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Pharmacokinetics of single doses of iptacopan

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KEY FINDINGS & CONCLUSIONS

- Following SAD administration, iptacopan demonstrated rapid absorption, a moderately long $t_{½}$, and low inter-subject variability in exposure parameters across all dose groups
- SAD of iptacopan demonstrated an under-proportional dose–exposure relationship, likely due to the high-affinity binding of iptacopan to factor B in systemic circulation
- Iptacopan was well tolerated in healthy participants in all dosing groups
- The results of this study demonstrate a favorable PK profile and support the clinical development of iptacopan

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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]
- Here we report the PK and safety of SAD of iptacopan in healthy participants as part of a Phase 1 study
- The objective was to evaluate the PK, safety, and tolerability of SAD of iptacopan in healthy participants

METHODS

Study Design

- A randomized, first-in-human, Phase 1 study; eligible participants included healthy males and females (of non-childbearing potential), 18–55 years of age
  - The study consisted of three parts: a SAD study, a MAD study, and a food-effect evaluation study
- The SAD phase was a participant-blinded, placebo-controlled study; eligible participants were randomized to receive a single oral dose of iptacopan (5 mg, 10 mg, 25 mg, 50 mg, 100 mg, 200 mg, or 400 mg) or matched placebo in a 3:1 ratio (**Figure 1**)

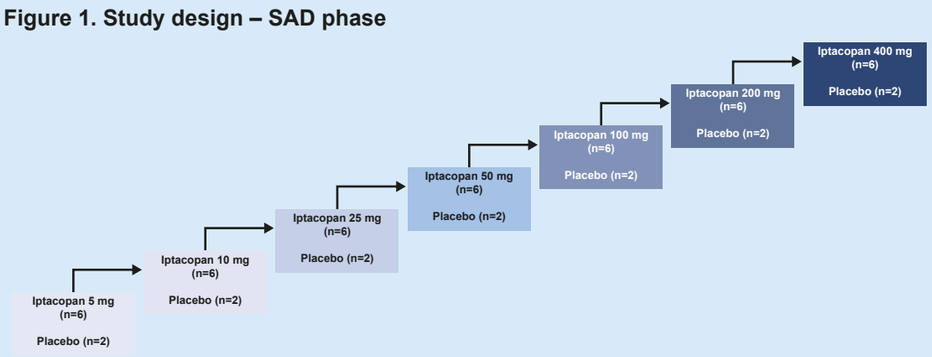
PK and safety assessments

- Blood samples for plasma PK analysis were collected at 18 timepoints: –1, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 h; 24 h (Day 2) and 36 h; 48 h (Day 3); 72 h (Day 4); and 96 h (Day 5)
  - Plasma concentrations of iptacopan were determined using a validated LC-MS/MS assay with an LLOQ of 1 ng/mL
- Safety assessments included reporting of AEs, physical examination, vital signs, ECG, and clinical laboratory evaluations

Statistical analysis

- The PK analysis set included all participants with available PK data; the safety analysis set included all participants that received any study drug
- Descriptive summary statistics for iptacopan PK parameters were analyzed by dose group and sampling timepoint
- An exploratory assessment of dose proportionality was performed by determining an estimate of the slope and 90% CI of the exponent from linear regression analysis of the log-transformed values (PK parameter and dose); the critical range for slope to conclude dose proportionality over the whole range was 0.95–1.05

Figure 1. Study design – SAD phase



SAD, single-ascending dose.

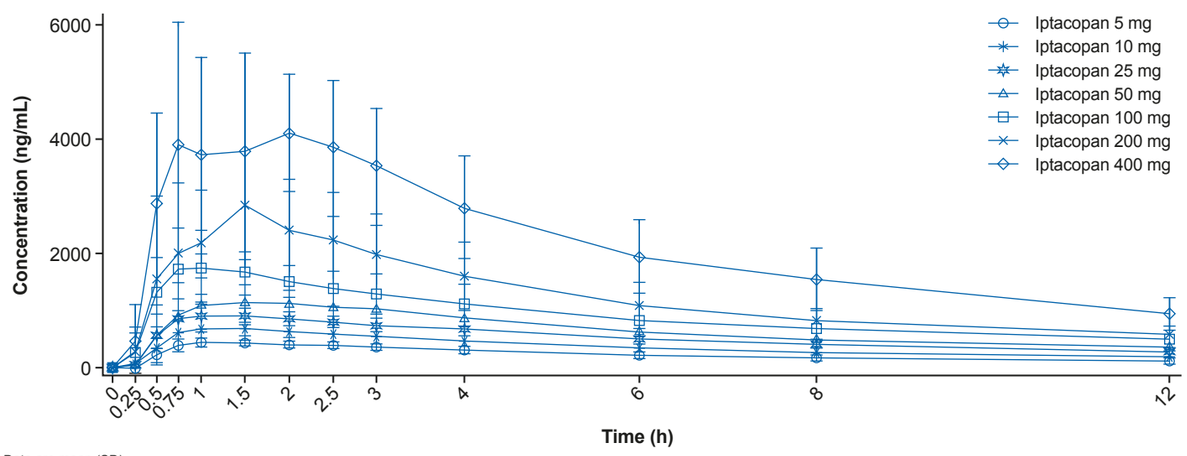
RESULTS

- 56 participants enrolled in the SAD phase; all participants completed the study
- Demographic data were similar across the iptacopan dose groups (**Table 1**)

PK assessment

- The mean plasma concentration–time profiles following a single oral dose (5–400 mg) of iptacopan on Day 1 (0–12 h) are shown in **Figure 2**
- At all doses, iptacopan was rapidly absorbed with a median T_{max} of 1.00–1.26 h, a mean $t_{½}$ of 14–18.4 h, a mean CL/F of 87.1–999 mL/h, and a mean Vz/F of 2120–20100 mL (**Table 2**)
- Over the dose range (5–400 mg), the mean C_{max} and mean $AUC_{0–∞}$ of iptacopan in plasma increased from 466–5070 ng/mL (10.9-fold increase) and 5300–61200 h.ng/mL (11.5-fold increase), respectively
  - The between-subject variability for iptacopan exposure was low to moderate, with a range of 11.4–26.2% for C_{max} and 21.3–33.2% for $AUC_{0–∞}$
- Across the dose range (5–400 mg), iptacopan exposure was not dose-proportional; the estimated slope and 90% CIs were lower than the critical range of 0.95 to 1.05 (**Table 3**)

Figure 2. Concentration–time profiles up to 12 h after a single dose of iptacopan



Data are mean (SD).
SD, standard deviation.

Table 1. Demographics

Characteristic	Iptacopan 5 mg (n=6)	Iptacopan 10 mg (n=6)	Iptacopan 25 mg (n=6)	Iptacopan 50 mg (n=6)	Iptacopan 100 mg (n=6)	Iptacopan 200 mg (n=6)	Iptacopan 400 mg (n=6)	Pooled placebo (n=14)	Total (N=56)
Age, years	43.5 (15.0)	44.0 (12.2)	44.2 (13.0)	39.5 (6.9)	37.2 (8.6)	46.0 (5.8)	42.7 (8.3)	41.6 (11.2)	42.2 (10.3)
Sex, n (%)									
Female	1 (17)	1 (17)	0	0	0	1 (17)	0	2 (14)	5 (9)
Male	5 (83)	5 (83)	6 (100)	6 (100)	6 (100)	5 (83)	6 (100)	12 (86)	51 (91)
Race, n (%)*									
White	5 (83)	6 (100)	6 (100)	5 (83)	6 (100)	6 (100)	6 (100)	13 (93)	53 (95)
Ethnicity, n (%)									
Not Hispanic or Latino†	5 (83)	6 (100)	6 (100)	6 (100)	5 (83)	6 (100)	6 (100)	14 (100)	54 (96)
Weight, kg	78.8 (5.7)	82.0 (12.3)	79.1 (10.2)	72.6 (7.4)	85.8 (8.9)	79.8 (11.9)	87.7 (12.0)	77.5 (8.8)	80.0 (10.0)
Height, cm	177.2 (11.5)	180.2 (5.5)	181.7 (6.6)	175.8 (5.9)	181.5 (3.7)	178.2 (7.7)	183.7 (11.2)	179.0 (8.0)	179.6 (7.8)
BMI, kg/m²	25.3 (3.0)	25.2 (2.4)	24.1 (3.8)	23.5 (3.0)	26.0 (2.4)	25.1 (2.6)	25.9 (1.2)	24.2 (2.2)	24.8 (2.5)

Data are mean (SD) unless stated otherwise.
*One participant each was enrolled from the following racial groups: 'Black or African American' (50 mg group), 'Asian' (pooled placebo group), or 'Other' (5 mg group); †Ethnicity for two participants was reported as 'Hispanic or Latino' (one each in the 5 mg and 100 mg group).
BMI, body mass index; SD, standard deviation.

Table 2. Plasma PK of iptacopan

PK parameter	Iptacopan 5 mg (n=6)	Iptacopan 10 mg (n=6)	Iptacopan 25 mg (n=6)	Iptacopan 50 mg (n=6)	Iptacopan 100 mg (n=6)	Iptacopan 200 mg (n=6)	Iptacopan 400 mg (n=6)
T_{max} (h), median (min–max)	1.01 (0.77–2.48)	1.00 (0.75–1.52)	1.13 (0.75–2.50)	1.26 (0.73–3.00)	1.00 (0.75–2.00)	1.13 (0.50–2.50)	1.25 (0.75–2.50)
C_{max} (ng/mL)	466 ± 70.3 (15.1)	714 ± 136 (19.0)	994 ± 211 (21.2)	1370 ± 155 (11.4)	1980 ± 459 (23.2)	3230 ± 844 (26.2)	5070 ± 1310 (25.9)
$AUC_{0–∞}$ (h.ng/mL)	5300 ± 1280 (24.2)	8440 ± 2080 (24.6)	12700 ± 2910 (23.0)	17500 ± 3730 (21.3)	25600 ± 8050 (31.5)	36500 ± 12100 (33.2)	61200 ± 15800 (25.9)
$t_{½}$ (h)	14.0 ± 2.37 (17.0)	15.2 ± 2.21 (14.6)	15.5 ± 5.18 (33.5)	18.4 ± 5.12 (27.9)	13.5 ± 2.58 (19.0)	18.0 ± 10.0 (55.7)	17.3 ± 3.05 (17.6)
CL/F (mL/h)	999 ± 274 (27.4)	1240 ± 290 (23.3)	2050 ± 424 (20.7)	2950 ± 532 (18.0)	4170 ± 1000 (24.0)	6040 ± 2050 (34.0)	6970 ± 2040 (29.3)
Vz/F (mL)	20100 ± 7020 (34.8)	26900 ± 5460 (20.3)	46400 ± 22800 (49.1)	78800 ± 29600 (37.5)	79900 ± 20900 (26.1)	138000 ± 38200 (27.6)	170000 ± 37900 (22.3)

Data are mean ± SD (CV%) unless stated otherwise.
$AUC_{0–∞}$, area under the curve from time 0 extrapolated to infinity; CL/F, apparent systemic (or total body) clearance from plasma following extravascular administration; C_{max}, maximum concentration; CV, coefficient of variation; max, maximum; min, minimum; SD, standard deviation; $t_{½}$, elimination half-life; T_{max}, time to maximum concentration; Vz/F, apparent volume of distribution.

Table 3. Dose proportionality analysis of iptacopan

PK parameter	Intercept (90% CI)	Slope (90% CI)	Dose proportionally across the whole range*
C_{max} (ng/mL)	5.26 (5.10, 5.42)	0.52 (0.48, 0.56)	No
$AUC_{0–∞}$ (h.ng/mL)	7.72 (7.53, 7.90)	0.53 (0.49, 0.58)	No

Pooled placebo data were excluded from the analysis.
*Iptacopan doses ranged from 5–400 mg.
$AUC_{0–∞}$, area under the curve from time 0 extrapolated to infinity; CI, confidence interval; C_{max}, maximum concentration.

Safety assessment

- 8/56 participants (14.3%) reported 11 AEs during the SAD phase; no serious AEs, AEs suspected to be related to the study drug, or AEs leading to discontinuation were reported
- Six participants who received any dose of iptacopan reported a total of nine AEs; seven of these were of mild intensity, and two were of moderate intensity
- Overall, the most commonly reported AEs (occurring in >1 participant) were headache (7.1%) and catheter-site reaction (3.6%)

Abbreviations

AE, adverse event; $AUC_{0–∞}$, area under the curve from time 0 extrapolated to infinity; BMI, body mass index; C3, complement 3; CI, confidence interval; CL/F, apparent systemic (or total body) clearance from plasma following extravascular administration; C_{max}, maximum concentration; CV, coefficient of variation; D, day; EoS, end-of-study; ECG, electrocardiogram; h, hour; IgA, immunoglobulin A; LC-MS/MS, liquid chromatography tandem mass spectrometry; LLOQ, lower limit of quantification; MAD, multiple-ascending dose; max, maximum; min, minimum; PK, pharmacokinetics; SAD, single-ascending dose; SD, standard deviation; $t_{½}$, elimination half-life; T_{max}, time to maximum concentration; Vz/F, apparent volume of distribution.

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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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