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

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EXECUTIVE SUMMARY: Early Phase Renal 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 renal 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 renal 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 renal 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 FDA and EMA. The renal impairment trial’s objectives are to:

- Assess the influence of renal impairment on pharmacokinetics of the drug and its metabolites
- Allow recommendations for dose adaptations in renally impaired patients
- Evaluate whether a drug can be removed by hemodialysis or peritoneal dialysis
- Evaluate the safety and tolerability of the study drug in this vulnerable, special population

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


- “Note For Guidance On The Evaluation Of The Pharmacokinetics Of Medicinal Products In Patients With Impaired Renal Function” – EMA, London, June 2004

- In addition, the FDA has issued a draft guidance: “Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling, March 2010”

The main difference comparing the draft FDA guidance (March 2010) to the actual guidance (May 1998) is the classification of the renal function, especially for the
normal renal function group (matched healthy volunteers). This has changed in the new guidance from 80 mL/min to >90mL/min. We recommend that based on the intention to treat population relevant upper values of the creatinine, clearance should be discussed as recommendations about dose adjustments should be based on comparisons to patients with renal functions that is typical for the usual patient population intended to treat with the IMP.

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**STUDY DESIGN**

While both the FDA’s and EMA’s published guidelines are similar, they differ in one important point: the FDA guidelines require inclusion of patients based on an estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault formula based on serum creatinine; however, the EMA guidelines recommend using a measured Glomerular filtration rate (mGFR) using endogenous (eg, 24-hour Creatinine clearance) or exogenous marker (ie, Iohexol clearance). Occasionally, both the glomerular filtration rates might vary considerably. For renal impairment trials, we usually recommend following the FDA guideline as serum creatinine is measured routinely during the screening process. This approach allows the determination of the Cockcroft-Gault estimation in any case, while the EMA guidelines require additional efforts, such as a 24-hour period of urine collection or the administration of exogenous markers (eg, Iohexol). Following the FDA guidance means less of a burden for patients enrolled in the study and a lower level of complexity with respect to the overall clinical conduct.

Depending on available preclinical and clinical data and the physicochemical properties of the compound, different designs are recommended. When no influence of renal impairment on pharmacokinetic parameters is expected, a trial in a reduced design, comparing severely impaired patients with healthy control subjects is recommended. In all other cases, the enrollment of patients with mild, moderate and severe impairment is recommended. Patients are usually classified as follows (Table 1):
The most common design is a single-dose administration of the study medication in 6 to 12 patients per severity group. The route of administration should be the same as the intended route of administration for the product. The administered dose should be selected so that even in subjects with severe renal impairment, who may have 10-to-100-fold higher PK levels than healthy subjects, the simulated plasma levels will not exceed the maximum tolerated plasma levels in healthy volunteers. Preferably, the same dose should be administered to all patients. If this is not possible, a dose reduction in more severe patients might be considered. Pharmacokinetic sampling schemes should be adopted to allow for the evaluation of the drug’s potentially prolonged half-life.

A discerning selection of inclusion and exclusion criteria for these types of trials is critical. Most renally impaired subjects suffer from other diseases, which include diabetes, hypertension and metabolic disorders (eg, 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 four to six patients per investigational site, per month.

Patients enrolled into these special population trials are often taking a variety of concomitant medications to treat the multiple concomitant diseases they have. On the other side, concomitant medication might be relevant drug/drug interaction partners 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 (our Medical Affairs group) that reviews every potential drug–drug interaction and the potential influences of co-diseases of every patient before and during the trial. Additionally, our experts are always available to discuss relevant medical aspects with study investigators and the sponsors’ medical experts.

<table>
<thead>
<tr>
<th>Renal Group</th>
<th>Description</th>
<th>Estimated Creatinine Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal Renal Function</td>
<td>CLCr &gt; 80mL/min/1.73m2</td>
</tr>
<tr>
<td>2</td>
<td>Mild Renal Impairment</td>
<td>50 &lt; CLCr&gt;80mL/min/1.73m2</td>
</tr>
<tr>
<td>3</td>
<td>Moderate Impairment</td>
<td>30 ≤ CLCr ≥ 50mL/min/1.73m2</td>
</tr>
<tr>
<td>4</td>
<td>Severe Renal Impairment</td>
<td>CLCr &lt; 30mL/min/1.73m2</td>
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Table 1: Patient Classification
In Table 2, we have provided the drugs typically used in subjects with renal impairment.

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Drug Class or Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive Drugs</td>
<td>ACE inhibitors, Calcium, Channel Blockers, eg, Dihydropyridines (nifedipine), central 2-Adrenergic Agonists, eg, Guanfacine, Peripheral 1-, -Adrenergic Antagonists</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Furosemide, Chlorthalidone, Amicloton, Hydrochlorothiazide</td>
</tr>
<tr>
<td>Uricostatic and Uricosuric Drugs</td>
<td>Allopurinol, Benzbromarone, Probenecid</td>
</tr>
<tr>
<td>Erythropoesis Stimulating Drugs</td>
<td>Ferrum, Erythropoietin (in more severe cases)</td>
</tr>
<tr>
<td>Hypolipidemic Drugs</td>
<td>Fibrates, Statines</td>
</tr>
<tr>
<td>H2 Receptor Antagonists</td>
<td>Ranitidine, Famotidine, (Cimetidine is not allowed)</td>
</tr>
<tr>
<td>Proton Pump Inhibitors</td>
<td>Omeprazole, Esomeprazole, Pantoprazole, Lansoprazole, Rabeprazole</td>
</tr>
<tr>
<td>Agents in Case of Secondary Hypoparathyroidsm</td>
<td>Vitamin D derivatives, eg, Calciferol, Calcium Preparations</td>
</tr>
<tr>
<td>Antidabetic Drugs</td>
<td>Insulin, Acarbose, Metformin, Sulfonyl Ureas (eg, Glibenclamide, Gliclazide, Glimerpiride), Repaglinide</td>
</tr>
<tr>
<td>Nutritional Supplementation</td>
<td>Mixture of Amino Acids, Unsaturated Fatty Acids, Potassium Preparations</td>
</tr>
<tr>
<td>Cardiac Glycoside</td>
<td>Digitoxin</td>
</tr>
</tbody>
</table>

Table 2: Drugs Administered to Subjects with Renal Impairment

PPS conducts renal impairment 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.

**CUSTOMIZED SOLUTIONS**

**Regulatory Aspects**

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 ethic committees, which speeds up approvals.
In compliance with Annex 13 to 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.

**Import and Distribution of Trial Medication**

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**Clinical Conduct**

PRA’s PPS group performs renal impairment trials in collaboration with an extensive network of nephrologists in Central Eastern European countries, such as Hungary, Poland, Czech Republic, and Slovakia. Centralized health-care systems with a limited number of hospitals focusing on certain diseases are characterized by huge outpatient clinics with excellent access to renal 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
Experience in Renally Impaired Studies

PRA has conducted more than 50 studies in mild, moderate, severe, and dialyzed renal disease patients within the last 20 years, with over 1200 subjects enrolled. Table 3 below depicts our study experience from the last five years.

<table>
<thead>
<tr>
<th>Renally Impaired Studies</th>
<th>2008-2013 (5 years):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies</td>
<td>Subjects Enrolled</td>
</tr>
<tr>
<td>21</td>
<td>471</td>
</tr>
</tbody>
</table>

Table 3: PRA Renally Impaired Study Experience
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 renal 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@prahs.com.