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Renal Impairment Study Designs: Trends, Optimization, Adaptive Approach. A Review.

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Abstract

Statement of Purpose, Innovation or Hypothesis

Renal impairment studies are required to assess the influence of renal impairment on pharmacokinetics (PK) of an investigational drug (ID) to an extent that the dose must be adjusted in the drug's labeling. Although the FDA guidance for Industry provides a clear approach on how to conduct these studies, many other designs/trials were typically conducted depending on the safety profile and characteristics of the ID. The objective is to describe different study designs and methodologies (e.g., subject matching techniques, the use of reduced PK study without end-stage renal disease patients) based on drug characteristics (CYP450 or transporters interaction/route of elimination) and the related PK outcomes on rate and extent of absorption (C_{max} and AUC).

Description of Methods and Materials

Ten renal impairment clinical trials (full and reduced PK) were selected and analyzed. The drug characteristics (elimination pathway, metabolism), safety profile, and pharmacokinetic profile were evaluated for trends and used to determine ideal study designs.

Data and Results

The healthy subjects were matched by gender (same ratio female/male between groups) with the severe group (reduced PK design) or with all groups (full PK design). They were also matched by weight (+/- 15%) and age (+/- 10 years). For most of the studies, subjects were matched by the pooled mean, except one study where the healthy subjects were matched one by one with the severe (based on weight and age). The mean estimated glomerular filtration rate (eGFR) was 103.0 mL/min/1.73m^2 for the healthy subjects (range 90-124) and 22.3 mL/min/1.73m^2 for the severe subjects (range 11-29). The severe subjects were not under dialysis and were classified as stage IV or stage V. In comparison to the traditional reduced or full PK study, some adaptive approaches offer an additional safety margin with a possibility to dose-adjust based on observed results, regardless of the administration route.
As expected, based on the drug characteristics and elimination pathways, the C_{max} and AUC have been modified in such a way that the results were 1) predictable and 2) the design was appropriate to conclude efficiency.

Interpretation, Conclusion or Significance

The different designs allowed us to draw conclusions regarding the effect of chronic renal failure on the drug's PK, and dose adjustment required in the drug labeling. The adaptive approach to the reduced or full PK study designs offer the advantage of conducting clinical trials based on the safety and PK profile of the drug.

Objectives

The objective was to describe the different study design methodologies (e.g., subject matching techniques, the use of reduced PK study without patients under dialysis) based on drug characteristics (CYP450 or transporters interaction/route of elimination), the expected PK outcomes on rate and extent of absorption (C_{max} and AUC) and the drug safety profile for renal impairment studies performed at Altasciences.

The study designs were chosen based on the FDA March 2010, Draft Guidance for Industry, '*Pharmacokinetics in Patients with Impaired Renal Function*' and improved based on PK characteristics and safety profiles.

Methods

Pharmacokinetics

The primary route of elimination is key to develop practical study design (urinary, metabolism or both). If accumulation is expected, an adaptive design (different renal groups, reducing the dose) may be recommended.

Safety

The safety profile of the drug is also evaluated. The safety margin of the drug is a factor to decrease the dose in case of important adverse events (e.g., cardiac effect, neurologic effect).

The selected studies were multi-center, non-randomized, open-label, single-dose, parallel group studies in a subject population comprised of adult male and female volunteers with various levels of renal function. Approximately eight subjects were to be enrolled in each renal function group.

Table 1. Renal Subjects Classification

Renal Function	Classification	Clinical Sites
Normal	eGFR ≥90 mL/min/1.73m^2	Altasciences
Mild Impairment	eGFR 60-89 mL/min/1.73m^2	Altasciences
Moderate Impairment	eGFR 30-59 mL/min/1.73m^2	Hospital or other clinical sites*
Severe Impairment	eGFR < 30 mL/min/1.73m^2	Hospital or other clinical sites*

Subjects

Severely renal impair subjects are usually not under dialysis and are classified as stage IV or stage V of chronic kidney disease

Matching

Two approaches were used for matching healthy subjects:

- Mean matching
- One-to-one matching

Healthy subjects are usually matched by gender (same ratio female/male between groups) with the severe renal impairment group (reduced PK design) or with all groups (full PK design). Mean matching is usually used for the weight (+/- 15%) and age (+/- 10 years) as the one-to-one matching implies recruitment difficulties. Based on our experience FDA and EMA allow the above mean matching to be reasonable for similarities between groups.

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Table 3. Demographic Data

	Healthy	Mild	Moderate	Severe
Age (years)	54 (32-71)	55 (32-76)	61 (31-77)	58 (26-77)
Sex	48%F/52%M	67%F/33%M	34%F/66%M	35%F/65%M
BMI (m^2/kg)	29.0 (21.1 - 38.6)	25.7 (20.5-32.2)	31.1 (23.0-41.8)	29.3 (19.6-41.8)
Weigh (kg)	82.3 (55.6-114.1)	72.2 (53.9-86.6)	89.0 (62.6-125.0)	84.4 (50.2-133.6)
eGFR (mL/min/1.73 m^2)	103.0 (90-124)	80.8 (60-89)	44.5 (27-59)	22.3 (11-29)

F: Female/M: Male, eGFR: estimated glomerular filtration rate, BMI: Body mass index

Support Services

In addition to the clinical conduct of the studies, Altasciences was involved in the strategic planning and evaluation of the trials:

- Clinical protocol development/review
  - Feasibility of PK study design (full, reduced, alternative designs)
  - PK sampling schedule, safety assessments, selection of population and matching criteria between normal and renal impaired subjects
- Trial design based on the FDA March 2010, Draft Guidance for Industry, '*Pharmacokinetics in Patients with Impaired Renal Function*'
- Project management
- Non-compartmental pharmacokinetic analysis with Phoenix® WinNonlin®
- Statistical analysis for evaluation of the relationship between renal function and the PK parameters (SAS®, Proc MIXED)
- Medical writing and PK interpretation

The different study design methodologies were based on:

- Drug characteristics (CYP450 or transporters interaction/route of elimination)
- Known PK of the drug (rate and extent of absorption (C_{max} and AUC))
- Potential for accumulation
- Safety profile (cardiac effects, neurologic effects, etc.)
- Subject-matching techniques
- Reduced or full PK study

Results

Table 2 summarizes study designs (metabolism and urinary recovery) and the observed impact of chronic renal failure on C_{max} and AUC.

Table 2. Study Design Summary

Drug/ Route	CYP450 metabolism	Urinary % Recovery	Design	C_{max}	AUC
A/oral	NA	Predominantly excreted unchanged in urine	Reduced PK study started with severe, continued with moderate and mild concurrently	(~ 2 fold)	(~ 3 fold)
B/oral	UGT (extensively)	Less than 4% for the parent and 75% to 90% is recovered in the urine as metabolite	Full PK study	Parent : Met : (~ 6 fold)	Parent : Met: (~ 6 fold)
C/oral	Extrahepatic and hepatic metabolism to some extent to inactive metabolites	Negligibly excreted unchanged in urine (less than 3%)	Reduced PK study started with severe, stopped after severe		
D/sub-cutaneous	Variable extent of metabolism to inactive metabolites	Approximately 50% excreted unchanged in urine	Reduced PK study started with severe, continued with moderate and mild concurrently		(~ 2 fold)
E/oral	Variable extent of metabolism	Approximately 10% excreted unchanged in urine and 60% excreted in faeces	Adaptive started with mild and moderate, exposure matching (moderate versus mild). Then continued with severe and healthy with or without dose adjustment based on safety and PK (not completed)	(~ 1.4 fold)	(~ 2 fold)
F/oral	Extrahepatic and hepatic metabolism to some extent	Approximately 60% excreted unchanged in urine	Reduced PK study started with severe, continued with moderate only		(~ 5.5 fold)
G/ sub-cutaneous	NAP	Approximately <2% excreted unchanged in urine	Adaptive, Reduced PK study started with moderate, Stopped after moderate.		
Com-bination H and I/oral	H and I extensively metabolized in the liver	H: Approximately <2% excreted unchanged in urine I: Approximately <20% excreted unchanged in urine	Full PK study	NA	NA
J/oral	<15% enzyme metabolism	25% excreted unchanged in urine	Full PK study		
K/topical	Extensively metabolized in the liver to inactive metabolites	Approximately <10% excreted unchanged in urine	Reduced PK study started with severe, continued with moderate and mild concurrently	Slightly higher (no change)	Slightly higher (no change)

NA: Not Available

Conclusion

The clinical studies were conducted based on the FDA March 2010, Draft Guidance for Industry, '*Pharmacokinetics in Patients with Impaired Renal Function*'. However, multiple factors can influence the study design such, as PK (elimination pathway), safety profile, timelines, and drug development priorities.

In comparison to the traditional reduced or full PK study, the adaptive approach offers the advantage of conducting clinical studies based on real-time safety and PK data, in case of accumulation or important expected safety concerns in a renal impaired population.

The reduced PK study is the most common and most convenient design in terms of timelines, costs and ethical considerations, number of subjects with renal impairment exposed to similar doses as healthy subjects, with a decreased safety margin.

The different designs (reduced, full and adaptive) allowed us to draw conclusions regarding the effect of chronic renal failure on the drug's PK, and dose adjustment required in the drug labeling.