Using Clinical Data and Physiologically Based Pharmacokinetic Modelling to Assess the Effect of Hepatic Impairment on Avapritinib Pharmacokinetics to Guide Dose Adjustment

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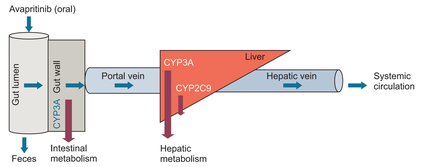
Poster Number A008

Introduction

- Avapritinib, a selective tyrosine kinase inhibitor, is approved for the treatment of adult patients with unresectable/metastatic gastrointestinal stromal tumors (GIST) harboring a *PDGFRA* exon 18 mutation (USA) or a D842V mutation (Europe). Avapritinib is also approved for adult patients with indolent systemic mastocytosis (ISM) in the USA and Europe, or advanced systemic mastocytosis (AdvSM) in the USA and in Europe after ≥1 prior therapy[1–6]
- The starting dose of avapritinib is 300 mg once daily (QD) in GIST, 200 mg QD in AdvSM and 25 mg QD in ISM
- Avapritinib is extensively metabolized by the liver and eliminated predominantly through biliary excretion (**Figure 1**). The oxidative metabolism of avapritinib is primarily mediated by cytochrome P450 (CYP) 3A4 with minor contributions from CYP2C9, producing the metabolite M499[1,2]

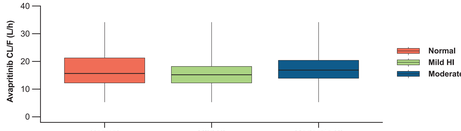
Figure 1: Avapritinib is metabolized by CYP3A4, minor route via CYP2C9 to form M499 which is eliminated primarily through biliary excretion



CYP, cytochrome P450.

- *Post hoc* population pharmacokinetic (PK) analysis in patients with GIST found no meaningful effect of mild or moderate hepatic impairment (HI) on avapritinib clearance (**Figure 2**)

Figure 2: Comparable avapritinib clearance in patients with GIST with normal hepatic function, mild hepatic impairment, and moderate hepatic impairment

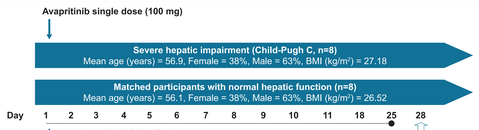


HI, hepatic impairment; h, hour.

- Significance of this work:
  - To assess the effect of severe HI on avapritinib PK, a single dose phase 1 study BLU-285-0107 was conducted
  - A physiologically based PK (PBPK) model was used to determine dose adjustments for avapritinib in patients with severe HI

Methods: Severe hepatic impairment study

Figure 3: Study design BLU-285-0107



Participants with normal hepatic function were matched in a 1:1 ratio to a participant with HI for age, body mass index, and sex.
BMI, body mass index; fu, fraction unbound; PK, pharmacokinetics.

- Study BLU-285-0107 assessed the effects of severe HI (Child-Pugh Class C) on avapritinib PK (total and unbound plasma) following a single 100 mg oral dose QD while fasting compared to participants with normal hepatic function. Study design is shown in **Figure 3**

Results: Severe hepatic impairment study

A clinically meaningful increase in unbound avapritinib, but not total avapritinib, was observed in participants with severe hepatic impairment (BLU-285-0107)

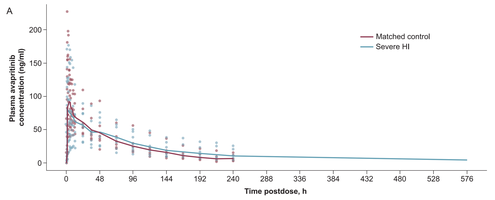
- The mean total concentration-time profiles and plasma PK parameters in participants with severe HI and normal hepatic function are presented in **Figure 5** and **Table 1**, respectively
- The median fraction unbound (fu) of avapritinib per the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) score were numerically higher in participants with severe HI compared to participants with normal hepatic function
- The mean half-life of avapritinib was 34% higher for participants with severe HI compared to those with normal hepatic function

Table 1. Statistical comparison of total and unbound plasma avapritinib PK parameters following a single dose of 100 mg avapritinib in participants with severe hepatic impairment and normal hepatic function (BLU-285-0107)

Parameter	Severe hepatic impairment (N=8)	Normal hepatic function (N=8)	GMR (%)[a]	90% CI
Unbound plasma avapritinib PK parameters				
C_{max} (ng/mL)	1.293	1.197	108.00	58.08–200.80
$AUCu_{0-inf}$ (h*ng/mL)	105.2	65.21	161.32	121.41–214.35
CluF (L/h)	950.6	1534	-	-
Total plasma avapritinib PK parameters				
C_{max} (ng/mL)	96.60	120.7	80.05	44.46–144.14
AUC_{0-inf} (h*ng/mL)	7861	6574	119.58	88.02–162.44

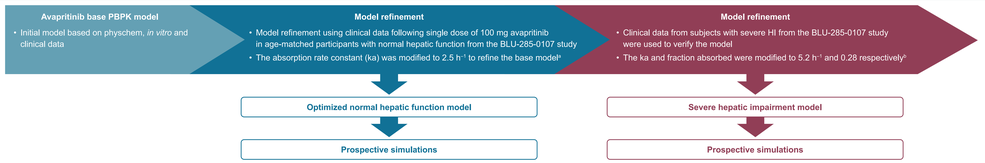
[a]GMR = 100 x (test/reference).
90% CI, 90% confidence interval; AUC_{0-inf}, area under the (total/unbound) avapritinib plasma concentration time curve from time 0 extrapolated to infinity; CluF, apparent oral clearance of unbound avapritinib unadjusted for bioavailability; C_{max}, maximum (total/unbound) avapritinib plasma concentration; GMR, Geometric Mean Ratio.

Figure 5. Linear scale (A) and semi-log (0–24 hours from dosing) (B) mean total plasma concentration–time profiles following a single dose of 100 mg avapritinib in participants with severe hepatic impairment and normal hepatic function overlayed with individual concentrations



Methods: Hepatic impairment PBPK model

Figure 4. PBPK modelling of avapritinib including hepatic function



A lower albumin binding was used when modelling GIST as compared to AdvSM and ISM; [a]Based on 10 virtual trials of eight participants with normal hepatic function under fasting conditions (3/8 female, age 47–63 years, fu 0.010, and accompanying sensitivity analysis). [b]Based on 10 virtual trials of eight participants with severe HI under fasting conditions (3/8 female, age 50–68 years, fu 0.0137).
fa, fraction absorbed; ka, absorption rate constant; PBPK, physiologically based pharmacokinetics.

Hepatic impairment PBPK model of avapritinib

- A PBPK model of avapritinib was developed including hepatic function which could be used to simulate avapritinib PK for normal to severe hepatic impairment (**Figure 4**)

Avapritinib hepatic impairment dose adjustment simulations

- PBPK model was used to simulate avapritinib plasma PK following QD dosing of avapritinib in participants with severe HI and normal hepatic function at a range of doses
- Dosing regimens were identified which resulted in steady state PK in severe HI which was within 2-fold of the PK in participants with normal hepatic function at the approved avapritinib doses (25 mg, 200 mg, and 300 mg)

Results: Hepatic impairment PBPK model

Avapritinib severe hepatic impairment PBPK model

Optimized normal hepatic function model

- Simulated concentration *versus* time profiles of total avapritinib and M499 were comparable to the clinical data (**Figure 7**)
- The simulated geometric mean area under the avapritinib plasma concentration time curve from time 0 extrapolated to infinity (AUC_{0-inf}), maximum avapritinib plasma concentration (C_{max}), and median time at which maximum avapritinib plasma concentration is reached (T_{max}) values for avapritinib (total and unbound) in participants with normal hepatic function were within 1.4-fold of the observed values (majority within 1.25-fold; **Table 2**) and these differences were considered minor

Table 2. Simulated and observed geometric mean avapritinib PK parameters in participants with normal hepatic function from BLU-285-0107

	Total avapritinib			Unbound avapritinib	
	AUC_{0-inf} (h.ng/mL)	C_{max} (ng/mL)	T_{max}[a] (h)	AUC_{0-inf} (h.ng/mL)	C_{max} (ng/mL)
Simulated	7663	90.4	2.50	78.3	0.93
CV%	62	53	1.45–5.10[b]	61	50
Observed	6574	121	2.25	65.2	1.2
CV%	42	51	1–4.83[b]	50	50
S/O	1.17	0.75	1.11	1.20	0.77

[a]T_{max}, median. [b]Range.
CV, coefficient of variation; S/O, simulated/observed; T_{max}, time at which maximum avapritinib plasma concentration is reached.

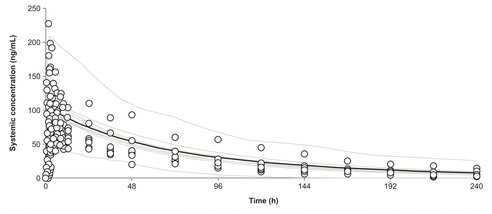
Severe hepatic impairment model

- The simulated geometric mean AUC_{0-inf}, C_{max}, and median T_{max} values for avapritinib (total and unbound) in severe HI following a single 100 mg QD oral dose were within 2-fold of the observed values (most within 1.5-fold; **Figure 8, Table 3**)
- The model predicted that severe HI would result in higher unbound concentrations of avapritinib consistent with the clinical study BLU-285-0107 (**Table 4**)

PBPK simulations of severe hepatic impairment dose adjustments

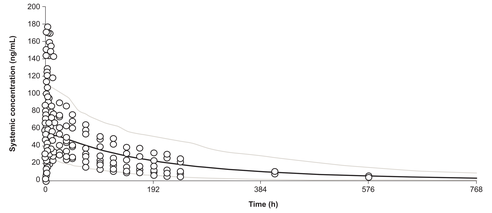
- Steady-state simulations indicated dose reductions from 300 mg QD to 200 mg QD (GIST), 200 mg QD to 100 mg QD (AdvSM), and 25 mg QD to 25 mg once every other day (QOD, ISM) would be appropriate for patients with severe HI (**Figure 9, Table 5**)
- The resulting avapritinib exposures were generally within ~0.8- to 1.25-fold of those in participants with normal hepatic function (**Figure 9, Table 5**)
- In the PBPK model, mild and moderate hepatic impairment had minimal impact on systemic exposures to total and unbound avapritinib consistent with a population PK analysis (data not shown)

Figure 6. Simulated and observed total avapritinib plasma concentration-time profiles of a single oral dose of 100 mg avapritinib in age-matched participants with normal hepatic function



Depicted are simulated (lines) and observed data (circles, n=8; Clinical Study BLU-285-0107). The grey lines represent the 5th and 95th percentiles and the solid black line the mean data for the simulated population (n=80).

Figure 7. Simulated and observed total avapritinib plasma concentration-time profiles of a single oral dose of 100 mg avapritinib in participants with severe HI



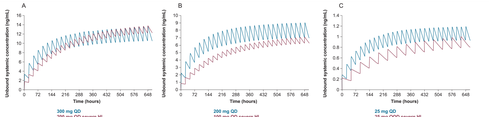
Depicted are simulated (lines) and observed data (circles, n=8; Clinical Study BLU-285-0107). The grey lines represent the 5th and 95th percentiles and the solid black line the mean data for the simulated population (n=80).

Table 3. Simulated and observed geometric mean avapritinib PK parameters in participants with severe hepatic impairment (fraction absorbed of 0.28 for avapritinib) from BLU-285-0107

	Total avapritinib			Unbound avapritinib	
	AUC_{0-inf} (h.ng/mL)	C_{max} (ng/mL)	T_{max}[a] (h)	AUC_{0-inf} (h.ng/mL)	C_{max} (ng/mL)
Simulated	10737	51.7	1.50	153	0.74
CV%	72	55	0.8–3.4[b]	64	45
Observed	7861	96.6	1.50	105	1.29
CV%	58	60	1-24[b]	71	82
S/O	1.37	0.54	1.00	1.46	0.57

[a]T_{max}, median. [b]Range

Figure 8. Simulations to support dose adjustments from 300 mg QD to 200 mg QD (A), from 200 mg QD to 100 mg QD (B), and from 25 mg QD to 25 mg QOD (C)



Panel A shows the simulated mean unbound avapritinib plasma concentration-time profiles on administration of multiple oral daily doses of avapritinib in participants for 28 days with normal hepatic function (300 mg QD) and severe hepatic impairment (200 mg QD). Panel B shows simulated mean unbound avapritinib plasma concentration-time profiles on administration of multiple oral daily doses of avapritinib in participants for 28 days with normal hepatic function (200 mg QD) and severe hepatic impairment (100 mg QD). Panel C shows simulated mean unbound avapritinib plasma concentration-time profiles on administration of multiple oral daily doses of avapritinib in participants for 28 days with normal hepatic function (25 mg QD) and severe hepatic impairment (25 mg QOD). The lines represent the men data for the simulated populations (n=100) of participants with normal hepatic function (black) and participants with severe hepatic impairment (red).
QD, once daily; QOD, once every other day.

Table 4. Summary of predicted geometric mean C_{max} and AUC ratios for avapritinib in participants with severe hepatic impairment *versus* normal hepatic function following multiple oral dosing of avapritinib

	Severe HI/ healthy	
	GMR $C_{max,ss}$	GMR $AUC_{0-tau,ss}$[a]
25 mg QD		
Avapritinib (total)	1.14	1.23
Avapritinib (unbound)	1.59	1.71
200 mg QD		
Avapritinib (total)	1.12	1.20
Avapritinib (unbound)	1.56	1.68
300 mg QD		
Avapritinib (total)	1.11	1.19
Avapritinib (unbound)	1.55	1.67

[a]$AUC_{tau,ss}$ was calculated from 648 hours to 672 hours (day 28).
$AUC_{tau,ss}$, area under the curve from time 0 to dosing interval at steady state; $C_{max,ss}$, maximum plasma concentration at steady state.

Table 5. Predicted C_{max} and AUC ratios for unbound avapritinib in patients with severe hepatic impairment receiving modified dose of avapritinib

Dose (regimen)	PBPK model estimates	
	$C_{max,ss}$	$AUC_{0-tau,ss}$[a]
200 mg QD severe HI/ 300 mg QD normal hepatic function	1.05	1.13
100 mg QD severe HI/ 200 mg QD normal hepatic function	0.80	0.87
25 mg QOD severe HI/ 25 mg QD normal hepatic function	0.86	0.92

[a]$AUC_{tau,ss}$ was calculated from 648 hours to 672 hours (day 28).

Conclusions

- Severe HI resulted in a clinically meaningful increase in unbound but not total avapritinib exposure in the clinical study (BLU-285-0107)
- PBPK modelling and simulations were leveraged to identify dose reductions in patients with severe hepatic impairment that would lead to exposures comparable to those of participants with normal hepatic function
- Based on PBPK modeling, a modified starting dose of avapritinib is recommended for patients with severe hepatic impairment (Child-Pugh Class C)
  - GIST: 200 mg QD (approved dose is 300 mg QD)
  - AdvSM: 100 mg QD (approved dose is 200 mg QD)
  - ISM: 25 mg QOD (approved dose is 25 mg QD)
- No dose modification is required for patients with mild or moderate HI

References

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Acknowledgements

The authors thank the participants, their families, all other investigators, and all investigational site members involved in this study. This study was funded by Blueprint Medicines Corporation. Writing and editorial support under the direction of the authors was provided by Akanksha Srivastava, MSc, and Travis Taylor, BA, all of Paragon (a division of Prime, Knutsford). Responsibility for all opinions, conclusions and data interpretation lies with the authors.

Conflicts of interest/disclosures

Anitha Suram is an employee and equity holder of Blueprint Medicines Corporation. For all author disclosures, please contact medinfo@blueprintmedicines.com.