Effect of hepatic impairment on tepotinib pharmacokinetics

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CONCLUSIONS

- **No clinically relevant changes in total or unbound tepotinib exposure were observed in participants with mild or moderate hepatic impairment (HI), compared to those with normal hepatic function**
- **No dose modification is required for tepotinib in its approved indication for patients with mesenchymal–epithelial transition factor (*MET*) exon 14 skipping non-small cell lung cancer (NSCLC) with mild to moderate HI**

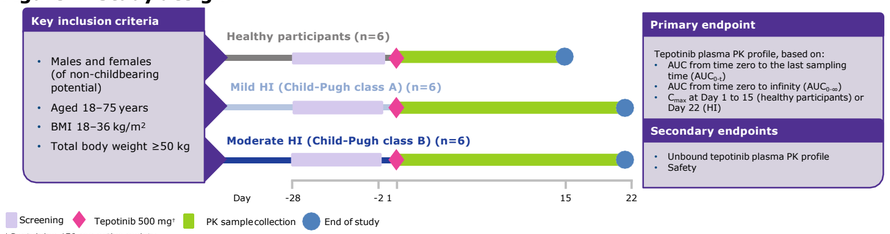
INTRODUCTION

- Tepotinib is an oral, once daily, highly selective, potent, MET inhibitor[1] first approved in Japan (2020) and subsequently in the USA, Brazil, Canada, and Switzerland (2021) for the treatment of advanced NSCLC with *MET*ex14 skipping,[2,3] based on data from the Phase II VISION study[4] (see Posters 1254P and 1255P)
- Tepotinib is subject to metabolism by CYP enzymes and biliary excretion; following a single oral dose of 498 mg radiolabeled tepotinib, approximately 78% of the dose is recovered in feces (45% unchanged) and 14% in urine (7% unchanged)[5]
- In VISION, patients with moderate or severe HI (total bilirubin >1.5-fold the ULN or AST/ALT >3-fold ULN) were excluded[5]
- This study aimed to investigate the effect of HI on the PK of tepotinib to determine if alterations of excretory and metabolic activities would necessitate a dose adjustment in patients with HI

METHODS

- This open-label, parallel-group, Phase I study (NCT03546608) included participants with mild (Child–Pugh A) and moderate (Child–Pugh B) HI, and healthy controls with normal hepatic function (age/weight/gender-matched to Child-Pugh B participants) (n=6 for all groups; **Figure 1**)
- Participants received a single dose of the clinically approved dose of 500 mg tepotinib (450 mg active moiety) after a standard breakfast
- Plasma samples were used to analyze exposure to both total tepotinib and its free (unbound) fraction

Figure 1. Study design



†Containing 450 mg active moiety.

RESULTS

Study population

- Of the 30 participants screened, 18 received tepotinib and completed the study
- Overall, most of the participants were male and most were white (**Table 1**)

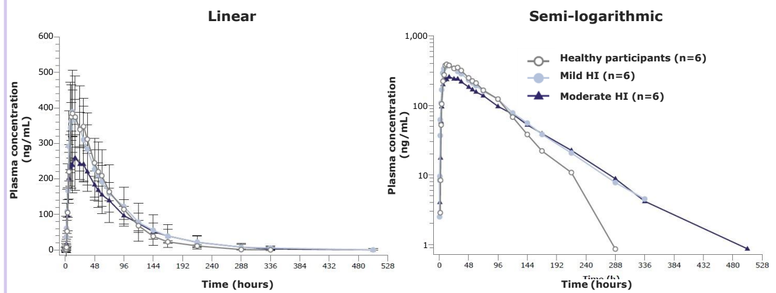
Table 1. Participant characteristics

	Healthy participants (n=6)	Mild HI (n=6)	Moderate HI (n=6)
Sex, n (%)			
Male	5 (83.3)	4 (66.7)	5 (83.3)
Female	1 (16.7)	2 (33.3)	1 (16.7)
Race, n (%)			
White	4 (66.7)	5 (83.3)	5 (83.3)
Black or African American	2 (33.3)	0 (0.0)	1 (16.7)
Asian	0 (0.0)	1 (16.7)	0 (0.0)
Age (years), median (range)	59 (47–68)	62 (53–63)	59 (49–73)
Weight (kg), median (range)	91.8 (78.3-115.9)	82.8 (65.4-95.1)	88.6 (67.5-119.5)
BMI (kg/m²), median (range)	30.35 (25.17–35.33)	29.45 (20.87–34.03)	27.52 (24.13–35.06)

Pharmacokinetics

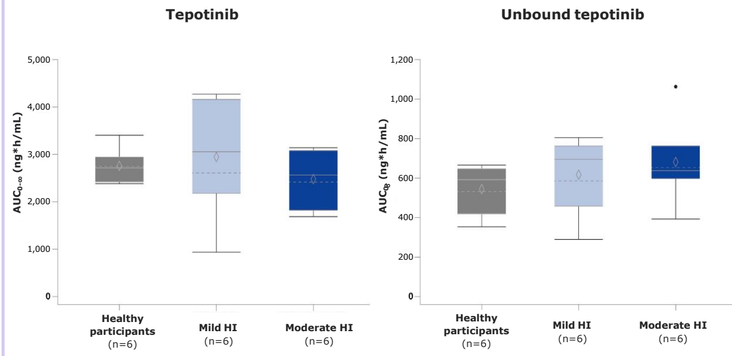
- Following a single dose of 500 mg tepotinib (450 mg active moiety), total tepotinib exposure was similar in participants with mild HI and healthy controls, with estimates of geometric mean ratios for $AUC_{0-\infty}$ and C_{max} from an analysis of variance close to 100% (**Figure 2** and **3, Table 2**)
- For participants with moderate HI, total tepotinib $AUC_{0-\infty}$ and C_{max} ratios were 12% and 29% lower, respectively, compared with healthy controls (**Figure 2** and **3, Table 2**)

Figure 2. Mean plasma concentration-time profile for tepotinib



No values were inputed for concentration below the lower limit of quantification in the semi-logarithmic scale.

Figure 3. Mean $AUC_{0-\infty}$ for total tepotinib and unbound tepotinib



Error bar whiskers indicate the range of values that are outside of the inter-quartile range (IQR), but within 1.5*IQR; box boundaries indicate 25th and 75th percentiles; solid lines indicate median; dotted lines indicate geometric mean; diamond indicates mean; black circle is an outlier.

- Unbound tepotinib exposure was similar in participants with mild and moderate HI and healthy controls
- Mean unbound tepotinib $AUC_{0-\infty}$ was 13% and 24% higher in participants with mild and moderate HI, respectively, compared with healthy controls (**Figure 3**); this is within the observed exposure variability and is not considered clinically relevant
- Exposure to free-fraction tepotinib was less dependent on liver function than total tepotinib exposure
- Increases in the tepotinib free fraction are in line with the known reduction in the synthesis of plasma proteins in HI[6]

Table 2. Tepotinib exposure

Comparison (versus normal hepatic function)	Total tepotinib PK parameter	Geometric mean ratio (%) (90% confidence interval)
Mild HI	$AUC_{0-\infty}$	94.99 (64.75, 139.35)
	C_{max}	102.45 (80.90, 129.73)
Moderate HI	$AUC_{0-\infty}$	87.92 (59.93, 128.98)
	C_{max}	71.02 (56.08, 89.93)

Safety

- Tepotinib was well tolerated in participants with mild or moderate HI
- Of the 18 participants, three experienced a treatment-emergent adverse event (TEAE): one healthy control and two participants with moderate HI
- Two of the three participants had TEAEs considered related to tepotinib; a healthy control experienced diarrhea (Grade 1) and a participant with moderate HI had bilateral rash on the arms (Grade 1)
- No participants had SAEs, Grade ≥ 3 TEAEs, discontinued due to a TEAE, or died during the study

CLINICAL IMPLICATION

- **Patients with mild or moderate hepatic impairment can receive tepotinib at the clinically approved dose**

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; $AUC_{0-\infty}$, area under the curve extrapolated to infinity; AUC_{0-t}, AUC from time zero to the last sampling time; BMI, body mass index; C_{max}, maximum plasma concentration; CYP, cytochrome P450; HI, hepatic impairment; MET, mesenchymal–epithelial transition factor; *MET*amp, *MET* amplification; *MET*ex14, *MET* exon 14; NSCLC, non-small cell lung cancer; PK, pharmacokinetic; SAE, serious adverse event; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

References: 1. Falchook GS, et al. *Clin Cancer Res.* 2020;26(6):1237–1246; 2. Japanese Ministry of Health, Labour and Welfare; TEPMETKO Prescribing Information. Published 2020; 3. FDA. TEPMETKO Prescribing Information. Published 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214096s000lbl.pdf. Accessed March 3, 2021; 4. Paik P, et al. *N Engl J Med*. 2020;383(10):931–943; 5. Johne A, et al. *Investigational New Drugs*. 2020;38:1507–1519; 6. Lala V, et al. Liver Function Tests. 2021 May 9. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 29494096.

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