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Single dose of iptacopan treatment rapidly decreases plasma complement Bb levels

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KEY FINDINGS & CONCLUSIONS

- Administration of either single or multiple doses of iptacopan in healthy participants resulted in a rapid decrease in plasma Bb, an AP activity biomarker, from 2 h post-dose
  - Decrease in plasma Bb was sustained through 24 h in participants who received 200 mg and 400 mg of iptacopan
  - The slope and magnitude of plasma Bb level reduction observed was without apparent dose-dependency for all multiple dose groups
  - Single and multiple dose groups exhibited a dose-dependent trend in upward trajectory toward baseline plasma Bb levels, consistent with more persistent inhibition of the AP with higher doses of iptacopan
  - No substantial change in plasma Bb was observed for subjects receiving placebo
- Iptacopan was well tolerated in healthy participants in all dosing groups
- The results of this first-in-human study support the clinical development of iptacopan and provide confidence of durable AP inhibition in patients treated with iptacopan

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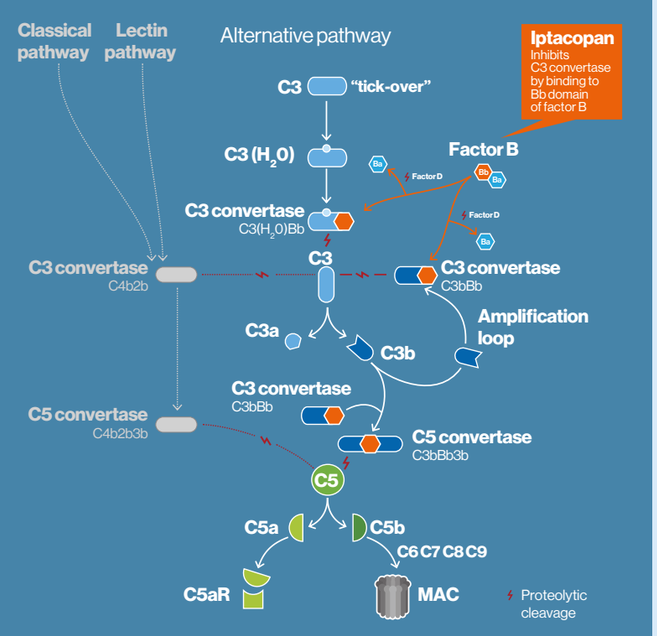
INTRODUCTION

- Iptacopan (LNP023) is an oral, first-in-class, highly potent, selective inhibitor of factor B, a key component of the alternative complement pathway (AP)[1] (**Figure 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]
- The complement fragment Bb, a biomarker of AP activity, was measured in healthy participants in a Phase 1 study to determine the effect of iptacopan on the AP
- The objectives of this study were:
  - To evaluate the effects of single- or multiple-ascending doses of iptacopan on the AP measured by plasma Bb levels
  - To evaluate the safety and tolerability of iptacopan in healthy participants

Figure 1. Study design



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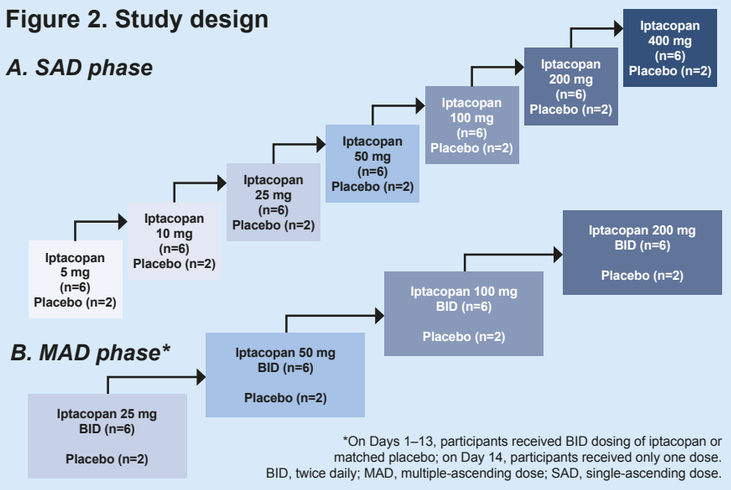
C, complement; MAC, membrane attack complex.

METHODS

Study design

- A first-in-human, Phase 1 study to assess the safety, tolerability, PK, and PD of iptacopan in healthy participants, 18–55 years of age
  - The study consisted of three parts: a single-ascending dose (SAD) study, a multiple-ascending dose (MAD) study, and a food-effect evaluation study
- In the SAD phase (**Figure 2A**), eligible participants were randomized in a 3:1 ratio to receive a single dose of iptacopan (5 mg, 10 mg, 25 mg, 50 mg, 100 mg, 200 mg, or 400 mg) or placebo
- In the MAD phase (**Figure 2B**), eligible participants were randomized in a 3:1 ratio to receive iptacopan (25 mg, 50 mg, 100 mg, or 200 mg) or matched placebo over a 14-day administration period
  - On Days 1–13, participants received BID dosing; on Day 14, participants received only one dose
  - A 5-day follow-up period included three follow-up evaluations and an EoS visit

Figure 2. Study design



*On Days 1–13, participants received BID dosing of iptacopan or matched placebo; on Day 14, participants received only one dose.
BID, twice daily; MAD, multiple-ascending dose; SAD, single-ascending dose.

Plasma Bb and safety assessments

- Circulating plasma Bb concentrations were measured using a validated immunoassay
  - In the SAD phase, plasma Bb was measured at 10 timepoints (up to 48 hours after iptacopan administration)
  - In the MAD phase, plasma Bb was measured at 12 timepoints (up to 24 hours after the last dose of iptacopan)
- Safety assessments included reporting of AEs, vital signs, ECG, and clinical laboratory evaluations

Statistical analysis

- Descriptive statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA)
- The PD analysis set included all participants with valid PD data; the safety analysis set included all participants that received any study drug

RESULTS

- The SAD and MAD phases included 56 and 32 participants, respectively; all participants completed the study
- Demographics were similar among participants in the SAD and MAD groups (**Table 1**)

Plasma Bb levels following SAD or MAD of iptacopan

- Plasma Bb levels at baseline varied among study participants (659–3920 ng/mL in the SAD phase; 965–2370 ng/mL in the MAD phase)
- Following iptacopan administration, plasma Bb levels decreased from baseline at 2 h post-dose in all dose groups (**Figure 3**)
- In the SAD phase, plasma Bb levels plateaued through 24 h post-dose and started to return toward baseline levels by 48 h post-dose in the 200 mg and 400 mg groups (**Figure 3A**)
  - In the lower dose groups (5–100 mg), an upward trajectory toward baseline was observed from 12 h post-dose
- In the MAD phase, the maximal decrease in Bb levels was seen 12–24 h after the first dose of iptacopan (**Figure 3B**)
  - Neither the magnitude nor slope of Bb decrease exhibited a dose-dependent trend
  - An upward trajectory toward baseline was observed 24 h after the last dose in the 25–100 mg groups; this upward trend was not observed in the 200 mg dose group
- Overall, no substantial changes in mean Bb level were observed in the pooled placebo groups

Table 1. Demographics

SAD of iptacopan

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)
Male sex, n (%)	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)
Black or African American	0	0	0	1 (17)	0	0	0	0	1 (2)
Asian	0	0	0	0	0	0	0	1 (7)	1 (2)
Other	1 (17)	0	0	0	0	0	0	0	1 (2)
Ethnicity, n%									
Hispanic or Latino	1 (17)	0	0	0	1 (17)	0	0	0	2 (4)
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)

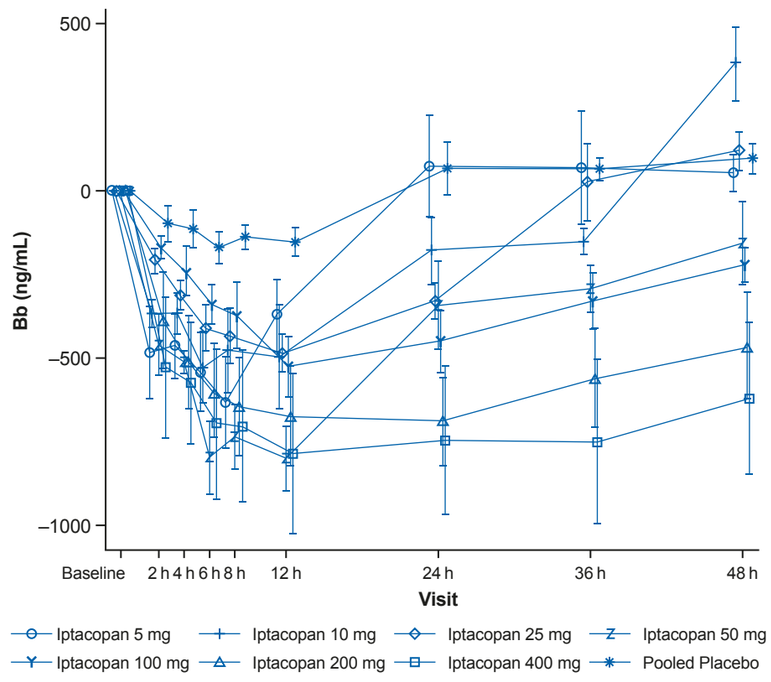
MAD of iptacopan

Characteristic	Iptacopan 25 mg BID (n=6)	Iptacopan 50 mg BID (n=6)	Iptacopan 100 mg BID (n=6)	Iptacopan 200 mg BID (n=6)	Pooled placebo (n=8)	Total (N=32)
Age, years	46.3 (9.2)	38.0 (12.7)	42.3 (12.4)	35.7 (12.4)	45.5 (9.6)	41.8 (11.3)
Male sex, n (%)	5 (83)	6 (100)	6 (100)	5 (83)	8 (100)	30 (94)
Race, n (%)						
White	6 (100)	6 (100)	6 (100)	6 (100)	8 (100)	32 (100)
Ethnicity, n%						
Hispanic or Latino	1 (17)	0	0	0	0	1 (3)
BMI, kg/m²	23.5 (1.7)	24.4 (2.4)	26.3 (3.3)	25.9 (2.3)	26.0 (1.3)	25.3 (2.4)

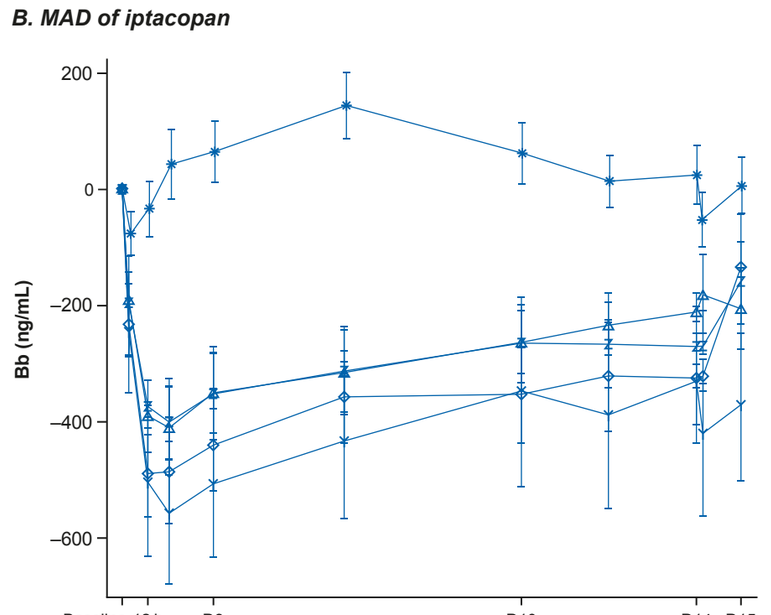
Data are mean (SD) unless stated otherwise.
BID, twice daily; BMI, body mass index; MAD, multiple-ascending dose; SAD, single-ascending dose; SD, standard deviation.

Figure 3. Mean (SE) change from baseline in plasma Bb levels

A. SAD of iptacopan



B. MAD of iptacopan



Data are mean (SE).
BID, twice daily; D, day; MAD, multiple-ascending dose; SAD, single-ascending dose; SE, standard error.

Safety assessment

- In the SAD phase, 8/56 participants (14.3%) reported 11 AEs (8 mild and 3 moderate severity); no serious AEs, AEs suspected to be related to the study drug, or AEs leading to discontinuation were reported
  - Headache (7.1%) and catheter-site reaction (3.6%) were the most commonly reported AEs; all other AEs occurred in only one participant per AE
- In the MAD phase, 20/32 participants (62.5%) reported 38 AEs (37 mild and 1 moderate severity); no serious AEs were reported, and no AEs led to the discontinuation of study drug
  - Headache (15.6%), medical device-site reaction (9.4%), back pain (6.3%), and sunburn (6.3%) were the most commonly reported AEs; all other AEs occurred in only one participant per AE

Abbreviations

AE, adverse event; AP, alternative completement pathway; BID, twice daily; BMI, body mass index; C, complement; D, day; ECG, electrocardiogram; EoS, end-of-study; IgA, immunoglobulin A; MAD, multiple-ascending dose; MAC, membrane attack complex; PD, pharmacodynamics; PK, pharmacokinetics; SAD, single-ascending dose; SD, standard deviation; SE, standard error.

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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. **JM*** is an employee of Novartis Institutes of BioMedical Research, 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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