Specifics of Phase I studies in Hepatic/Renal impaired subjects

28Sep2023

Hepatic and Renal Insufficiency Studies are a Hybrid of Early and Late Stage Clinical Study Aspects

Phase 1 Study Aspects

- PK study but in patients with some age/size matched HV control subjects
- Small number of patients
- Short treatment duration – usually single dose
- Open label – no randomization
- Precise timing of PK samples from time of dose
- Many samples / measurements for 48-96 hours
- Individual or group control matching strategies permitted
- Special sample handling sometimes required (e.g. plasma protein binding)

Multi-Site Study Aspects

- Small number of sites – usually 2-3
- One or two patients at a time
- Tracking enrollment important to evenly fill cohorts across sites
- Concurrent medications can be a major recruiting and study execution challenge

What is unique and/or challenging about R/H impairment subjects?

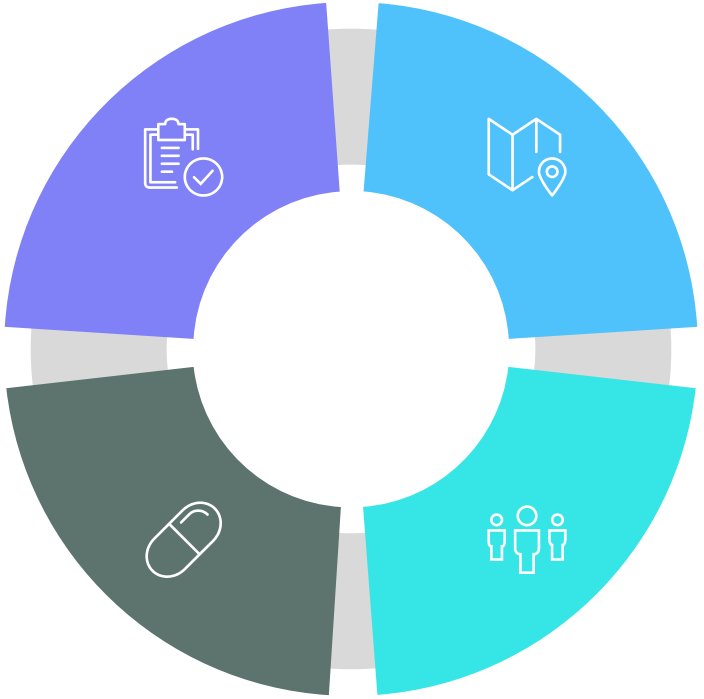
- **Renal Impairment Studies**
  - Take a cocktail of medications for cardiovascular disease, diabetes mellitus, peripheral vascular disease, obesity, hypertension (refractory), metabolic bone disease, peptic ulcer disease, platelet dysfunction
  - Finding healthy older subjects that meet healthy normal creatinine clearance can be challenging
  - GFR formula have known limitations
  - Recent FDA guidance has made it more difficult to find severely impaired subjects; classification requirements have changed
  - Investigators/site staff have developed relationships with these subjects and work with them often

- **Hepatic Impairment Studies**
  - Severely impaired patients are of fragile health and often waiting for liver transplant; short window of availability
  - Usually allow smokers since many patients with impaired liver function are smokers (associated with lifestyle)
  - Patients may have diabetes, hypertension, bleeding disorders, GI hemorrhage
  - Investigators/site staff have developed relationships with these subjects and work with them often

Four Unique Tasks for CPMs in Managing Hepatic or Renal Impairment Studies

Ensuring that **healthy control subjects** recruited into the study meet the **patient-matching criteria** established by the protocol.

Ensuring appropriate **review of concomitant medications** that a patient will be taking is allowed by the protocol prior to dosing.



Tracking enrollment of patients and control subjects by site to ensure that any allocation targets defined in the protocol are met.

Ensuring that patients are **assigned to the correct cohort** based on degree of impairment as assessed by equations and criteria defined in the protocol.

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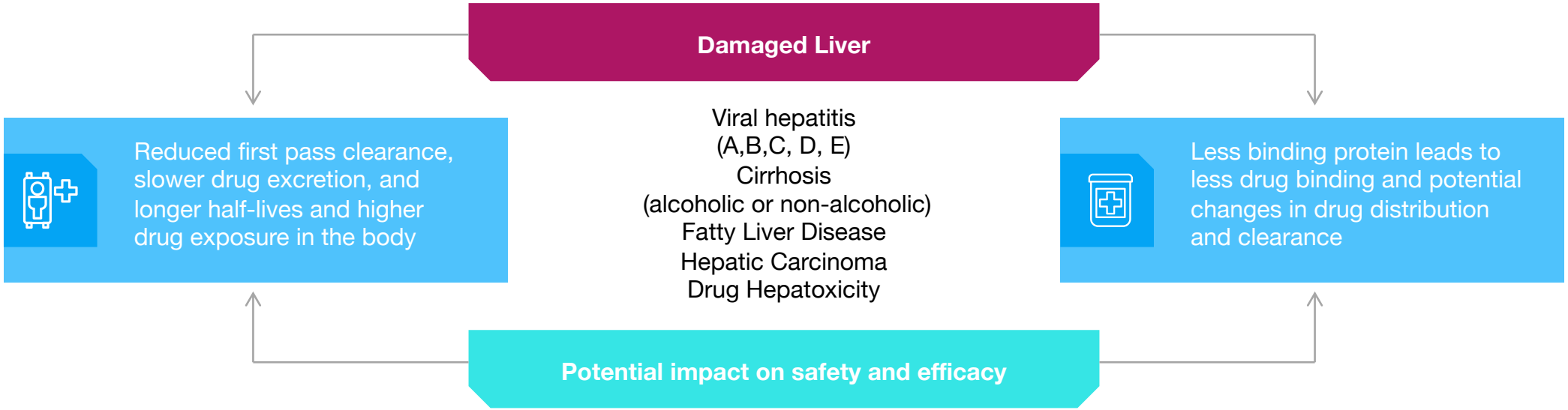
Translating Science to Medicine

Hepatic Impairment

Why Hepatic Insufficiency PK Studies?

For 90% of marketed drugs, the liver is an important organ for removing active drug from the body
- metabolism → chemically changes molecule
- transport into bile duct → excretion into small intestine

Liver is site of synthesis for plasma proteins that bind drugs and other substances



Can be mitigated by adjusting dose downward but need to know by how much in mild, moderate or severe situations

Guidelines

- FDA:
  - Guidance for Industry Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling Second level
    - May 2003 Clinical Pharmacology Fourth level
- https://www.fda.gov/media/71311/download

- EMA
  - GUIDELINE ON THE EVALUATION OF THE PHARMACOKINETICS OF MEDICINAL PRODUCTS IN PATIENTS WITH IMPAIRED HEPATIC FUNCTION.
    - DATE FOR COMING INTO OPERATION - August 2005 Fourth level
- https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-pharmacokinetics-medicinal-products-patients-impaired-hepatic-function_en.pdf

Child-Pugh Classification System

Child – Turcotte – Pugh Classification for Severity of Cirrhosis

Clinical and Lab Criterias	Points*		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (mg/dL)	>3.5	2.8-3.5	<2.6
Prothrombin time ▪ Seconds prolonged ▪ International normalized ratio	<4 <1.7	4.6 1.7-2.3	>6 <2.3

***Child – Turcotte – Pugh Class obtained by adding score for each parameter (total points)**
Class A = 5 to 6 points (least severe liver disease)
Class B = 7 to 9 points (moderately severe liver disease)
Class C = 10 to 15 points (most severe liver disease)

Features of Hepatic Insufficiency Studies

Patients must have **diagnosis** of some degree of **liver disease** or impairment as evident by one or more of the following: elevated liver enzyme tests, jaundice, ascites, bruising, itchy skin, GI disturbance, ultrasound scan (e.g Fibroscan), MRI, liver biopsy.

Severely impaired patients are hardest to find and drive study conduct timelines and number of sites.

- Severe hepatic disease patients are of fragile health, often waiting for liver transplant, thus they may be available to participate in studies for a short window of time.

If drug is predominantly cleared by liver, then severely-impaired patients may need to be studied depending on safety concerns.

Consider other drugs the patients are currently taking. Need to ensure the PK results are do to hepatic insufficiency and not false changes due to drug interactions. This can be managed by withholding for a few hours known metabolic and drug transport inhibitors.

Consider including smokers (if CYP1A plays little or no role in test drug's metabolism) since many patients with impaired liver function are smokers (associated with lifestyle),

In addition these subjects may have diabetes, hypertension, bleeding disorders, GI hemorrhage

Study Design

Full Study

- 3 Patient Cohorts and Control group
  - Mild, Moderate, & Severe Impairment
  - Min 6 per cohort

Reduced Study

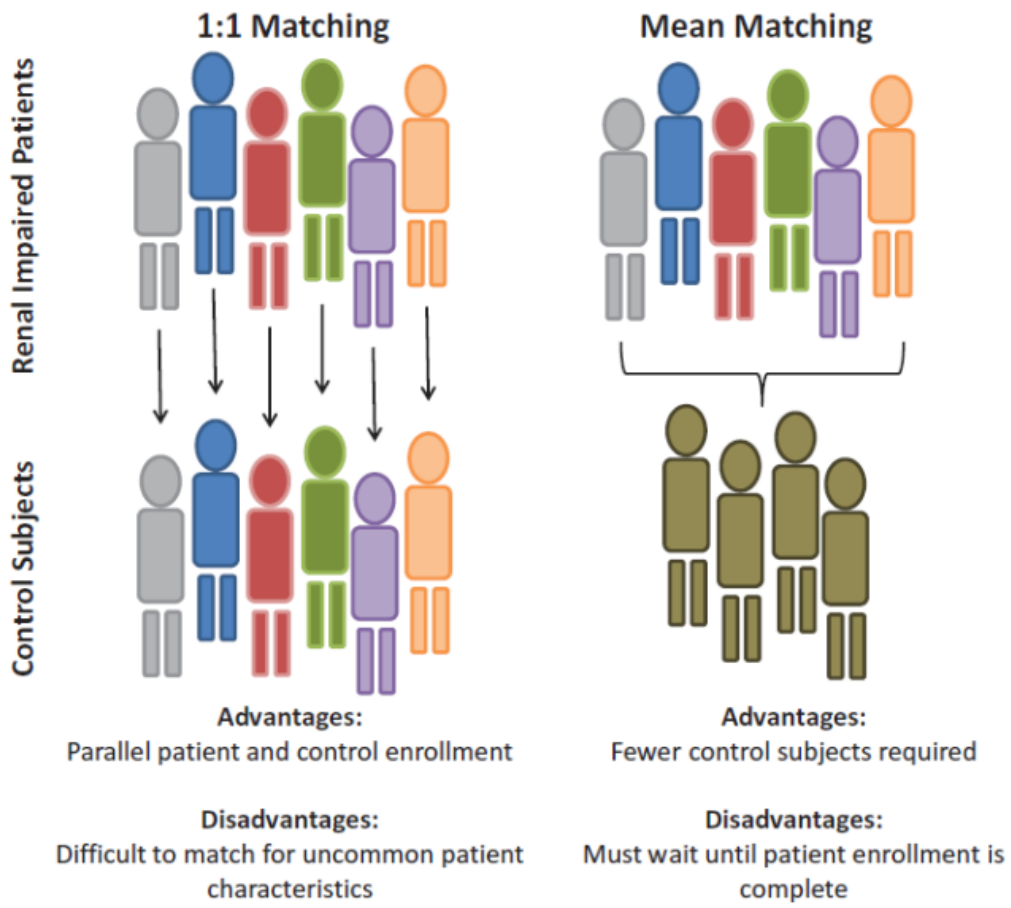
- Moderate Patients and Control group
  - Findings in the moderate category would apply to mild patients
  - For labelling purposes, dosing in the severe category would be generally be contraindicated
  - Min 8 per cohort

Study Design

- Single- or Multiple Dose
- Parallel or Adaptive/Staged
- Individual or mean matched controls

Healthy Control Matching

- Match demographic-anthropometric parameters (i.e., sex, age, body weight and/or BMI)
- Typical: age ± 10 years, BMI ± 5-20%
- Control group should also reflect the demographics of intended patient population, i.e., elderly group for an Alzheimer's medication.



Paglialunga S., et al. Exp Rev Clin Pharmacol (2017)

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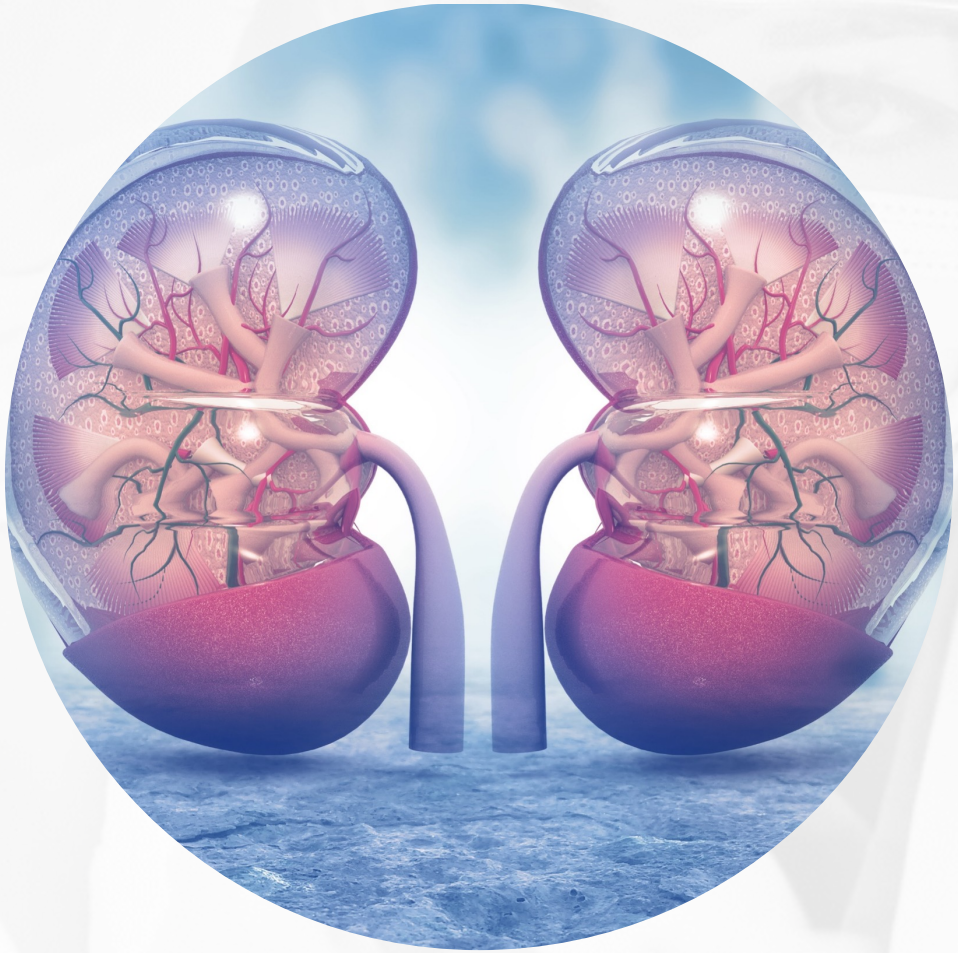
Translating Science to Medicine

Renal Impairment

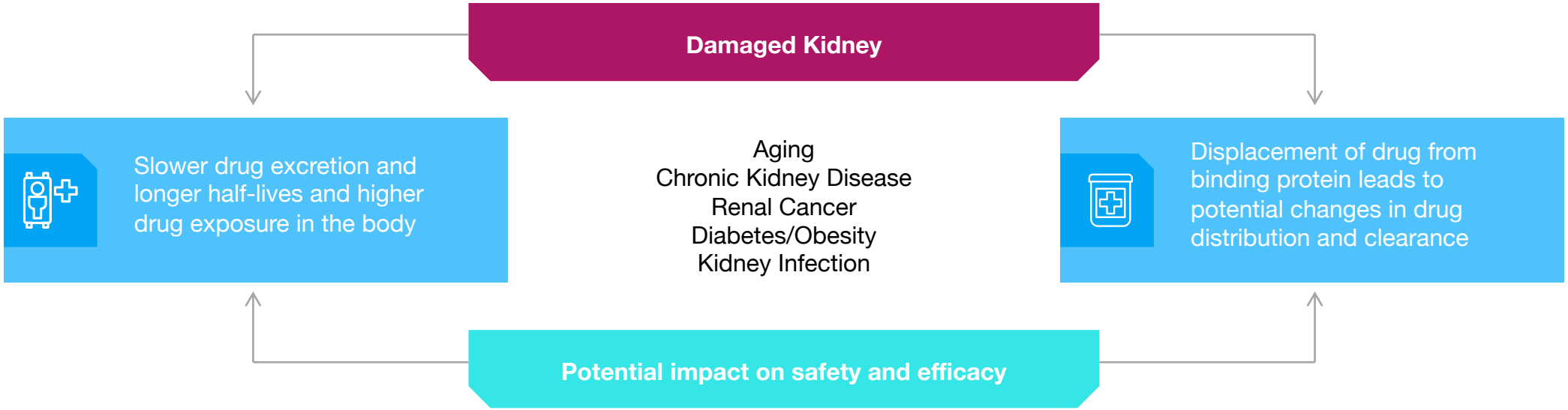


Why Renal Insufficiency PK Studies?

For many marketed drugs, the kidney is an important organ for removing active drug and metabolites from the body:

- filtration of unbound drug by the glomerulus,
- reabsorption of drug back into the systemic circulation or secretion of drug back into nephron by active transporters in the proximal & distal tubules.

The kidney can also metabolize some drugs, but to a much smaller extent than liver.



Can be mitigated by adjusting dose downward but need to know by how much in mild, moderate or severe situations

Classification of Degree of Renal Impairment - Differences Between FDA and EMA Guidance

Description	GFR (mL/min/1.73m²)	GFR (mL/min)*
	FDA	EMA
Normal Renal Function	>=90	>80
Mild Impairment	60-89	50-80
Moderate Impairment	30-59	30-<50
Severe Impairment	15-29	<30
End Stage Renal Disease	<15 Not on Dialysis	Requires Dialysis
	Requiring Dialysis	

*EMA does not agree with FDA that GFR adjusted for body surface area is the best measure for GFR.

This means that large patients might fall into different groups depending on what GFR method is used.

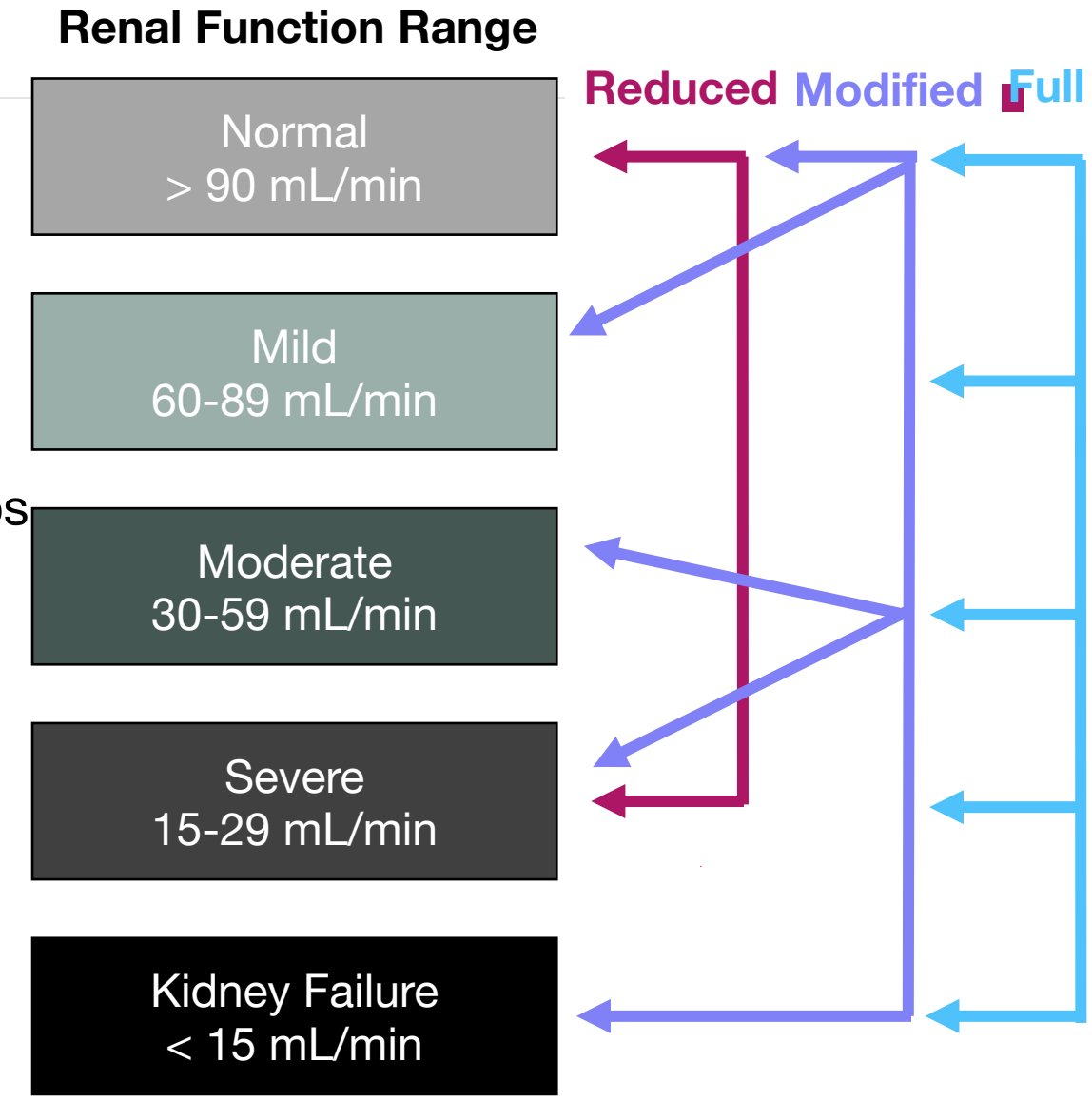
Important to determine if sponsor is planning to use the study to support FDA or EMA filing or both.

Guidelines

- FDA:
  - Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing
    - DRAFT GUIDANCE
  - September 2020 Clinical Pharmacology Revision 2
  - https://www.fda.gov/media/78573/download
- EMA
  - Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function
  - Date for coming into effect 1 July 2016
- https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-pharmacokinetics-medicinal-products-patients-decreased-renal-function_en.pdf

Study Design

- **Full PK Design**
  - Likely to be used in renal impaired patients; and
  - Substantially eliminated by the renal route
- **Modified PK Design**
  - Wide therapeutic range drugs can consider 3 groups normal to mild and moderate to server and kidney failure
- **Reduced PK Design**
  - Likely to be used in renal impaired patients; and
  - Predominantly eliminated via non-renal routes
  - If a clinically relevant PK effect is observed, all stages of renal function should be explored
- Parallel, Adaptive/Staged



Impact of the Revised FDA Guidance on Renal Impairment PK Study Enrollment, Clinical Site Location and Trial Duration

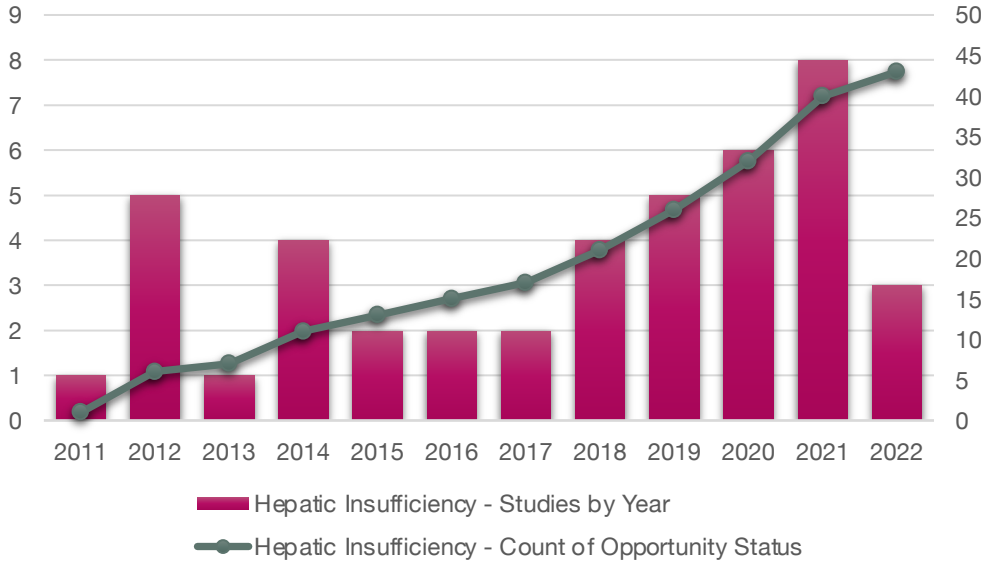
In 2020, the FDA updated the draft renal impairment (RI) pharmacokinetics (PK) guidance, impacting study design and sample size. An analysis of RI PK studies conducted before and after the guidance release was performed to address how the industry has responded to these recommendations.

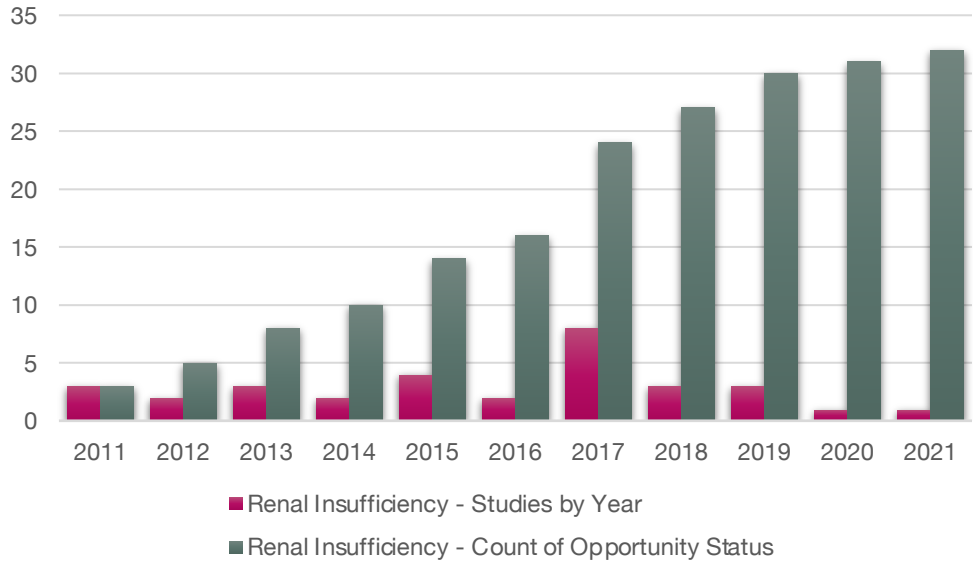
	Participants		KF Cohort	Clinical Site Number & Geography (%)						Duration
Trial Start	Study Ave	Cohort Ave	Studies (%)	Sites Ave	US	EU	Asia	2 or more	Other / NR	Months Ave*
Pre-Guidance	28 (14-48)	8 (6-14)	27%	2 (1-6)	51%	35%	5%	11%	-	9 (1-22)
Post-Guidance	28 (12-48)	8 (6-14)	42%	2 (1-5)	50%	21%	17%	8%	4%	8 (1-18)
Ongoing	33 (16-64)	9 (6-16)	42%	2 (1-7)	52%	15%	12%	6%	15%	11 (5-21)**

Data presented at average (range) or percentage. *Duration = Primary Completion Date – Start Date.
**Estimated dates. KF = kidney failure; NR = not reported

The revised guidance recommends to perform sample size justification based on drug PK variability, which can drive number of patient per cohort to 14 or more. While the updated guidance did not seem to have an immediate impact on sample size, ongoing studies are enrolling 5 more participants than previously. This may extend study duration by several months and potentially delay phase 2/3 study initiation. In addition, more studies are also seeking to enroll kidney failure patients, either as part of a reduced design or because the drug may be intended for this population.

Renal & Hepatic Impairment Studies – Overall Celerion Experience



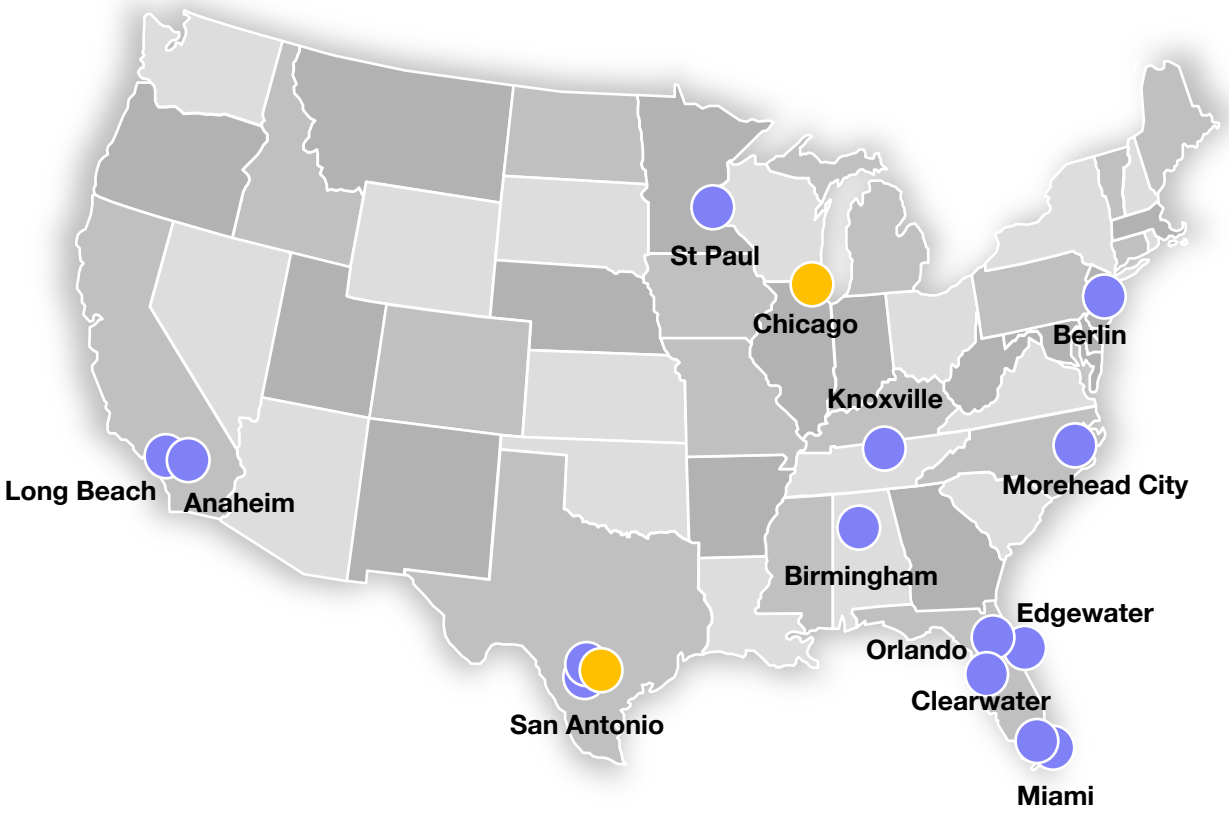


Experience

- 43 Hepatic insufficiency studies in last 10+ years
- 32 Renal Impairment studies in last 10+ years
- Optimization of IE criteria and protocol design
- Experts in HI /RI pharmacology studies
  - Experienced Project Managers
  - CRAs in close proximity to the site

Source: SFDC

Celerion Renal & Hepatic Site Network in the US



Hepatic & Renal Impairment Sites

Renal Impairment Sites

Hepatic Impaired Subjects in Network

- Mild = 1,500
- Moderate = 1,000
- Severe = 200

Renal Impaired Subjects in Network

- Mild = 15,000
- Moderate = 22,000
- Severe = 5,500
- Renal Failure = 5,000

Celerion Renal & Hepatic Site Network - Europe

Hepatic & Renal Impairment Sites

Hepatic Impairment Sites

Hepatic Impaired Subjects in Network

- Mild = 150
- Moderate = 80
- Severe = 50

Renal Impaired Subjects in Network

- Mild = 350
- Moderate = 100
- Severe = 50
- Renal Failure = 30

Access to many hepatology, nephrology GI and internal medicine centers across the countries

At least 50 GPs referrals per indication

Main challenge – willingness of subjects to join

THANK YOU