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Absorption and disposition of a first-in-class alternative complement pathway factor B inhibitor: Iptacopan

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Conclusions

- After a single 100 mg dose, iptacopan was rapidly absorbed with a T_{max} of 1.51 h, and had a medium-to-low clearance with a mean CL/F of 4.42 L/h and $t_{½}$ of 12.5 h
- Total radioactivity exposure was slightly higher than iptacopan exposure in plasma, indicating limited exposure to metabolites of iptacopan
- Both iptacopan and its metabolites showed a preferential distribution toward plasma rather than blood cells
- The mean recovery of total radioactivity was 96.4% of the administered dose
  - Radioactivity was excreted predominately in feces
- Administration of iptacopan was well tolerated in healthy participants
- The results of this study support favorable absorption and disposition characteristics for iptacopan

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]
- ADME studies provide a comprehensive overall picture of the disposition of a drug in the systemic circulation and excreta[7]

Objective

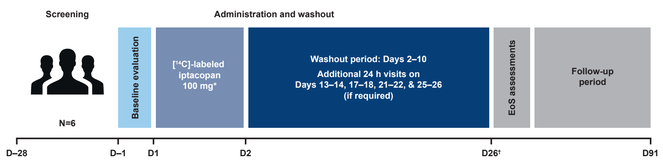
- To investigate the ADME characteristics, PK, safety, and tolerability of iptacopan following a single 100 mg oral of dose [^{14}C]-labeled iptacopan in healthy participants

Methods

Study design

- A single-center, open-label, Phase 1 study; eligible participants included males and females (of non-childbearing potential) aged 18–55 years
  - Participants requiring medications other than paracetamol were excluded due to the potential risk of drug–drug interactions
- The study comprised three phases: screening, administration and washout, and follow-up (**Figure 1**)
  - On Day 1, participants received a single oral 100 mg dose containing 3.7 MBq (100 µCi) of [^{14}C]-labeled iptacopan
  - Participants were domiciled until Day 10 and completed the end-of-study visit once release criteria were met. If release criteria were not met, participants returned for additional overnight visits for further monitoring and sample collection

Figure 1. Study design



Release criteria (from Day 10):

1. Radioactivity recovery in excreta >90% OR combined urinary and fecal excretion <1% of the administered dose for 2 consecutive days
2. Total radioactivity in plasma <5% of C_{max} based on 'Quick-count' radioactivity analysis

*[^{14}C]-labeled iptacopan was administered on the morning of Day 1 with 240 mL of non-carbonated water;
†The date of the EoS assessments was dependent on when the participant met the study release criteria.
C_{max}, maximum concentration; D, day; EoS, end-of-study; h, hour.

PK and safety assessments

- Plasma PK, whole blood PK, urine, and fecal samples were collected at baseline, pre-dose on Day 1, up to 10 days after iptacopan administration, and, if required, at the 24 h visits up to Day 26
- Total radioactivity concentrations in urine and feces were analyzed by the PRA Health Sciences Bioanalytical Laboratory using a validated LSC method
  - The mass balance of [^{14}C]-labeled iptacopan-related radioactivity recovered in urine and feces was calculated as a percentage of the administered dose
- Characterization and identification of metabolites in plasma and excreta samples were conducted using LC-MS/MS
- Safety assessments included reporting of AEs, physical examinations, vital signs, electrocardiogram, and clinical laboratory evaluations

Statistical analysis

- The sample size (N=6) was based on precedent studies and ethical considerations
- The safety analysis set included all participants that received the study drug
- The PK analysis set included all participants with ≥1 valid PK measurement
  - Participants that vomited at any time following dose administration ≤8 h post-dose were considered unevaluable
  - PK parameters were derived using non-compartmental methods with Phoenix WinNonlin Version 8.1 (Pharsight Corp., Certara Company, Princeton, New Jersey, USA)

Results

- A total of six participants were enrolled; all participants completed the study
  - All participants were male with a mean age of 31.5 years (**Table 1**)

Table 1. Demographics

Characteristic	Iptacopan 100 mg (N=6)
Age, years	31.5 (10.1)
Sex, n (%)	
Male	6.0 (100.0)
Race, n (%)	
Caucasian	5.0 (83.3)
Native American	1.0 (16.7)
Ethnicity, n (%)	
Not Hispanic or Latino	6.0 (100.0)
Weight, kg	81.7 (9.0)
Height, cm	179.7 (9.4)
BMI, kg/m^2	25.3 (2.2)

Data are mean (SD), unless stated otherwise.
BMI, body mass index; SD, standard deviation.

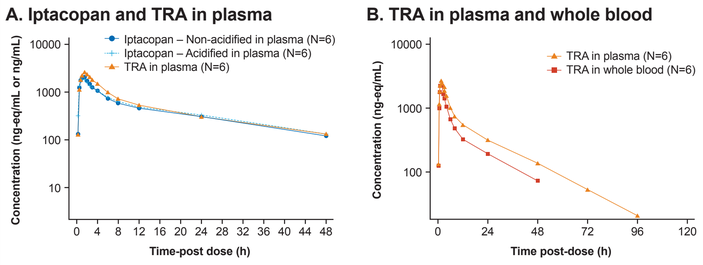
PK of iptacopan in plasma

- After a single 100 mg dose, iptacopan was rapidly absorbed with a median T_{max} of 1.51 h (**Figure 2A; Table 2**)
- The C_{max}, AUC_{last}, and $AUC_{0-\infty}$ of iptacopan in plasma ranged from 1710–2360 ng/mL, 17420–29461 h.ng/mL, and 17487–29493 h.ng/mL, respectively (**Table 2**)
  - The between-subject variability for iptacopan exposure was low and below 19%
- The PK profile of iptacopan was characterized by a medium-to-low clearance with a mean CL/F of 4.42 L/h and a $t_{½}$ of 12.5 h (**Table 2**)
- The PK parameters of iptacopan in non-acidified and acidified plasma were comparable (**Table 2**)

PK of total radioactivity in plasma and whole blood

- Total radioactivity exposure was higher in plasma than in whole blood, indicating a preferential distribution of iptacopan toward plasma rather than blood cells (**Figure 2B**)
  - Whole blood to plasma ratios for total radioactivity concentrations increased to 0.96 at 1 h post-dose and gradually decreased to 0.52 at 48 h post-dose
- The PK parameters of total radioactivity in plasma and whole blood showed low between-participant variability, both in terms of C_{max}, AUC_{last}, and $AUC_{0-\infty}$ (**Table 3**)
- The mean $t_{½}$ of total radioactivity in plasma and whole blood was 14.9 h and 16.1 h, respectively (**Table 3**)

Figure 2. Concentration–time profiles of iptacopan and total radioactivity in plasma and whole blood*



Data are mean (SD).
*Iptacopan (non-acidified) and iptacopan (acidified) were measured in ng/mL, whereas total radioactivity in plasma was measured in ng-eq/mL.
h, hour; SD, standard deviation; TRA, total radioactivity.

Table 2. PK of iptacopan in plasma

Statistic	C_{max} (ng/mL)	T_{max} (h)	AUC_{last} (h.ng/mL)	$AUC_{0-\infty}$ (h.ng/mL)	$t_{½}$ (h)	CL/F (L/h)	Vz/F (L)
Iptacopan (non-acidified)							
Mean (SD)	2145 (247)	–	23278 (4285)	23317 (4279)	12.5 (2.7)	4.42 (0.84)	77.4 (9.8)
CV (%) mean	11.5	–	18.4	18.4	21.4	19.10	12.6
Geo-mean	2132	–	22943	22983	12.3	4.35	76.9
CV (%) geo-mean	12.2	–	19.0	18.9	20.3	18.90	12.6
Median (min, max)	2195 (1710, 2360)	1.51 (0.77, 1.55)	24009 (17420, 29461)	24049 (17487, 29493)	12.0 (9.5, 17.3)	4.16 (3.39, 5.72)	76.0 (66.7, 91.3)
Iptacopan (acidified)*							
Mean (SD)	1977 (225)	–	24637 (4834)	24676 (4830)	12.8 (3.1)	4.19 (0.88)	74.8 (10.6)
CV (%) mean	11.4	–	19.6	19.6	24.3	21.00	14.1
Geo-mean	1965	–	24223	24264	12.5	4.12	74.1
CV (%) geo-mean	12.0	–	20.7	20.6	23.6	20.60	14.4
Median (min, max)	2035 (1590, 2190)	1.51 (0.77, 1.55)	26010 (18406, 30937)	26047 (18477, 30973)	11.8 (9.2, 18.0)	3.84 (3.23, 5.41)	75.6 (63.1, 86.3)

*Acidification of plasma was conducted to stabilize acyl glucuronide metabolites and investigate the potential impact of sample acidification on iptacopan plasma PK parameters.
$AUC_{0-\infty}$, 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; CL/F, apparent oral clearance; C_{max}, maximum concentration; CV, coefficient of variation; geo-mean, geometric mean; max, maximum; min, minimum; PK, pharmacokinetics; SD, standard deviation; $t_{½}$, half-life; T_{max}, time to maximum concentration; Vz/F, apparent volume of distribution.

Table 3. PK of the total radioactivity of iptacopan in plasma and whole blood

Statistic	C_{max} (ng-eq/mL)	T_{max} (h)	AUC_{last} (h.ng-eq/mL)	$AUC_{0-\infty}$ (h.ng-eq/mL)	$t_{½}$ (h)
Plasma					
Mean (SD)	2687 (266)	–	27226 (3299)	27771 (3130)	14.9 (3.2)
CV (%) mean	9.9	–	12.1	11.3	21.3
Geo-mean	2676	–	27062	27627	14.7
CV (%) geo-mean	9.6	–	12.1	11.2	21.0
Median (min, max)	2656 (2366, 3173)	1.51 (1.02, 1.55)	27016 (23648, 32039)	27456 (24428, 32516)	14.5 (10.8, 20.5)
Whole blood					
Mean (SD)	2336 (302)	–	17187 (1691)	18375 (1972)	16.1 (4.8)
CV (%) mean	12.9	–	9.8	10.7	29.8
Geo-mean	2320	–	17116	18286	15.5
CV (%) geo-mean	13.0	–	10.1	10.8	30.1
Median (min, max)	2298 (1894, 2815)	1.29 (0.77, 1.55)	17105 (14521, 19115)	18602 (15664, 21184)	15.7 (9.8, 24.5)

$AUC_{0-\infty}$, 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; CV, coefficient of variation; geo-mean, geometric mean; max, maximum; min, minimum; PK, pharmacokinetics; SD, standard deviation; $t_{½}$, half-life; T_{max}, time to maximum concentration.

Comparison of exposure to iptacopan and total radioactivity

- The mean $t_{½}$ of total radioactivity was slightly longer compared with iptacopan exposure in plasma at 14.9 h and 12.5 h, respectively (**Table 2; Table 3**)
- Geo-mean plasma iptacopan $AUC_{0-\infty}$ (non-acidified) was approximately 83.2% of geo-mean plasma total radioactivity $AUC_{0-\infty}$, indicating limited exposure to metabolites

Excretion

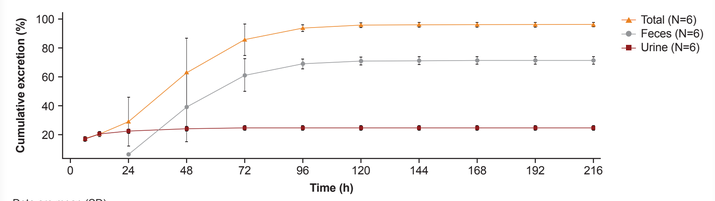
- The mean recovery of total radioactivity was 96.4% of the administered dose (**Table 4**)
  - Radioactivity was predominantly excreted in feces (71.5%) vs urine (24.8%)
- On average, 24.7% of the radioactivity was recovered in the urine within 72 h post-dose, and 71.1% of radioactivity was recovered from feces within 120 h post-dose (**Figure 3**)

Table 4. Radioactivity recovery of iptacopan in urine and feces

Statistic	Urine (Fe [%])	Feces (Fe [%])	Total (Fe [%])
Mean (SD)	24.8 (1.7)	71.5 (2.8)	96.4 (1.6)
CV (%) mean	6.9	3.9	1.7
Median (min, max)	25.2 (21.9, 27.1)	72.0 (66.9, 74.2)	96.7 (94.0, 98.5)

CV, coefficient of variation; Fe, fraction excreted; max, maximum; min, minimum; SD, standard deviation.

Figure 3. Total radioactivity recovery of iptacopan in urine and feces



Data are mean (SD).
h, hour; SD, standard deviation.

Metabolite profiling

- Two acyl glucuronide metabolites, M8 and M9, were detected in plasma at 8.1% and 5.2% of total circulating drug-related material, respectively
  - The pharmacologic activity of M8 and M9 are 27- and 150-fold less potent than iptacopan, respectively, and are therefore considered not active
- Metabolite profiling in excreta showed that metabolites formed by oxidative pathways accounted for approximately 50% of the administered dose
- Mean oral absorption was estimated to be ≥70.6% of the administered dose (24.8% of urinary excreted radioactivity plus 45.8% of dose in feces attributable to metabolites)

Safety

- 3/6 participants (50%) reported ≥1 TEAE; no serious AEs were reported, and no AEs led to study discontinuation (**Table 5**)
  - Four TEAEs reported were related to the administration of iptacopan; these included fatigue, oral herpes, and headache
  - All TEAEs were mild and had resolved by the end of the study

Table 5. TEAEs

TEAE, n (%)	Iptacopan 100 mg (N=6)
No. of participants with ≥1 TEAE	**3 (50.0)**
Headache	2 (33.3)
Eyelid irritation	1 (16.7)
Abdominal discomfort	1 (16.7)
Fatigue	1 (16.7)
Oral herpes	1 (16.7)
Hematoma	1 (16.7)

MedDRA version 22.0 was used for the reporting of AEs. A subject with multiple AEs was counted only once in the 'participants with ≥1 TEAE' row.
MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

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Disclosures

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

Abbreviations

ADME, absorption, distribution, metabolism, and excretion; 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; BMI, body mass index; C3, complement 3; C_{max}, maximum concentration; CL/F, apparent oral clearance; CV, coefficient of variation; D, day; EoS, end-of-study; Fe, fraction excreted; geo-mean, geometric mean; h, hour; IgA, immunoglobulin A; LC-MS/MS, liquid chromatography tandem mass spectrometry; LSC, liquid scintillation counting; max, maximum; MedDRA, Medical Dictionary for Regulatory Activities; min, minimum; PK, pharmacokinetics; PRA, Pharmaceutical Research Associates; SD, standard deviation; $t_{½}$, half-life; TEAE, treatment-emergent adverse event; T_{max}, time to maximum concentration; TRA, total radioactivity; Vz/F, apparent volume of distribution.

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