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Assessment of drug interactions with Iptacopan

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Conclusions

- CYP2C8 (clopidogrel) and OATP (cyclosporine) inhibition had no clinically relevant effects on the plasma PK of iptacopan
- The presence of iptacopan had minimal-to-no effects on the PK of the P-gp substrate (digoxin), or the OATP substrate (rosuvastatin)
- Overall, administration of iptacopan with study drugs was well tolerated, with no serious AEs
- The results of this study provide reassurance that iptacopan can be used in patients on complex drug regimens, including inhibitors of CYP2C8 and OATP and substrates of P-gp and OATP, without clinically relevant, iptacopan-related DDIs

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]
- Medical management can be complex for patients with complement-mediated kidney disease;[7–9] evaluating potential DDIs is key to understanding the safety and efficacy of iptacopan administration
- The active uptake of iptacopan into hepatocytes is likely mediated by OATP; iptacopan is predominantly cleared by hepatic metabolism (mainly CYP2C8-mediated oxidation, glucuronidation, and biliary excretion via P-gp transporter), and, to a lesser extent, direct renal excretion[10,11]

Objectives

- To investigate the effect of clopidogrel (CYP2C8 inhibitor) and cyclosporine (OATP inhibitor) on the PK of iptacopan
- To assess the effect of iptacopan on the PK of digoxin (P-gp substrate) and rosuvastatin (OATP substrate)
- To assess the safety and tolerability of iptacopan in the absence or presence of clopidogrel, cyclosporine, digoxin, and rosuvastatin

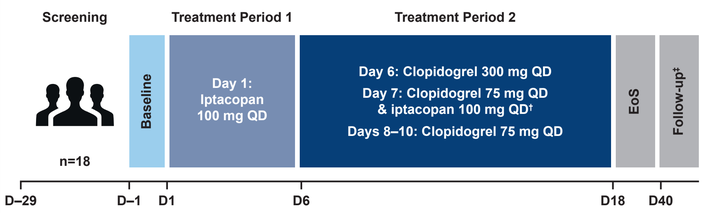
Methods

Study design

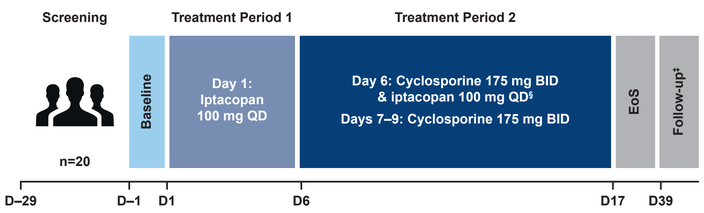
- An open-label, three-cohort, two-period, fixed-sequence, DDI Phase 1 study in healthy participants aged 18–55 years
- Participants were enrolled into one of three cohorts (**Figure 1**)
- All drugs were administered orally, and all perpetrator drugs used were dosed to a steady state

Figure 1. Study design

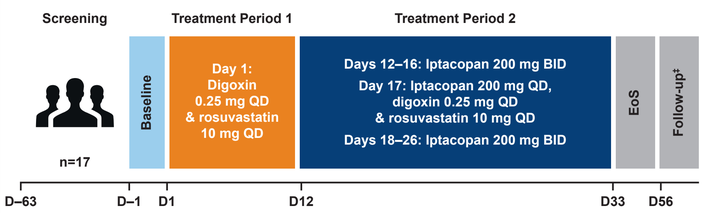
Cohort 1: Iptacopan as a victim of CYP2C8 inhibition (clopidogrel)*



Cohort 2: Iptacopan as a victim of OATP inhibition (cyclosporine)*



Cohort 3: Iptacopan as a perpetrator of P-gp (digoxin) and OATP (rosuvastatin)



*A lower iptacopan dose of 100 mg was used when co-administered with clopidogrel or cyclosporine to provide an increased safety margin for 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.
BID, twice daily; CYP2C8, cytochrome P450 2C8; D, day; DDI, drug–drug interaction; EoS, end-of-study; h, hour; OATP, organic anion transporting polypeptides; QD, once daily.

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 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 were determined using non-compartmental methods with Phoenix WinNonlin Version 8.0 or higher (Pharsight Corp., Certara Company, Princeton, New Jersey, USA)
- To compare treatments, log-transformed PK parameters were assessed using an ANOVA model with treatment as a fixed effect and participant as a random effect

Results

- In total, 56 healthy participants enrolled in the study
  - One participant in Cohort 2 did not receive the study drug and was excluded from analyses
- The mean age of participants was 40.9 years, and most (92.7%) were male and White
  - 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)
BMI, kg/m²	25.1 (3.2)	24.4 (2.5)	26.2 (2.8)	25.2 (2.9)

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

Iptacopan as a victim of CYP2C8 or OATP inhibition

CYP2C8 inhibitor (clopidogrel)

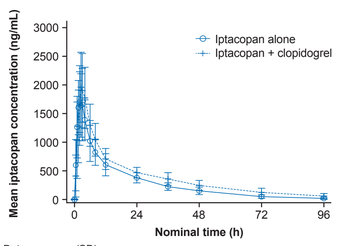
- Median T_{max} following a single 100 mg dose of iptacopan was 1.51 h (min–max: 1.00–4.00 h) in the absence of clopidogrel and 2.50 h (min–max: 1.50–5.98 h) in the presence of clopidogrel
- In the presence of clopidogrel, the geo-mean C_{max} of iptacopan increased by 5% and the total exposure (AUC_{last} and $AUC_{0-\infty}$) increased by 33% and 36%, respectively (**Figure 2A; Table 2**)

OATP inhibitor (cyclosporine)

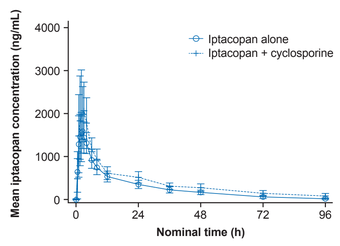
- OATP inhibition followed a similar trend to CYP2C8 inhibition: median T_{max} following a single 100 mg dose of iptacopan was 2.00 h (min–max: 1.00–4.00 h) and 2.50 h (min–max: 1.00–4.03 h) in the absence and presence of cyclosporine, respectively
- In the presence of cyclosporine, the geo-mean C_{max} of iptacopan increased by 41%, and total exposure (AUC_{last} and $AUC_{0-\infty}$) increased by 46% and 50%, respectively (**Figure 2B**; **Table 2**)

Figure 2. Concentration–time profiles of iptacopan

A. CYP2C8 inhibition (clopidogrel)



B. OATP inhibition (cyclosporine)



Data are mean (SD).
CYP2C8, cytochrome P450 2C8; h, hour; OATP, organic anion transporting polypeptides; SD, standard deviation.

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

PK parameter	Cohort 1: Iptacopan	Cohort 1: Iptacopan + clopidogrel	Cohort 2: Iptacopan	Cohort 2: Iptacopan + cyclosporine
C_{max} (ng/mL)	n=18	n=18	n=19	n=15
Adjusted geo-mean (90% CI)	1944.28 (1745.97, 2165.10)	2043.92 (1835.46, 2276.07)	1803.29 (1618.37, 2009.33)	2539.62 (2276.39, 2833.28)
Geo-mean ratio (90% CI)	1.05 (0.97, 1.14)		1.41 (1.35, 1.47)	
Intra-participant CV%*	14.02		6.31	
AUC_{last} (h.ng/mL)	n=18	n=18	n=18	n=15
Adjusted geo-mean (90% CI)	27081.88 (24449.64, 29997.50)	35940.72 (32447.44, 39810.08)	25872.59 (23483.32, 28504.95)	37686.59 (34158.66, 41578.89)
Geo-mean ratio (90% CI)	1.33 (1.26, 1.40)		1.46 (1.39, 1.52)	
Intra-participant CV%*	9.58		7.15	
$AUC_{0-\infty}$ (h.ng/mL)	n=18	n=17	n=18	n=13
Adjusted geo-mean (90% CI)	27714.38 (24813.29, 30954.65)	37800.85 (33817.24, 42253.72)	26610.59 (23985.42, 29523.07)	40012.00 (35941.71, 44543.24)
Geo-mean ratio (90% CI)	1.36 (1.28, 1.45)		1.50 (1.42, 1.59)	
Intra-participant CV%*	10.59		8.33	

Data are shown for participants with non-missing values.
*CV% is calculated as 100*SQRT(exp(MSE)-1).
$AUC_{0-\infty}$, area under the curve from time 0 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; CV, coefficient of variation; geo-mean, geometric mean; MSE, mean square error; PK, pharmacokinetics; SQRT, square root.

Iptacopan as a perpetrator of P-gp and OATP inhibition

- Co-administration of iptacopan 200 mg had no effect on the median T_{max} of digoxin (P-gp substrate) or rosuvastatin (OATP substrate)

P-gp inhibition (digoxin)

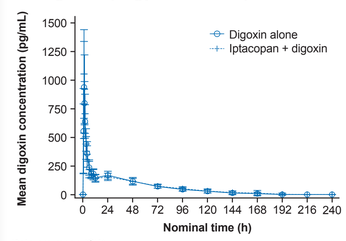
- In the presence of iptacopan, the geo-mean C_{max} of digoxin increased by 8%, and total exposure (AUC_{last} and $AUC_{0-\infty}$) remained virtually unchanged (**Figure 3A**; **Table 3**)

OATP inhibition (rosuvastatin)

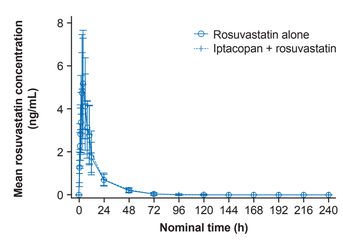
- Geo-mean C_{max} of rosuvastatin and total exposure (AUC_{last} and $AUC_{0-\infty}$) were similar in the absence and presence of iptacopan (**Figure 3B**; **Table 3**)

Figure 3. Concentration–time profiles in the absence and presence of iptacopan

A. Digoxin (P-gp substrate)



B. Rosuvastatin (OATP substrate)



Data are mean (SD).
h, hour; OATP, organic anion transporting polypeptides; P-gp, P-glycoprotein; SD, standard deviation.

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

PK parameter	Cohort 3: Digoxin	Cohort 3: Digoxin + iptacopan	Cohort 3: Rosuvastatin	Cohort 3: Rosuvastatin + iptacopan
C_{max} (ng/mL or pg/mL*)	n=17	n=17	n=17	n=17
Adjusted geo-mean (90% CI)	977.76 (860.79, 1110.62)	1054.39 (928.25, 1197.67)	4.94 (4.17, 5.85)	4.95 (4.18, 5.85)
Geo-mean ratio (90% CI)	1.08 (0.94, 1.24)		1.00 (0.87, 1.15)	
Intra-participant CV%†	23.15		23.08	
AUC_{last} (h.ng/mL or h.pg/mL*)	n=17	n=17	n=17	n=17
Adjusted geo-mean (90% CI)	13930.19 (12553.28, 15458.12)	13916.84 (12541.25, 15443.30)	61.46 (50.77, 74.41)	63.50 (52.45, 76.88)
Geo-mean ratio (90% CI)	1.00 (0.90, 1.11)		1.03 (0.92, 1.16)	
Intra-participant CV%†	17.79		19.79	
$AUC_{0-\infty}$ (h.ng/mL or h.pg/mL*)	n=17	n=16	n=17	n=17
Adjusted geo-mean (90% CI)	15508.81 (14069.64, 17095.19)	15836.60 (14338.60, 17491.11)	66.17 (55.26, 79.25)	66.90 (55.87, 80.12)
Geo-mean ratio (90% CI)	1.02 (0.93, 1.12)		1.01 (0.91, 1.12)	
Intra-participant CV%†	15.14		17.39	

Data are shown for participants with non-missing values.
*The PK units for digoxin were in picograms whereas units for rosuvastatin were in nanograms; †CV% is calculated as 100*SQRT(exp(MSE)-1).
$AUC_{0-\infty}$, area under the curve from time 0 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; CV, coefficient of variation; geo-mean, geometric mean; MSE, mean square error; PK, pharmacokinetics; SQRT, square root.

Safety assessment

- 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 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
- No deaths, serious AEs, or clinically relevant abnormalities in laboratory parameters or vital signs were reported

References

1. Schubart A et al. *Proc Natl Acad Sci U S A*. 2019;116:7926–31.
2. ClinicalTrials.gov. NCT04820530. Accessed: January 19, 2023.
3. ClinicalTrials.gov. NCT04817618. Accessed: January 19, 2023.
4. ClinicalTrials.gov. NCT04578834. Accessed: January 19, 2023.
5. ClinicalTrials.gov. NCT04889430. Accessed: January 19, 2023.
6. ClinicalTrials.gov. NCT05755386. Accessed: March 7, 2023.
7. Bektas M et al. *J Manag Care Spec Pharm*. 2020;26:S14–20.
8. Goodship THJ et al. *Kidney Int*. 2017;91:539–51.
9. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. *Kidney Int*. 2021;100:S1–276.
10. Jang JH et al. *Blood Adv*. 2022;6:4450–60.
11. Data on File. LNP023C1. LNP023 Summary of Clinical Pharmacology Studies, Novartis Pharmaceuticals Corp; March 2023.

Abbreviations

AE, adverse event; ANOVA, analysis of variance; $AUC_{0-\infty}$, 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; BID, twice daily; BMI, body mass index; C3, complement 3; CI, confidence interval; C_{max}, maximum concentration; CV, coefficient of variation; CYP2C8, cytochrome P450 2C8; D, day; DDI, drug–drug interaction; EoS, end-of-study; geo-mean, geometric mean; h, hour; IgA, immunoglobulin A; LC-MS/MS, liquid chromatography tandem mass spectrometry; max, maximum; min, minimum; MSE, mean square error; OATP, organic anion transporting polypeptides; P-gp, P-glycoprotein; PK, pharmacokinetics; QD, once daily; SD, standard deviation; SQRT, square root; T_{max}, time to maximum concentration.

Disclosures

RS, **BS**, and **AT** are employees of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA. **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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