (eg, Glibenclamide, Gliclazide, Glimerpiride), Repaglinide</td>
</tr>
<tr>
<td>Cardiac Glycoside</td>
<td>Digoxin, Digitoxin</td>
</tr>
<tr>
<td>Others</td>
<td>Lactulose, Cholestyramine</td>
</tr>
</tbody>
</table>

Table 3: Drugs Administered to Subjects with Hepatic Impairment
CUSTOMIZED SOLUTIONS

Regulatory Aspects

PPS conducts hepatically impaired trials in Central and Eastern European countries that belong to the European Union and have implemented the European Clinical Trial Directive. These countries offer a reliable and stable regulatory environment for submission and conduct of early phase patient trials.

The regulatory and ethics committee reviews are performed in parallel, while the clinical trial application reviews have to be completed within 60 calendar days without any pre-defined submission dates.

Submission documents are generated in close collaboration with our sponsors. Whenever needed, country-specific fact sheets are provided to our sponsors to prepare submission documents. As demonstrated in Figure 1, PRA has significant global experience serving as an applicant to regulatory authorities and ethics committees, which speeds up approvals.

![Figure 1: PRA PPS Regulatory and Ethics Committee Approval Timelines (2014)](image)

Import and Distribution of Trial Medication

In compliance with Annex 13 of the GMP, limited drug preparation/manufacturing processes can be performed at the site, which includes the reconstitution of parenteral or oral formulations and the administration of study drugs out of a bulk container.

If more complex manufacturing processes are required, PRA's GMP-licensed pharmacy in The Netherlands can be used, and the manufacturing, QP release and distribution of study drugs within the European Union can be easily arranged. PRA can also handle all labeling and translation requirements.
Clinical Conduct

PRA’s PPS group performs hepatic impairment trials in collaboration with an extensive network of hepatologists and general practitioners in Central and Eastern European countries, such as Hungary, Poland, the Czech Republic, and Slovakia. Centralized healthcare systems with a limited number of hospitals focusing on certain diseases are characterized by huge outpatient clinics with excellent access to hepatically impaired patients. We offer an innovative and highly flexible model that enables us to define the appropriate operational strategy according to project-specific requirements. We develop tailor-made solutions based upon three core elements:

- **PRA Phase I patient units**: Study performance in one of our own Phase I facilities in Prague, Budapest, or Bratislava

- **PRA-operated sites**: PRA medical and clinical operational staff supports study conduct at external hospitals, establishing a Phase I setting at sites with direct access to patient populations

- **PRA-managed sites**: Management of independent, specialized, investigational sites in the Central and Eastern Europe

We offer 30 PRA beds in Clinical Pharmacology Units in Budapest (HU), Prague (CZ) and Bratislava (SK). In addition, we have been transforming the traditional patient Phase I approach for more than 20 years through our close collaboration with local medical communities and hospital investigators.

While operating out of external hospital sites, local PRA study team members ensure high-quality Phase I/II study conduct by:

- **Enabling a Phase I setting in hospitals** (provision of source document, equipment, eg, freezers, centrifuges, ECG machines and blood pressure measurement devices).

- **Local study management** (contracting, training, logistics of laboratory and pharmacy supplies, investigator payments, EC/RA submission, and essential documents).

- **Training of hospital staff** according to PRA standards in advance of the study initiation visit.

- **Support by on-site PRA medical/clinical staff** performing study-related activities (preparation of samples, ECG recording, documentation, etc) allowing the hospital investigator to focus on medical care and patient recruitment.
Best of Both Worlds

PRA operational teams apply the following resources, tools and best practices to support investigators:

• Clinical study set-up, including:
  – GCP environment
  – validated equipment
  – clinical trial materials
  – training
• Patient enrollment
• Study processes/procedures
• Clinical trial documentation and administration

PRA’s approach allows investigators and hospital staff to focus on:

• Recruitment.
• Patient care.
• Safety.

Our unique and flexible operational approach, combined with our scientific/medical expertise, ensures the delivery of the highest quality data at expedited recruitment rates.

Our clients benefit from recruitment rates that are up to 10 times higher than in traditional monitor-based study management approaches, providing significant time and cost savings.
CONTACT INFORMATION

For further information or to discuss any aspect of PRA’s services offered in the field of hepatic impairment trials, please contact your Business Development Manager or the employees listed below:

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PRA Health Sciences delivers innovative drug development solutions that improve patients’ lives. Our people are passionate about clinical research, working tirelessly to provide quality results for clients. We offer exceptional experience across all phases, therapeutic areas, and a broad spectrum of solutions, ranging from full-service clinical development to our pioneering Embedded model.

With 11,000+ employees covering 80+ countries, we bolster an impressive global presence with keen local insights. Our project teams harness their understanding of local regulations, standards of care, and cultural customs to effectively align our approaches with each study’s unique goals.

At PRA, we love what we do because we are making a difference in the lives of patients and their family members worldwide. Over the years, we have contributed to the development of numerous drugs now available to countless patients. From our scientific and medical experts to therapeutically aligned project managers and monitors, we provide the commitment and expertise needed for today’s complex studies.

To learn more about PRA, please visit www.prahs.com or email us at prahealthsciences@pra.com.