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Assessment of drug interactions with iptacopan

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KEY FINDINGS & CONCLUSIONS

- Co-administration of clopidogrel or cyclosporine, which inhibit the main pathways attributed to iptacopan clearance (CYP2C8 and OATP, respectively), had no clinically meaningful effects on the $t_{½}$, distribution, or CL/F of iptacopan
- Similarly, iptacopan had no impact on the distribution or clearance of the P-gp substrate, digoxin, and the OATP substrate, rosuvastatin
- Co-administration of iptacopan with the study drugs was well tolerated, with no severe or serious AEs

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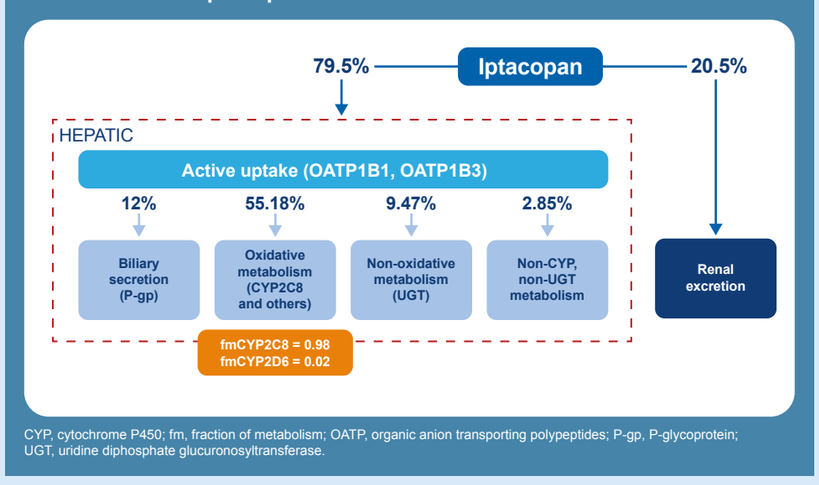
INTRODUCTION

- 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 glomerulonephritis, IgA nephropathy, atypical hemolytic uremic syndrome, and immune complex-mediated membranoproliferative glomerulonephritis[2–6]
- The medical management of complement-mediated kidney diseases can be complex, typically involving several different medications[7–9]; therefore, evaluating potential DDIs is key to understanding the safety and efficacy of iptacopan administration
- The active uptake of iptacopan into hepatocytes is mediated by drug transporters OATP1B1/1B3; the main pathways attributed to iptacopan clearance are hepatic metabolism (mainly CYP2C8-mediated oxidation and, to a lesser extent, glucuronidation and biliary excretion via P-gp transporter), with a minor contribution from direct renal excretion[10,11] (**Figure 1**)
- The objectives were:
  - To determine the effects of clopidogrel (moderate CYP2C8 inhibitor) and cyclosporine (strong OATP inhibitor) on the distribution and clearance of iptacopan in plasma
  - To assess the effect of iptacopan on the distribution and clearance of digoxin (P-gp substrate) and rosuvastatin (OATP substrate) in plasma
  - To assess the safety and tolerability of iptacopan in the absence or presence of clopidogrel, cyclosporine, digoxin, and rosuvastatin

Figure 1. Fractional contribution of drug elimination pathways to the clearance of iptacopan[11]



CYP, cytochrome P450; fm, fraction of metabolism; OATP, organic anion transporting polypeptides; P-gp, P-glycoprotein; UGT, uridine diphosphate glucuronosyltransferase.

METHODS

Study design

- An open-label, three-cohort, two-period, fixed-sequence, DDI Phase 1 study; eligible participants included healthy males and females (of non-childbearing potential) who were 18–55 years of age
- Participants were enrolled into one of three cohorts (**Figure 2**)
- All study drugs were administered orally, and all perpetrator drugs used were dosed to a steady state

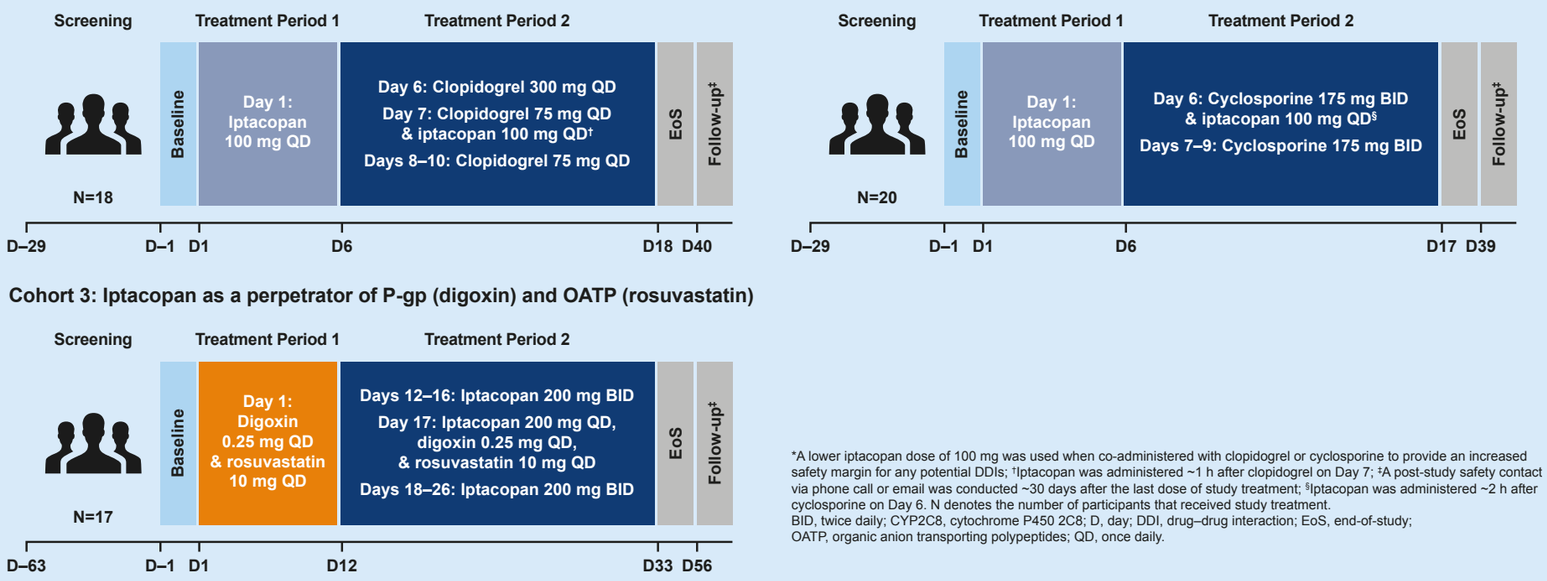
PK and safety assessments

- In Cohorts 1 and 2, plasma PK samples were collected up to 96 h after administration of iptacopan (Treatment Period 1) and after co-administration of iptacopan and clopidogrel or cyclosporine (Treatment Period 2)
- In Cohort 3, plasma PK samples were collected up to 240 h (10 days) after digoxin and rosuvastatin co-administration (Treatment Period 1) and after co-administration of iptacopan, digoxin, and rosuvastatin (Treatment Period 2)
- Plasma concentrations of iptacopan, digoxin, and rosuvastatin were determined by validated LC-MS/MS
- Safety assessments included reporting of AEs, vital signs, electrocardiogram, and clinical laboratory evaluations

Statistical analysis

- The PK analysis set included all participants with ≥1 valid PK measurement; the safety analysis set included all participants who received ≥1 dose of study drug
- PK parameters for iptacopan, digoxin, and rosuvastatin were determined using non-compartmental methods with Phoenix WinNonlin Version 8.0 or higher (Pharsight Corp., Certara Company, Princeton, New Jersey, USA)

Figure 2. Study design



*A lower iptacopan dose of 100 mg was used when co-administered with clopidogrel or cyclosporine to provide an increased safety margin for any potential DDIs; †Iptacopan was administered ~1 h after clopidogrel on Day 7; ‡A post-study safety contact via phone call or email was conducted ~30 days after the last dose of study treatment; §Iptacopan was administered ~2 h after cyclosporine on Day 6. N denotes the number of participants that received study treatment.
BID, twice daily; CYP2C8, cytochrome P450 2C8; D, day; DDI, drug–drug interaction; EoS, end-of-study; OATP, organic anion transporting polypeptides; QD, once daily.

RESULTS

- In total, 56 healthy participants enrolled in the study
  - One participant in Cohort 2 did not receive study treatment and was excluded from the analyses
- The mean age of participants was 40.9 years, and most were male (92.7%) and White (92.7%)
  - All other baseline demographics were balanced across the cohorts (**Table 1**)

Table 1. Demographics

Characteristic	Cohort 1 (n=18)	Cohort 2 (n=20)	Cohort 3 (n=17)	Total (N=55)
Age, years	37.1 (13.1)	41.6 (10.6)	44.2 (9.8)	40.9 (11.4)
Sex, n (%)				
Male	17 (94.4)	19 (95.0)	15 (88.2)	51 (92.7)
Race, n (%)				
White	17 (94.4)	20 (100)	14 (82.4)	51 (92.7)
American Indian/ Alaska Native	1 (5.6)	0	1 (5.9)	2 (3.6)
Other	0	0	2 (11.8)	2 (3.6)
Ethnicity, n (%)*				
Hispanic or Latino	2 (11.1)	1 (5.0)	3 (17.6)	6 (10.9)
Not Hispanic or Latino	15 (83.3)	19 (95.0)	14 (82.4)	48 (87.3)
Weight, kg	82.2 (11.7)	77.8 (9.9)	82.2 (10.5)	80.6 (10.7)
Height, cm	180.8 (6.8)	178.5 (5.8)	177.3 (7.8)	178.9 (6.8)

Data are mean (SD) unless stated otherwise.
*Ethnicity was defined as 'Unknown' in one participant in Cohort 1.
SD, standard deviation.

Iptacopan as a victim of CYP2C8 or OATP inhibition

- The mean plasma concentration–time profiles of iptacopan in the absence and presence of clopidogrel or cyclosporine are shown in **Figure 3**

CYP2C8 inhibitor (clopidogrel)

- The median T_{max} of iptacopan following a single 100 mg dose was 1.51 h (min–max: 1.00–4.00 h) in the absence of clopidogrel and 2.50 h (min–max: 1.50–5.98 h) in the presence of clopidogrel
- The geo-mean $t_{½}$ of iptacopan was 16.5 h when administered alone and 21.5 h in the presence of clopidogrel (**Table 2**)
- The geo-mean CL/F of iptacopan in the absence and presence of clopidogrel was 3.61 L/h and 2.62 L/h, respectively; Vz/F of iptacopan was similar whether administered alone or administered with clopidogrel (**Table 2**)

OATP inhibitor (cyclosporine)

- The median T_{max} of iptacopan following a single 100 mg dose was 2.00 h (min–max: 1.00–4.00 h) in the absence of cyclosporine and 2.50 h (min–max: 1.00–4.03 h) in the presence of cyclosporine
- The geo-mean $t_{½}$ of iptacopan was 15.8 h when administered alone and 23.7 h in the presence of cyclosporine (**Table 2**)
- The geo-mean CL/F of iptacopan was 3.76 L/h in the absence of cyclosporine and 2.65 L/h in the presence of cyclosporine; Vz/F of iptacopan was similar whether administered alone or with cyclosporine (**Table 2**)

Table 2. Impact of CYP2C8 and OATP inhibitors on the PK of iptacopan

	Cohort 1		Cohort 2	
PK parameter	Iptacopan (n=18)	Iptacopan + clopidogrel (n=17)	Iptacopan (n=18)	Iptacopan + cyclosporine (n=13)
$t_{½}$ (h)				
Mean (SD)	17.2 (5.4)	22.5 (7.1)	16.6 (5.6)	24.2 (4.7)
Geo-mean	16.5	21.5	15.8	23.7
Geo-mean CV%*	29.3	29.7	34.1	21.5
CL/F (L/h)				
Mean (SD)	3.72 (0.93)	2.72 (0.76)	3.87 (1.03)	2.75 (0.85)
Geo-mean	3.61	2.62	3.76	2.65
Geo-mean CV%*	26.2	29.5	24.8	28.0
Vz/F (L)				
Mean (SD)	89.5 (31.6)	82.6 (13.8)	87.5 (19.7)	91.8 (15.3)
Geo-mean	85.7	81.5	85.5	90.5
Geo-mean CV%*	28.6	17.3	22.8	17.2

Data are shown for participants with non-missing values.
*Geo-mean CV% is calculated as SQRT(exp(variance for log-transformed data)–1)*100.
CL/F, apparent total body clearance of drug from plasma; CV, coefficient of variation; geo-mean; geometric mean; PK, pharmacokinetics; SD, standard deviation; SQRT, square root; $t_{½}$, elimination half-life; Vz/F, apparent volume of distribution during the terminal phase.

Iptacopan as a perpetrator of P-gp and OATP inhibition

- The mean plasma concentration–time profiles of digoxin or rosuvastatin in the absence and presence of iptacopan are shown in **Figure 4**

P-gp inhibition (digoxin)

- The median T_{max} of digoxin in both the absence and presence of iptacopan was virtually unchanged at 1.00 h (min–max: 0.50–2.00 h) and 1.00 h (min–max: 0.50–2.05 h), respectively
- The geo-mean $t_{½}$ of digoxin was comparable in the absence and presence of iptacopan (**Table 3**)
- Similarly, the CL/F and Vz/F of digoxin, whether administered alone or co-administered with iptacopan, were unaffected

OATP inhibition (rosuvastatin)

- The median T_{max} of rosuvastatin in both the absence and presence of iptacopan were similar at 4.00 h (min–max: 3.00–10.00 h) and 4.00 h (min–max: 2.00–6.00 h), respectively
- The geo-mean $t_{½}$ of rosuvastatin in the absence and presence of iptacopan remained unchanged (**Table 3**)
- The CL/F and Vz/F of rosuvastatin, whether administered alone or co-administered with iptacopan, were unaffected

Table 3. Impact of iptacopan on the PK of digoxin and rosuvastatin, respectively

	Cohort 3			
PK parameter	Digoxin (n=17)	Digoxin + iptacopan (n=16)	Rosuvastatin (n=17)	Rosuvastatin + iptacopan (n=17)
$t_{½}$ (h)				
Mean (SD)	42.8 (11.3)	42.7 (9.75)	15.0 (11.4)	12.8 (2.54)
Geo-mean	41.4	41.3	13.0	12.6
Geo-mean CV%*	27.0	28.3	50.7	21.0
CL/F (L/h)				
Mean (SD)	16.5 (3.86)	16.3 (3.97)	166 (86.8)	164 (76.0)
Geo-mean	16.1	15.8	151	149
Geo-mean CV%*	22.7	25.2	44.4	45.7
Vz/F (L)				
Mean (SD)	997 (281)	970 (230)	3270 (2190)	2910 (1160)
Geo-mean	963	944	2830	2710
Geo-mean CV%*	27.0	25.2	55.0	40.9

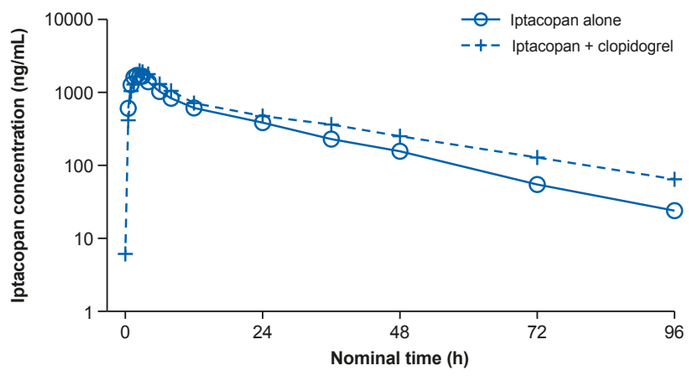
Data are shown for participants with non-missing values.
*Geo-mean CV% is calculated as SQRT(exp(variance for log-transformed data)–1)*100.
CL/F, apparent total body clearance of drug from plasma; CV, coefficient of variation; PK, pharmacokinetics; SD, standard deviation; SQRT, square root; $t_{½}$, elimination half-life; Vz/F, apparent volume of distribution during the terminal phase.

Safety assessment

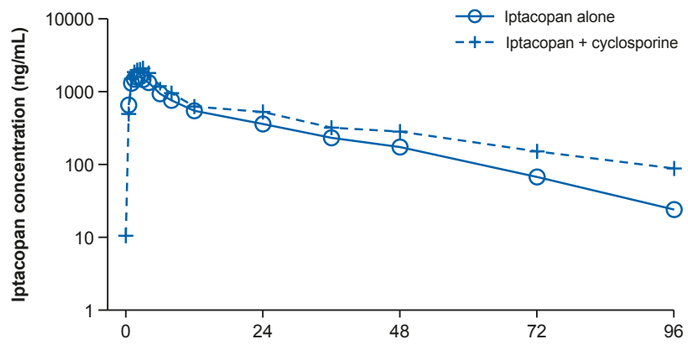
- No deaths, serious AEs, or clinically relevant abnormalities in laboratory parameters or vital signs were reported
- In Cohort 1, 10 participants (55.6%) experienced 23 AEs; all were mild
  - AEs suspected to be related to the study drugs were reported by 22.2% of participants, of which 4/8 AEs were suspected to be related to iptacopan alone
  - No AEs led to study discontinuation
- In Cohort 2, 12 participants (60.0%) experienced 28 AEs, including six moderate AEs; the remainder were mild
  - AEs suspected to be related to the study drugs were reported by 40.0% of participants, of which 7/16 AEs were related to iptacopan alone
  - Two participants (10.0%) discontinued the study post-administration of iptacopan, with one AE suspected to be related to the study drug
- In Cohort 3, 10 participants (58.8%) experienced 29 AEs, of which six were moderate and the rest mild
  - AEs suspected to be related to the study drugs were reported by 29.4% of participants, of which 9/13 AEs were related to iptacopan alone
  - One participant (5.9%) discontinued the study during Treatment Period 2 due to four TEAEs suspected to be related to iptacopan

Figure 3. Concentration–time profiles of iptacopan

A. CYP2C8 inhibition (clopidogrel)



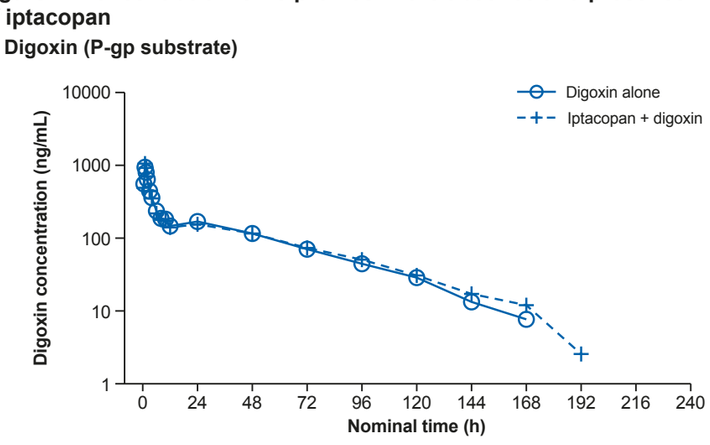
B. OATP inhibition (cyclosporine)



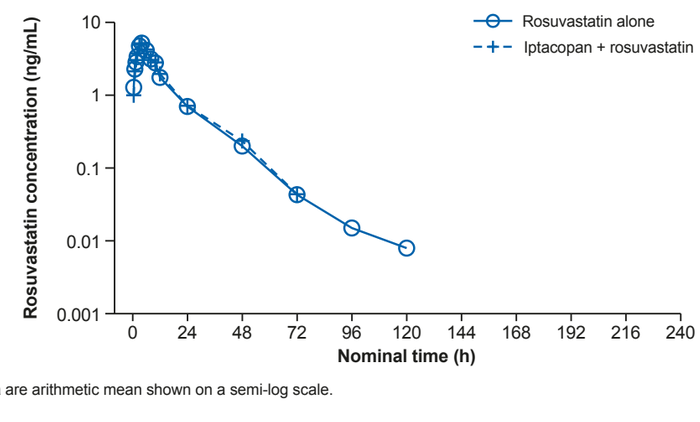
Data are arithmetic mean shown on a semi-log scale.

Figure 4. Concentration–time profiles in the absence and presence of iptacopan

A. Digoxin (P-gp substrate)



B. Rosuvastatin (OATP substrate)



Data are arithmetic mean shown on a semi-log scale.

Abbreviations

AE, adverse event; BID, twice daily; C3, complement 3; CL/F, apparent total body clearance of drug from plasma; CV, coefficient of variation; CYP, cytochrome P450; CYP2C8, cytochrome P450 2C8; D, day; DDI, drug–drug interaction; EoS, end-of-study; fm, fraction of metabolism; geo-mean, geometric mean; h, hours; IgA, immunoglobulin A; LC-MS/MS, liquid chromatography tandem mass spectrometry; max, maximum; min, minimum; OATP, organic anion transporting polypeptides; P-gp, P-glycoprotein; PK, pharmacokinetics; QD, once daily; SD, standard deviation; SQRT, square root; $t_{½}$, elimination half-life; T_{max}, time to maximum concentration; UGT, uridine diphosphate glucuronosyltransferase; Vz/F, apparent volume of distribution during the terminal phase.

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