Effect of Renal Impairment on Drugs Primarily Eliminated by Metabolism or Biliary Excretion: Review of Data from HCV DAA Drugs and Literature

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Introduction

- Renal impairment (RI) can lead to alterations in non-renal clearance for drugs that are primarily eliminated by non-renal pathways
  - Changes in drug-metabolizing enzymes and transporters
  - Uremic toxins
- Hepatitis C virus (HCV) direct acting antiviral (DAA) agents are primarily eliminated via metabolism or biliary excretion
  - Daclatasvir (DCV), Asunaprevir (ASV), and Beclabuvir (BCV) – all <10% of dose eliminated in urine
- Study design can influence the interpretation of renal impairment study results

Objective and Methods

- Assess the utility of reduced RI study designs on dosing recommendations using data from BMS DAAs and other marketed DAAs
- Evaluate the impact of RI on PK of drugs eliminated primarily by non-renal pathways
- Compare the results of full vs reduced study designs for BMS DAA drugs along with data for other published DAAs
- Employ literature review of RI studies to evaluate and compare:
  - The frequency of full vs reduced study designs
  - PK changes in RI subjects for drugs that are primarily eliminated renally compared to non-renal and mixed pathways
  - Key words - renal impairment study, reduced design, hepatic clearance and metabolism

DCV and ASV Renal Impairment Studies

- DCV:
  - Initially conducted only in ESRD subjects on HD vs healthy controls
  - Expanded to moderate and severe renal impairment based on results from ESRD
  - 60 mg single dose evaluated
- ASV
  - Conducted in ESRD subjects on HD vs healthy controls
  - 100 mg BID softgel capsule administered for 7 days

DCV and ASV Renal Impairment Studies

ASV Renal Impairment Study

- Reduced design – ESRD on HD and Healthy Controls (HC) only
- ASV AUCTAU,u GMR
  - ESRD/HC 0.803 (0.5561, 1.161)
- Conclusion – no effect of RI on ASV PK but observation from DCV study caused some uncertainty

DCV Renal Impairment Study

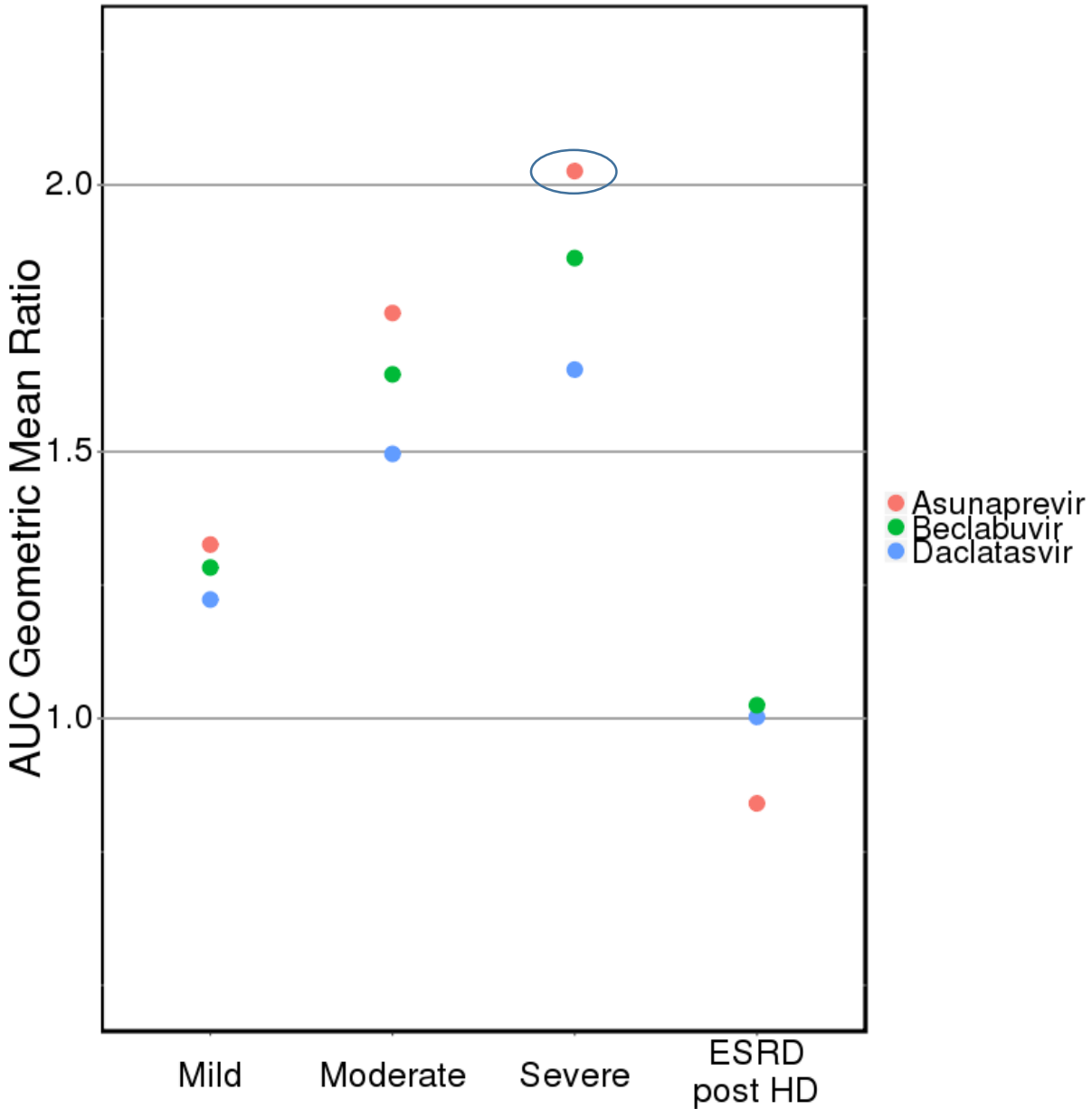
- Full design: moderate (MI), severe (SI), ESRD on HD, and HC
- DCV AUCINF,u GMR
  - MI/HC 1.728 (1.047, 2.854)
  - SI/HC 1.684 (1.181, 2.402)
  - ESRD/HC 1.201 (0.903, 1.596)
- Conclusion - No dose adjustment recommended for DCV

Because of higher GMR for DCV in MI and SI groups, DCV 3DAA renal impairment study was conducted using a full design

DCV-TRIO Renal Impairment Study

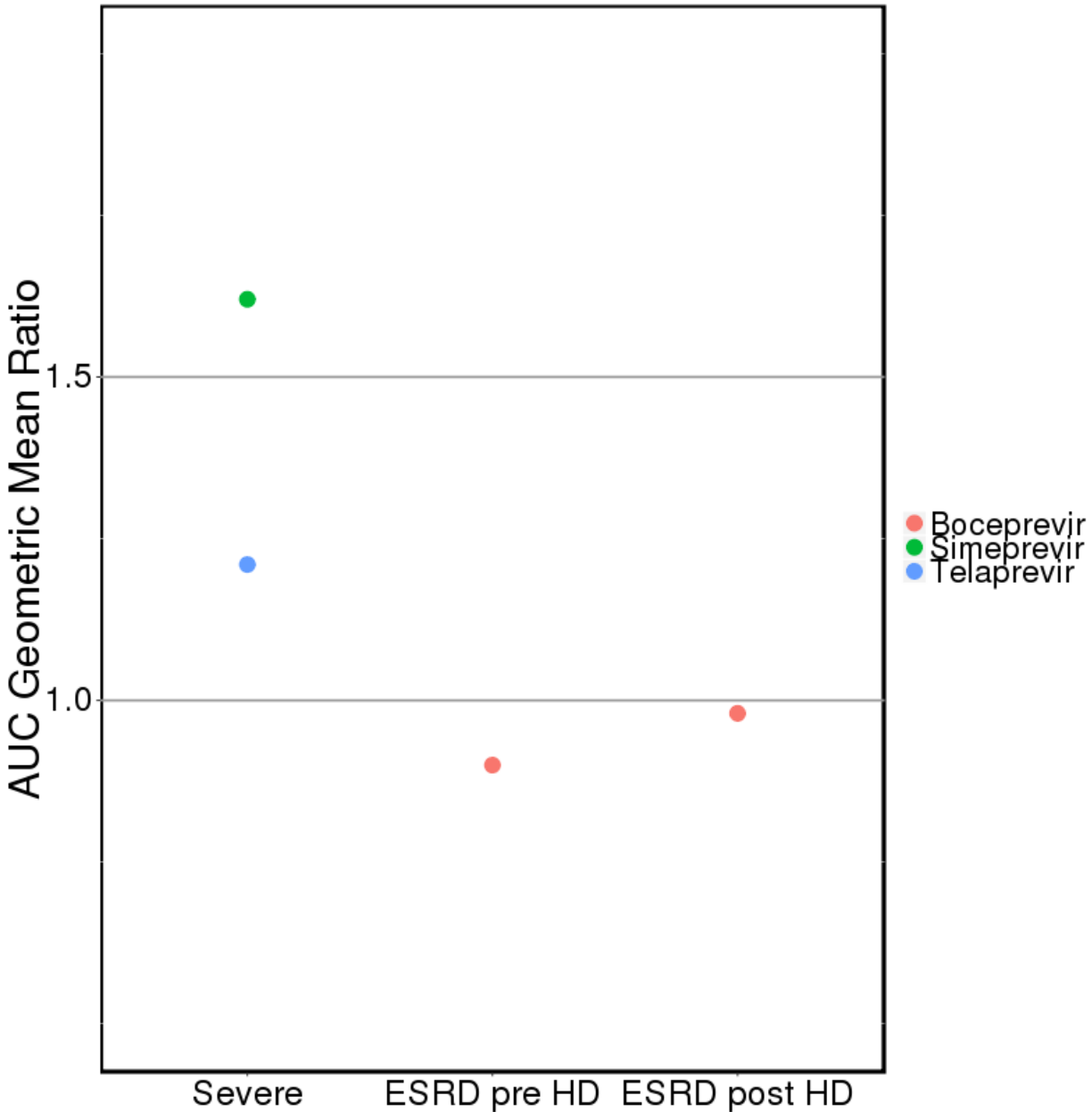
- Study Design
  - Mild, moderate, and severe RI subjects
    - DCV-TRIO FDC + 75 mg BCV administered BID on Days 1-9 and morning dose on Day 10
  - ESRD on HD
    - DCV-TRIO FDC + additional 75 mg BCV (to achieve higher exposures observed in HCV patients) administered BID on Days 1-11 and morning dose on Day 12
  - Healthy controls (N=8)

Renal Impairment Study – DCV-TRIO



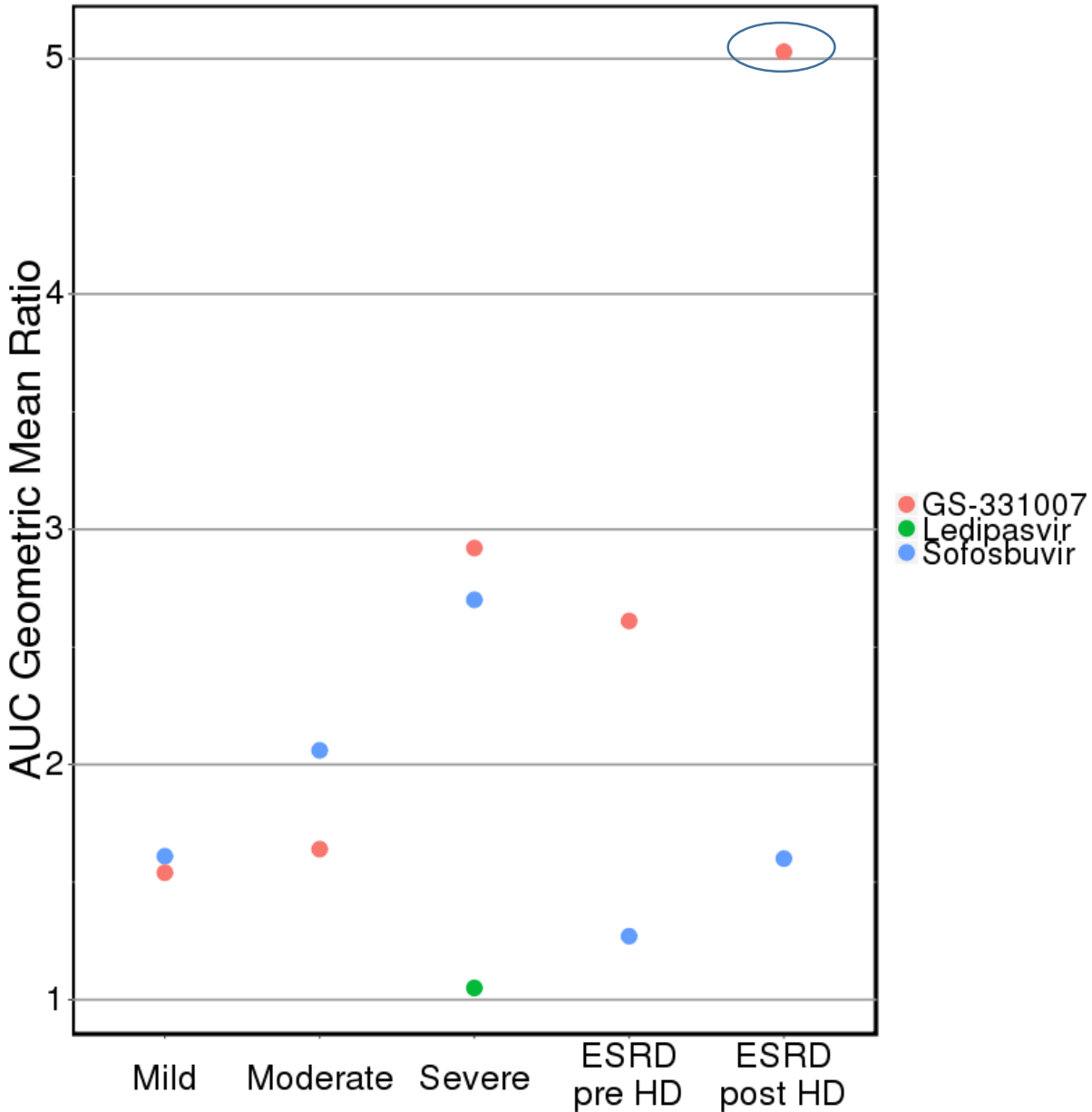
- ASV dose recommended to be reduced by half in subjects with severe renal impairment not on HD due to >2-fold increase in exposure
- DCV data similar to individual study
- DCV-TRIO regimen dose recommended to be reduced in half in patients with SI based on ASV data

Renal Impairment Studies - HCV Protease Inhibitors



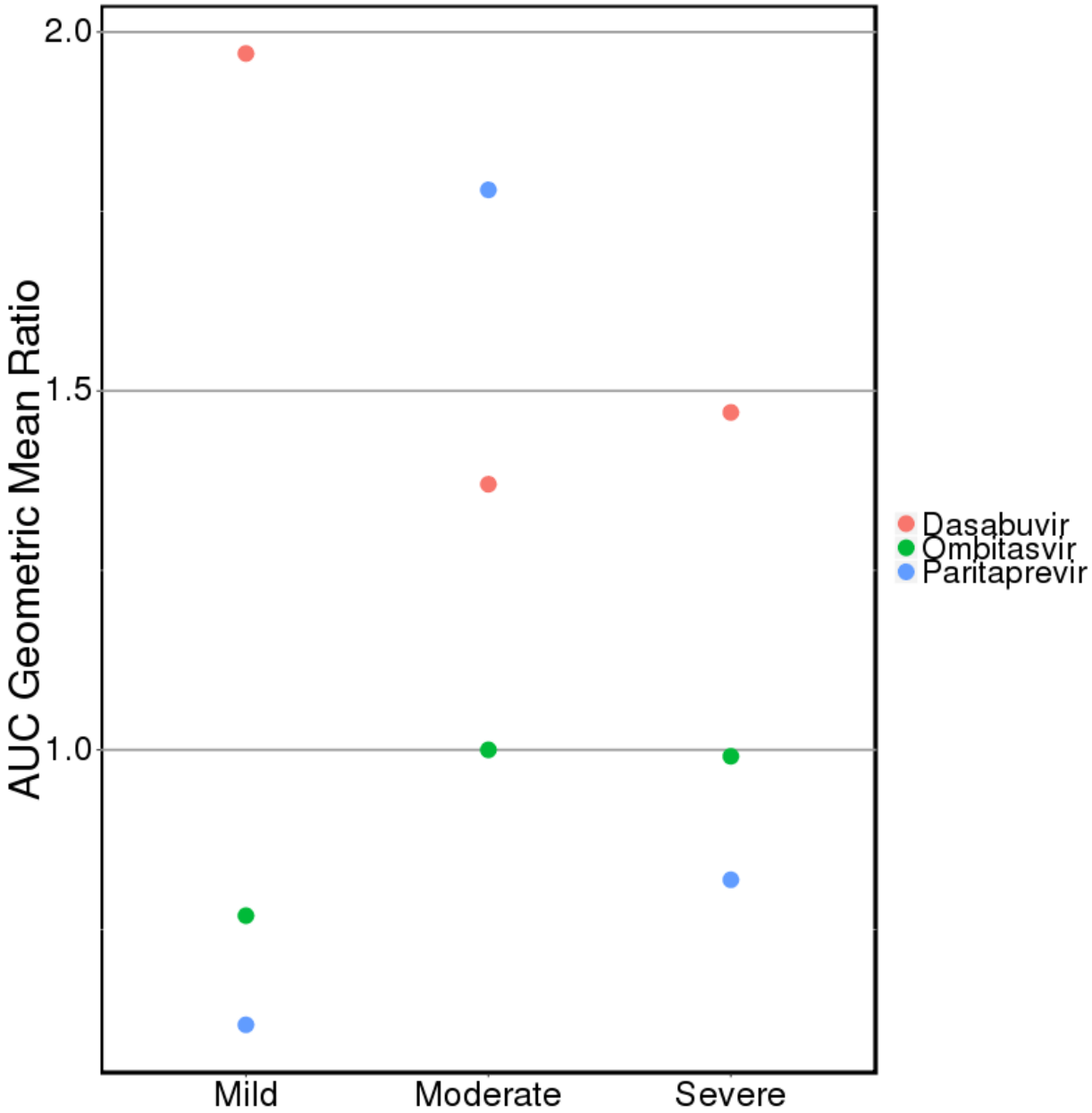
- All 3 protease inhibitors conducted studies using a reduced design
  - Boceprevir evaluated ESRD subjects only
  - Simeprevir and Telaprevir studied subjects with severe RI not on HD
- No dose adjustment is recommended for these PI's in subjects with any degree of renal impairment

Renal Impairment Studies - Sofosbuvir based regimens



- Effect of renal impairment on SOF and GS-331007 (SOF analyte of interest) was evaluated using a full design
- Based on data for GS-331007 in ESRD SOF is not recommended for use in subjects with severe renal impairment or ESRD
- No dose adjustment required in any other group
- Ledipasvir used a reduced design (SI only) - no dose adjustment was recommended

Renal Impairment Study - Viekira Pak



- All components of Viekira Pak studied using a full design without ESRD subjects
- No dose adjustment is recommended for any component of Viekira Pak for any degree of renal impairment

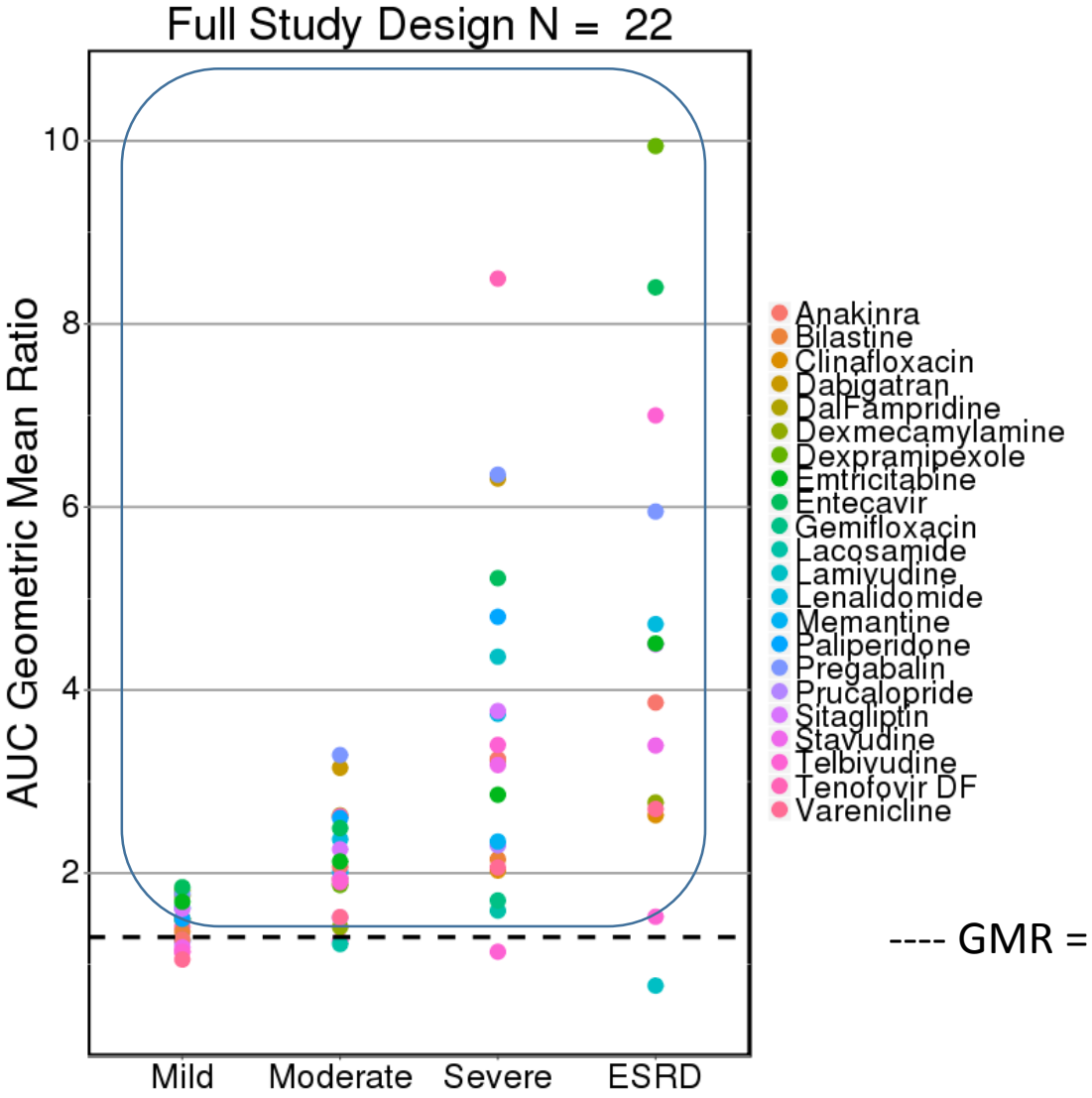
Renal Impairment Studies – Literature Review

Mode of Elimination	Total N	N (%) using full design	Dose Adjustment N (%)
Predominant Renal Elimination	27	22 (81.5%)*	26 (96.3%)
Predominant metabolism and transport	38	26 (68.4%)**	14 (37%); 3/14 (21.4%) evaluated in a full design
Mixed renal and metabolism	10	8 (80%)	5 (50%); All 5 evaluated in a full design

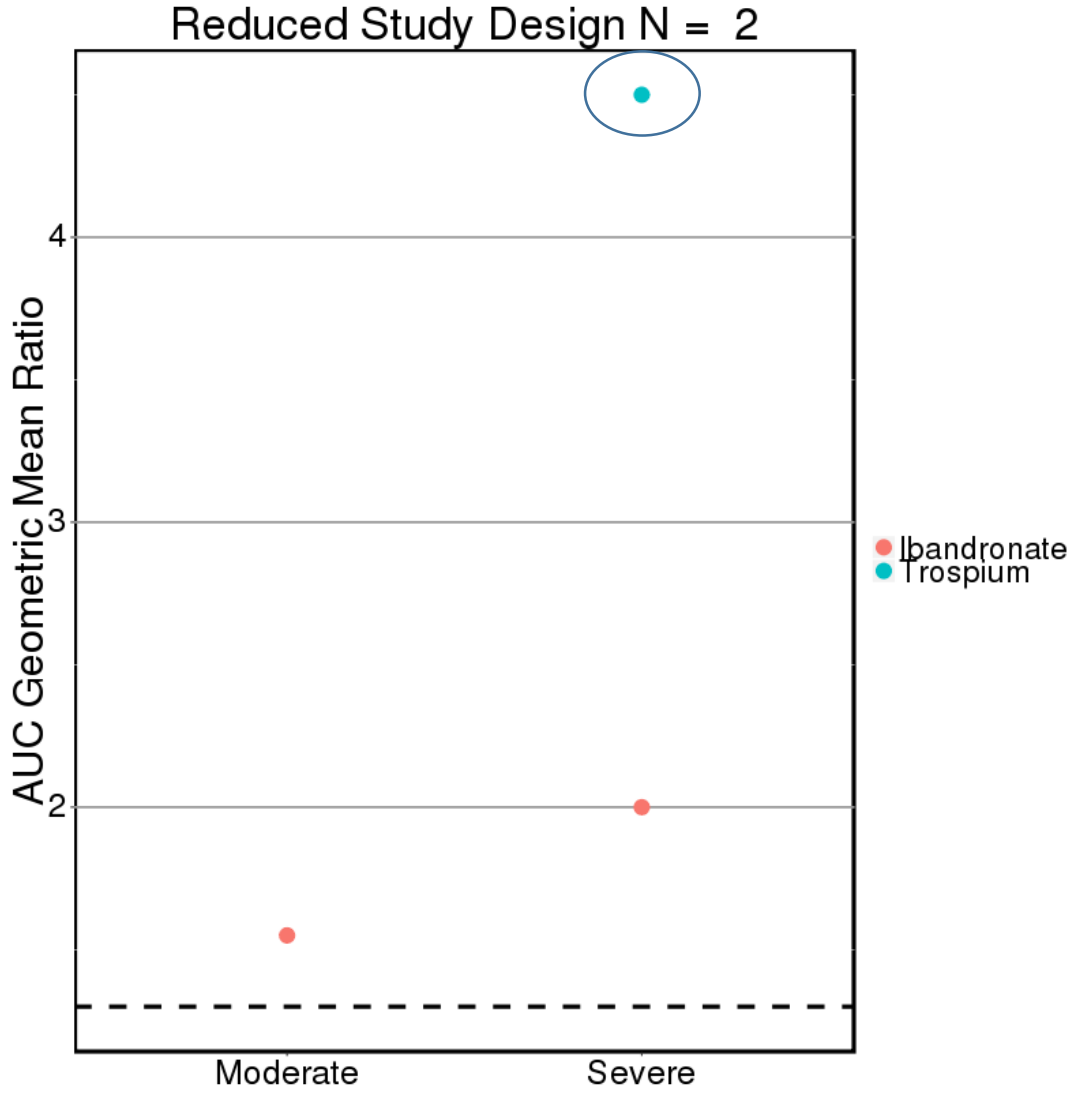
* Of remaining 5 drugs, reduced study design was conducted for 3 drugs and no design was specified for other 2 drugs

** Other 12 drugs were evaluated using a reduced study design

Literature Review – Renal Clearance as an Predominant Route

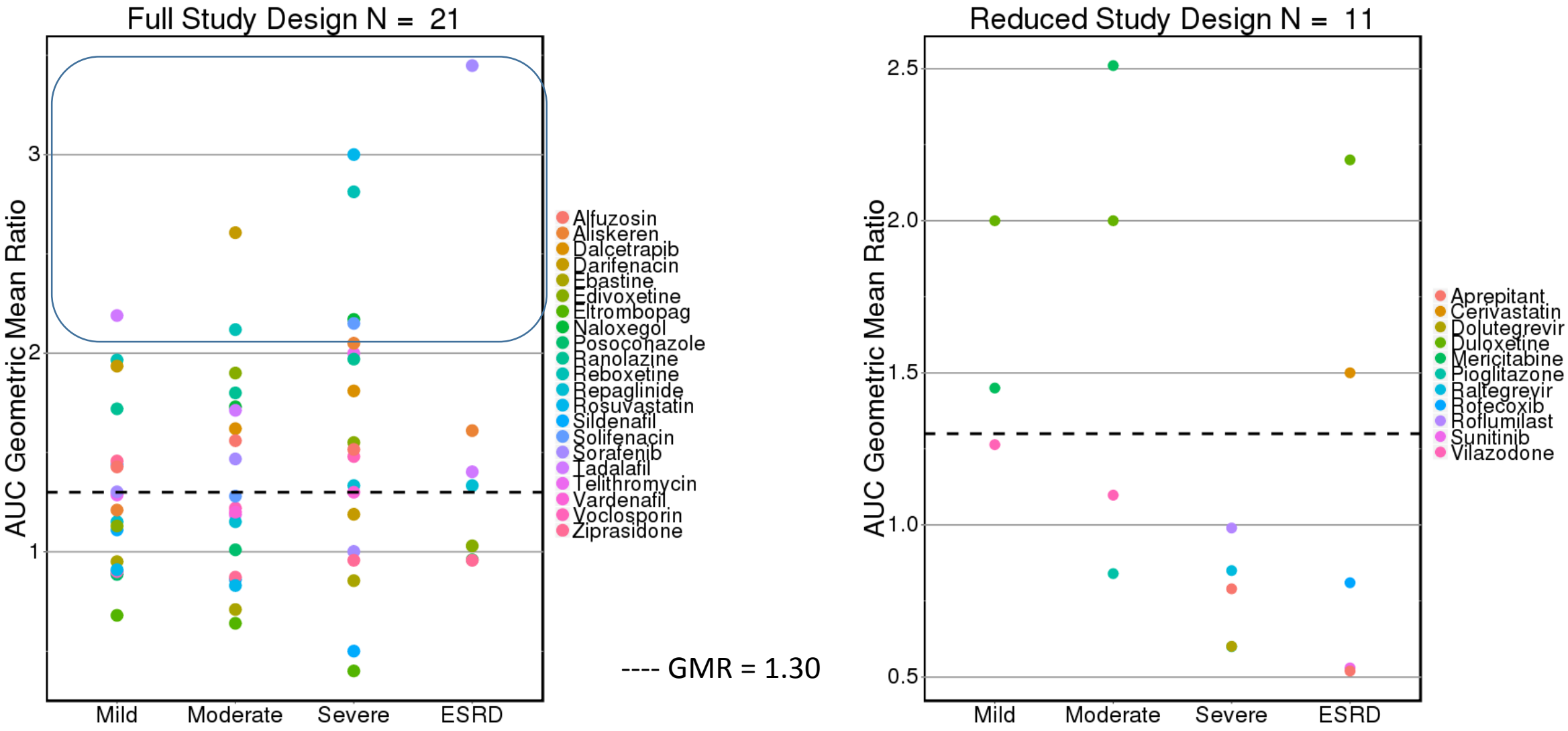


---- GMR = 1.30



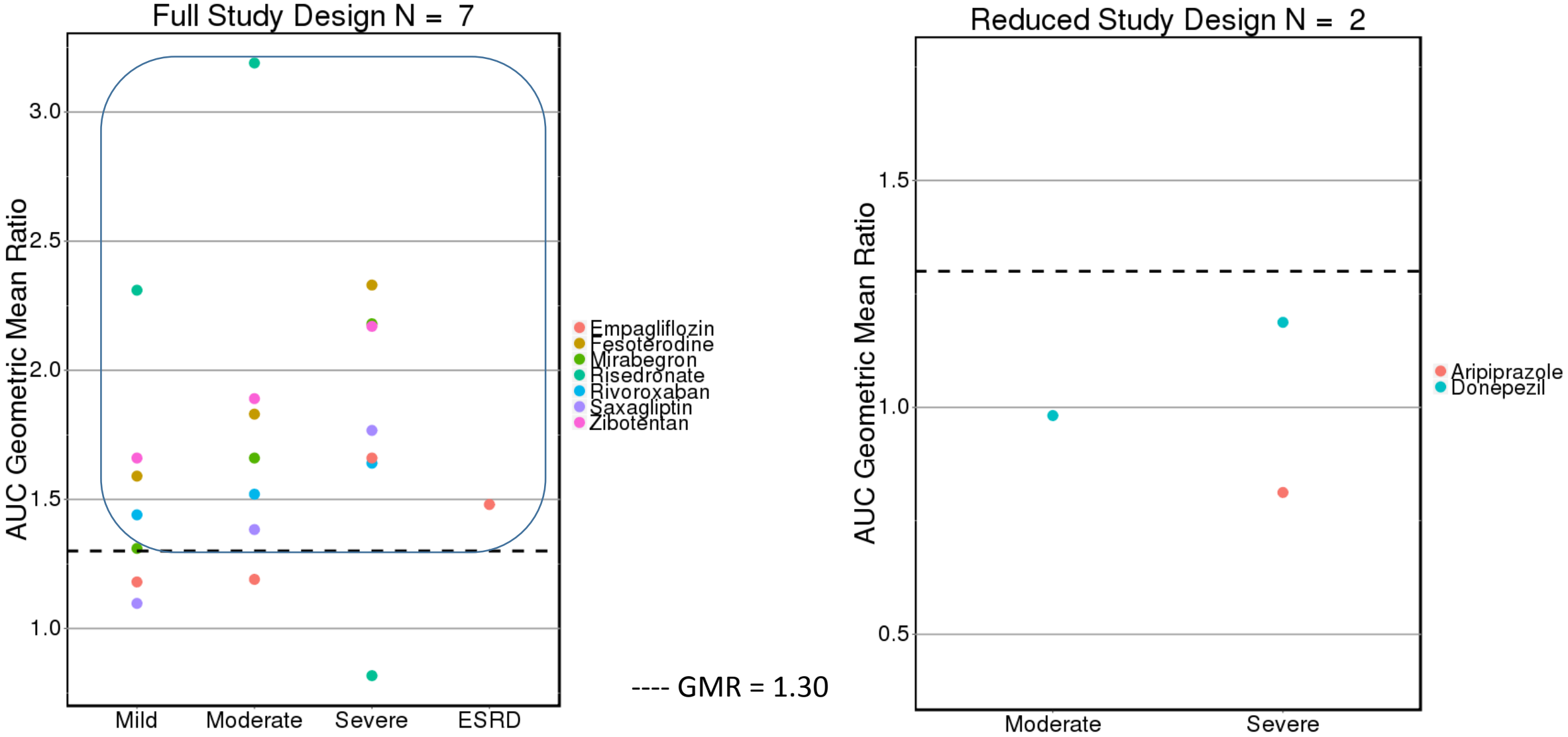
- Majority of drugs with renal clearance as a predominant route of elimination evaluated the effect of RI using a full design
- For majority of drugs an increase in exposure > 2-fold was observed starting with moderate RI

Literature Review – Hepatic Clearance as an Important Route



- Despite renal clearance not being a predominant route of elimination, majority of drugs utilized a full design
- For many of these drugs significant increases in exposure were observed

Literature Review – Renal/Hepatic Clearance Routes



- Despite having mixed clearance mechanisms majority of drugs in this category utilized a full design
- For many of these drugs a significant increase in exposure was observed

Discussion

- In-house BMS results and literature data indicate that subjects with RI can have significantly higher exposure for drugs eliminated primarily via metabolism or via transporter-mediated pathways
  - Alterations in enzymes and transporters may lead to changes in renal function
  - Removal of uremic factors with HD may mask effects of RI
- Literature review indicates that
  - Majority of drugs (22/27) primarily eliminated by renal clearance (fe ≥ 30%) employed a full design and 96.3% of those recommend a dose adjustment in RI
  - For drugs cleared by hepatic metabolism or transport, studies were conducted using a full design in 68% cases, and dose adjustment was recommended only for 37% of them (14/38)

Summary

- Results from in house and literature review indicate that renal impairment has an impact on the exposure of drugs with elimination primarily via metabolism and/or transporter mediated pathways
- Sponsors should carefully consider sub-groups included in a reduced study design
  - At minimum use severe renal impairment not on dialysis
  - Using only ESRD-subjects on HD may not sufficiently characterize exposures across the range of renal impairment

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