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Assessment of the effect of hepatic impairment on iptacopan pharmacokinetics

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KEY FINDINGS & CONCLUSIONS

- Following a single oral 200 mg dose of iptacopan in participants with mild, moderate, or severe HI or matched healthy participants with normal hepatic function:
  - PK of total plasma iptacopan (C_{max}, AUC_{last}, and $AUC_{0-\infty}$) were similar in all groups, with no apparent impact of HI; these results indicate that no dose adjustment is required in patients with HI
  - PK of unbound plasma iptacopan increased with the severity of HI; this may be a result of decreased hepatic factor B synthesis due to HI[9,10] but factor B levels were not determined in this study
- Iptacopan was well tolerated in all participants and no safety or tolerability concerns were identified

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INTRODUCTION

- Iptacopan (LNP023) is an oral, first-in-class, highly potent, selective inhibitor of factor B, a key component of the alternative complement pathway[1]
- Phase 3 studies are currently ongoing to investigate the efficacy and safety of iptacopan in patients with paroxysmal nocturnal hemoglobinuria, C3 glomerulopathy, IgA nephropathy, atypical hemolytic uremic syndrome, and immune complex-mediated membranoproliferative glomerulonephritis[2–6]
- Iptacopan is predominantly cleared by hepatic metabolism (CYP2C8-mediated oxidation and direct glucuronidation); it is, therefore, important to understand the impact of HI on iptacopan PK to inform its clinical use[7]
- The objective was to assess the PK, safety, and tolerability of iptacopan in participants with HI, compared with participants with normal hepatic function

METHODS

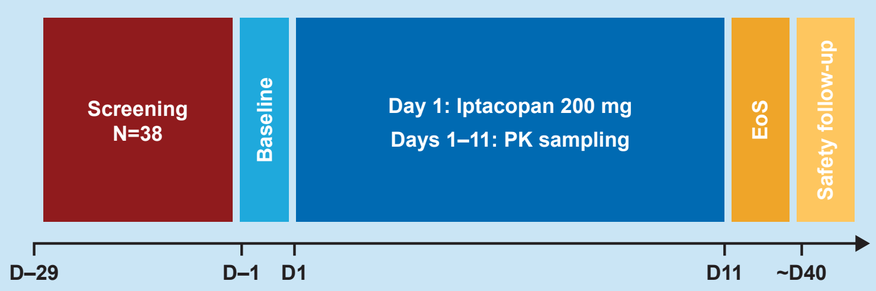
Study Design

- A Phase 1, open-label, parallel-group study of single-dose iptacopan (200 mg) in adult participants (18–75 years of age) with HI and matched healthy controls[8] (**Figure 1**)
  - HI was classified according to CP score as mild (CP score 5–6), moderate (CP score 7–9), severe (CP score 10–15), or normal liver function (the control group)
  - Controls were matched to participants with HI with respect to sex, age (±10 years), body weight (±15%), and smoking status
- Participants with severe HI were enrolled following an interim safety analysis performed at 240 h in participants with mild/moderate HI and matched controls (minimum n=3 per group)

PK and safety assessments

- Blood samples for plasma PK analysis were taken at 23 time points over 11 days (0–240 h)
  - Total plasma concentrations of iptacopan were determined using a validated LC-MS/MS method
  - Unbound plasma iptacopan concentrations were determined using a validated ultrafiltration method
- Safety assessments included reporting of AEs, vital signs, ECG, and clinical laboratory evaluations

Figure 1. Study design



D, day; EoS, end-of-study; PK, pharmacokinetics.

Statistical analysis

- The PK analysis set included all participants with an evaluable PK profile; the safety analysis set included all participants who received the study drug
- Formal statistical analyses were performed for primary PK parameters to compare data from each HI group with the control group
  - A linear model was fitted to the log-transformed PK parameters; median T_{max} was compared between groups using the Hodges–Lehmann estimator

RESULTS

- In total, 38 participants enrolled; all participants completed the study
- Demographic data and baseline characteristics are shown in **Table 1**

Table 1. Demographics and baseline disease characteristics

Characteristic	Control (n=16)	Mild HI (n=8)	Moderate HI (n=8)	Severe HI (n=6)	Total (N=38)
Age, years	58.3 (10.2)	63.6 (8.6)	61.4 (5.7)	49.2 (11.6)	58.6 (10.1)
Sex, n (%)					
Male	9 (56.3)	5 (62.5)	4 (50.0)	2 (33.3)	20 (52.6)
Female	7 (43.8)	3 (37.5)	4 (50.0)	4 (66.7)	18 (47.4)
Race, n (%)					
White	15 (93.8)	7 (87.5)	8 (100)	6 (100)	36 (94.7)
Other	1 (6.3)*	1 (12.5)†	0	0	2 (5.3)
Ethnicity, n (%)*					
Hispanic or Latino	11 (68.8)	5 (62.5)	7 (87.5)	4 (66.7)	27 (71.1)
BMI, kg/m²	29.2 (3.6)	31.7 (2.7)	32.1 (5.5)	30.2 (4.7)	30.5 (4.1)
CP total score	–	5.4 (0.5)	7.5 (0.5)	10.3 (0.5)	7.5 (2.1)‡

Data are mean (SD) unless stated otherwise.
*Black or African American; †American Indian or Alaska Native; ‡n=22.
BMI, body mass index; CP, Child–Pugh; HI, hepatic impairment; SD, standard deviation.

Total plasma iptacopan PK

- Following a single dose of iptacopan 200 mg, total iptacopan was rapidly absorbed; plasma concentrations declined in either a bi- or multi-phasic manner (**Figure 2**)
  - The terminal elimination phase varied by group and was slowest in participants with severe HI
- Total iptacopan C_{max}, AUC_{last}, and $AUC_{0-\infty}$ values were comparable between HI groups and the control group; all GMRs (HI vs control) were within ±10% of 1.00 with associated 90% CIs within ±25% of 1.00 (**Table 2**)
- There was no statistically significant increase in T_{max} for participants with HI vs the control group (**Table 2**)

Unbound plasma iptacopan PK

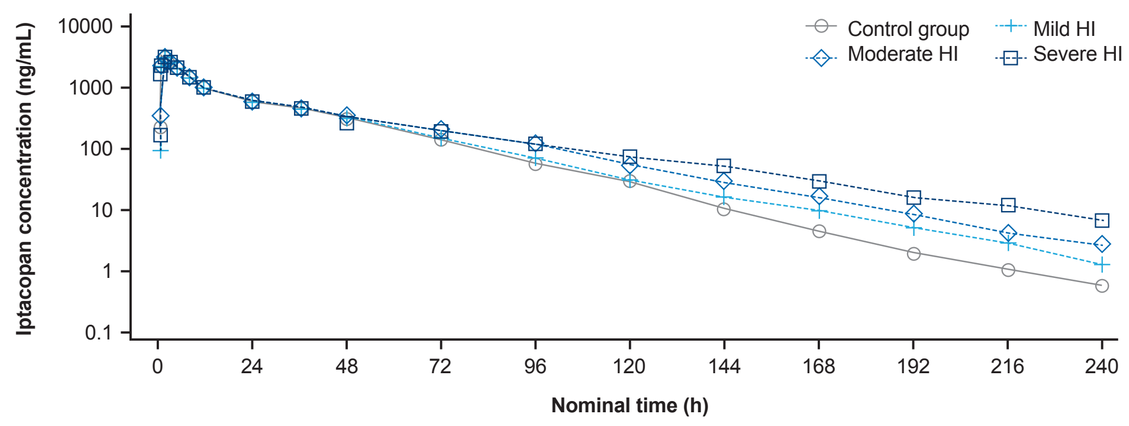
- Peak unbound plasma iptacopan exposures increased in the HI groups vs the control group (**Figure 3**)
  - The terminal elimination phase increased in moderate and severe HI
- Unbound iptacopan C_{max}, AUC_{last}, and $AUC_{0-\infty}$ increased with increasing severity of HI; all GMRs (HI vs control) were consistently greater than 1.25, and all 90% CIs exceeded 1.00 (**Table 3**)
- There was no statistically significant increase in T_{max} for participants with HI vs the control group (**Table 3**)

Table 2. PK of total plasma iptacopan

PK parameter	Control (n=16)	Mild HI (n=8)	Moderate HI (n=8)	Severe HI (n=6)
C_{max} (ng/mL)	3490 (25.1)	3560 (36.2)	3230 (22.3)	3260 (25.9)
GMR vs Control (90% CI)	–	1.04 (0.89, 1.22)	0.95 (0.82, 1.11)	0.92 (0.77, 1.10)
AUC_{last} (h.ng/mL)	52300 (23.7)	52200 (27.5)	52900 (30.3)	57700 (37.5)
GMR vs Control (90% CI)	–	1.03 (0.88, 1.21)	1.01 (0.86, 1.19)	1.03 (0.85, 1.25)
$AUC_{0-\infty}$ (h.ng/mL)	52300 (23.8)	52200 (27.5)	53000 (30.4)	58000 (37.7)
GMR vs Control (90% CI)	–	1.03 (0.88, 1.22)	1.01 (0.86, 1.19)	1.03 (0.85, 1.25)
T_{max} (h), median (min–max)	2.5 (1.0–4.0)	1.9 (1.0–3.0)	1.5 (0.75–4.0)	3.0 (0.97–4.0)
Median difference vs Control (90% CI)	–	−0.50 (−1.25, 0.00)	−0.88 (−1.50, 0.00)	0.25 (−0.53, 1.50)

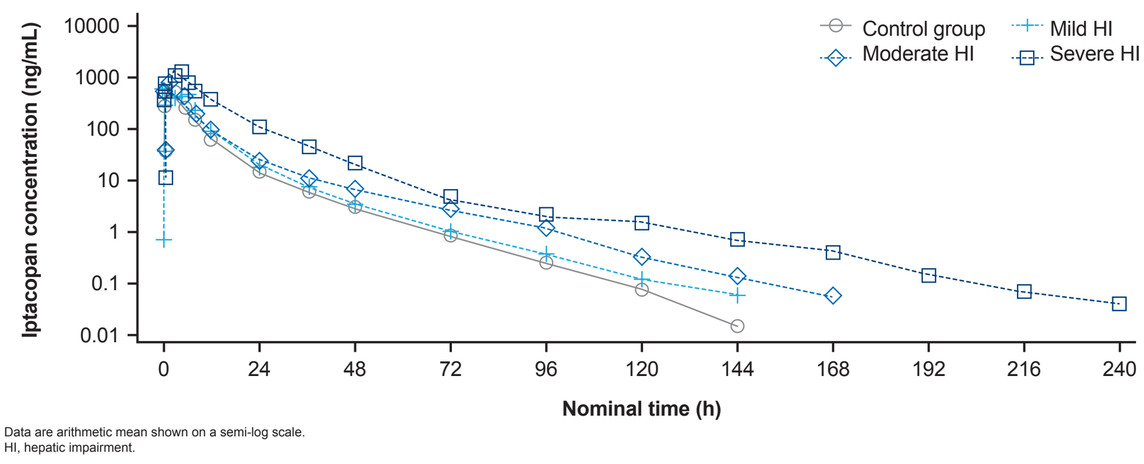
Data are shown as geo-mean (CV%) unless stated otherwise.
$AUC_{0-\infty}$, area under the curve from time 0 extrapolated to infinity; AUC_{last}, area under the curve from time 0 to time of the last measurable concentration; C_{max}, maximum concentration; CI, confidence interval; CV, coefficient of variation; geo-mean, geometric mean; GMR, geometric mean ratio; HI, hepatic impairment; max, maximum; min, minimum; PK, pharmacokinetics; T_{max}, time to maximum concentration.

Figure 2. Concentration–time profiles of total plasma iptacopan



Data are arithmetic mean shown on a semi-log scale.
HI, hepatic impairment.

Figure 3. Concentration–time profiles of unbound plasma iptacopan



Data are arithmetic mean shown on a semi-log scale.
HI, hepatic impairment.

Table 3. PK of unbound plasma iptacopan

PK parameter	Control (n=16)	Mild HI (n=8)	Moderate HI (n=8)	Severe HI (n=6)
C_{max} (ng/mL)	711 (32.1)	905 (70.0)	1070 (41.8)	1450 (17.9)
GMR vs Control (90% CI)	–	1.38 (1.11, 1.71)	1.67 (1.35, 2.08)	2.11 (1.63, 2.73)
AUC_{last} (h.ng/mL)	3800 (26.6)	5350 (56.3)	5550 (42.2)	13700 (33.2)
GMR vs Control (90% CI)	–	1.48 (1.26, 1.73)	1.58 (1.35, 1.85)	3.72 (3.09, 4.47)
$AUC_{0-\infty}$ (h.ng/mL)	3800 (26.5)	5370 (56.1)	5560 (42.2)	13700 (33.2)
GMR vs Control (90% CI)	–	1.48 (1.27, 1.73)	1.58 (1.35, 1.85)	3.71 (3.08, 4.47)
T_{max} (h), median (min–max)	2.25 (1–4)	1.88 (1–3)	2.25 (0.75–3)	3.5 (1–4)
Median difference vs Control (90% CI)	–	−0.50 (−1.25, 0.00)	−0.50 (−1.50, 0.00)	1.00 (−0.53, 1.50)

Data are shown as geo-mean (CV%) unless otherwise stated.
$AUC_{0-\infty}$, area under the curve from time 0 extrapolated to infinity; AUC_{last}, area under the curve from time 0 to time of the last measurable concentration; C_{max}, maximum concentration; CI, confidence interval; CV, coefficient of variation; geo-mean, geometric mean; GMR, geometric mean ratio; HI, hepatic impairment; max, maximum; min, minimum; PK, pharmacokinetics; T_{max}, time to maximum concentration.

Safety assessment

- One participant with moderate HI experienced two AEs (basal ganglia hemorrhage and acute respiratory failure) considered not to be related to the study treatment
  - The basal ganglia hemorrhage occurred after the EoS visit and was classified as a serious AE
- No other AEs were reported, and there were no clinically relevant findings in clinical laboratory evaluations, ECG, or vital signs

Abbreviations

AE, adverse event; $AUC_{0-\infty}$, area under the curve from time 0 extrapolated to infinity; AUC_{last}, area under the curve from time 0 to time of the last measurable concentration; CI, confidence interval; C_{max}, maximum concentration; CP, Child–Pugh; CV, coefficient of variation; CYP2C8, cytochrome P450 2C8; D, day; ECG, electrocardiogram; EoS, end-of-study; GMR, geometric mean ratio; HI, hepatic impairment; IgA, immunoglobulin A; LC-MS/MS, liquid chromatography tandem mass spectrometry; max; maximum; min, minimum; PK, pharmacokinetics; SD, standard deviation; T_{max}, time to maximum concentration.

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Disclosures

RS is an employee of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA. **GJ** is an employee of Novartis Pharma AG, Basel, Switzerland. **PKN** is an employee of Novartis Healthcare Pvt. Ltd., Hyderabad, India. **KK** is an employee of Novartis Institutes of BioMedical Research, Cambridge, Massachusetts, USA.

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