Interim Analysis of a Phase 2 Dose Ranging Study to Investigate the Efficacy and Safety of Iptacopan in Primary IgA Nephropathy

P221

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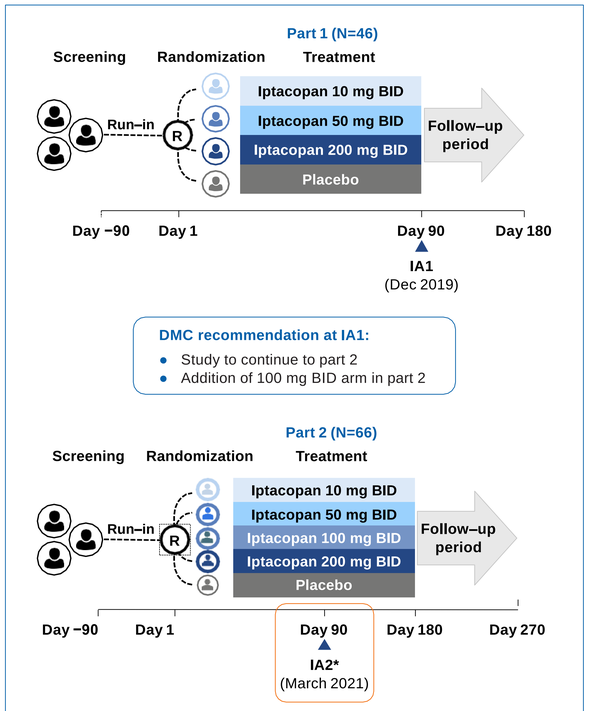
Introduction

- IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide with a global incidence of ~25/million/year[1]
- IgAN is characterized by deposits of IgA1–containing immune complexes in the glomerular mesangium and kidney biopsies often stain positive for components of the alternative pathway (AP)[2–5]
- There are no effective and well tolerated targeted therapies approved for IgAN that slow or prevent progression to kidney failure[6,7]
- **Iptacopan (LNP023)** is an oral, highly potent, selective small–molecule inhibitor which binds factor B and its catalytically active fragment Bb. This suppresses activity of the AP C3 convertase, and thus, activation of the amplification loop to prevent downstream generation of the AP C5 convertase complex, opsonization, and formation of C5a anaphylatoxins and the membrane attack complex (MAC)[8]
- Iptacopan was safe, and well tolerated in first–in–human studies[9]
- Given the role of the AP in the pathogenesis of IgAN, inhibition of the AP with iptacopan may provide a therapeutic strategy to halt disease progression

Study design

Figure 1: An adaptive seamless, randomized, double–blind, placebo controlled, dose–ranging study



*Analysis includes patients pooled from parts 1 and 2 of the study (N=112).
BID, twice daily; DMC, data monitoring committee; IA, interim analysis; R, randomization.

Methods

Primary objective

- To evaluate the dose response relationship of iptacopan on the reduction in proteinuria versus placebo after 90 days of treatment

Secondary objectives

- To assess safety and tolerability of iptacopan, eGFR, and biomarkers reflecting activity of the alternative complement pathway

Key eligibility criteria[10]

Key inclusion criteria

- Age ≥18 years with biopsy–verified IgAN within the prior 3 years
- UPCR of ≥0.8 g/g or urine protein of ≥0.75 g/24h at screening and urine protein of ≥0.75 g/24h at the end of run–in period
- eGFR of ≥30 mL/min/1.73 m^2
- Body weight of ≥35 kg; BMI of 15–38 kg/m^2
- On supportive care including a maximally tolerated dose of an ACEi/ARB, antihypertensive therapy, or diuretics for ≥90 days before study treatment
- Vaccination against *Neisseria meningitidis, Streptococcus pneumonia*,* and *Haemophilus influenza**

Key exclusion criteria

- Crescent formation in ≥50% of glomeruli
- Previous treatment with immunosuppressive agents† within 90 days of starting the study treatment
- Patients with transplanted organs
- History of immunodeficiency diseases or HIV positive
- Chronic infection with HBV or HCV
- History of severe allergic reactions, malignancy of any organ system, porphyria metabolic disorder, or drug or alcohol abuse
- Any surgical or medical condition that might significantly alter the absorption, distribution, metabolism, or excretion of the drugs

*If available, and as per local regulations; †Cyclophosphamide or mycophenolate mofetil, or cyclosporine, systemic corticosteroids.
ACEi, angiotensin–converting enzyme inhibitor; ARB, angiotensin–receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgAN, immunoglobulin A nephropathy; UPCR, urine protein–to–creatinine ratio.

Results

Baseline characteristics and demographics

- Treatment groups were mostly balanced in terms of demographics and baseline characteristics (Table 1)
  - However, at baseline, proteinuria levels were numerically lower in placebo and iptacopan 200 mg BID groups; eGFR was lower in iptacopan 50 mg and 200 mg BID groups

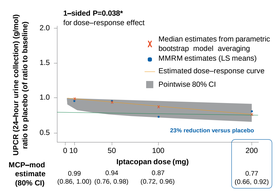
Table 1: Baseline characteristics and demographics

	Iptacopan				Placebo n=25
	10 mg BID n=20	50 mg BID n=19	100 mg BID n=22	200 mg BID n=26	
Age, years	39.2 (12.42)	36.6 (8.42)	36.0 (13.15)	42.5 (15.76)	39.4 (11.00)
Male (%)	45%	68%	50%	58%	72%
Asian ethnicity (%)	45%	47%	55%	46%	44%
BMI, kg/m^2	26.3 (5.51)	25.8 (4.37)	26.1 (4.60)	25.8 (4.44)	25.4 (3.69)
UPCR, mg/mmol*	214.1 (122.29)	188.2 (90.38)	203.4 (98.29)	151.0 (109.46)	146.6 (61.62)
UPCR <200 mg/mmol (%)	55%	53%	68%	85%	80%
eGFR, mL/min/1.73 m^2	66.0 (28.51)	53.8 (22.73)	67.0 (31.75)	57.9 (28.92)	65.7 (32.60)
SBP, mmHg	134.4 (11.65)	122.6 (12.15)	125.0 (11.30)	125.7 (11.66)	125.5 (11.37)

Data are mean (SD) unless otherwise specified.
*UPCR sampled from a 24–hour urine collection at baseline.
BID, twice daily; BMI, body mass index; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; SD, standard deviation; UPCR, urine protein–to–creatinine ratio.

Results: Efficacy

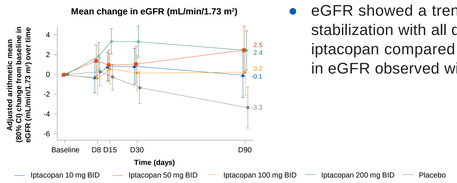
Figure 2: Iptacopan showed dose–dependent reduction in proteinuria at Day 90 versus placebo



*Multiplicity–adjusted P–value; analysis adjusted for baseline UPCR (24–hour) and ancestry.

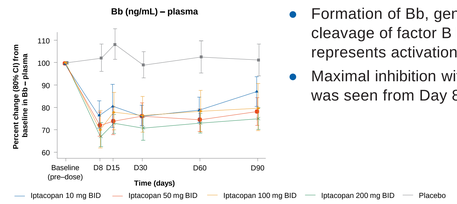
- Treatment with iptacopan 200 mg BID led to a 23% (80% CI: 8%, 34%) reduction in 24–hour UPCR at 90 days
- A significant dose–response effect of iptacopan versus placebo (1–sided P=0.038*) was observed
- Iptacopan treatment was associated with a trend toward lower first morning void UPCR levels

Figure 3: Treatment with iptacopan was associated with stabilization of eGFR



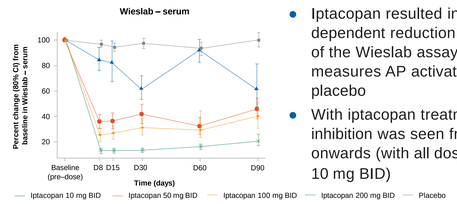
- eGFR showed a trend towards stabilization with all doses of iptacopan compared with a decline in eGFR observed with placebo

Figure 4: Iptacopan reduces alternative pathway biomarker levels in plasma



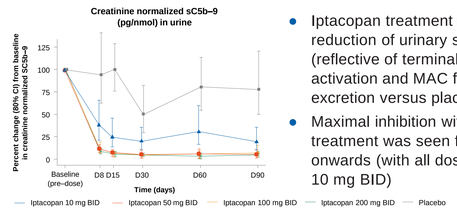
- Formation of Bb, generated by cleavage of factor B by factor D, represents activation of the AP
- Maximal inhibition with iptacopan was seen from Day 8 onwards

Figure 5: Dose-dependent reduction in serum levels of alternative pathway biomarkers by iptacopan



- Iptacopan resulted in a dose–dependent reduction in serum levels of the Wieslab assay (which measures AP activation) versus placebo
- With iptacopan treatment, maximal inhibition was seen from Day 8 onwards (with all doses except 10 mg BID)

Figure 6: Iptacopan reduces levels of alternative pathway biomarkers in urine



- Iptacopan treatment results in reduction of urinary sC5b–9 (reflective of terminal pathway activation and MAC formation) excretion versus placebo
- Maximal inhibition with iptacopan treatment was seen from Day 8 onwards (with all doses except 10 mg BID)

AP, alternative pathway; BID, twice daily; CI, confidence interval; D, day; eGFR, estimated glomerular filtration rate; LS, least squares; MAC, membrane attack complex; MCP–mod, multiple comparison procedure–modelling; MMRM, mixed model repeated measurements; sC5b–9, soluble C5b–9; UPCR, urine protein–to–creatinine ratio.

Results: Safety – Iptacopan treatment was well tolerated

- Overall, 61% of patients experienced treatment emergent adverse events (AEs) up to Day 90
- There was no evidence of a dose–dependent occurrence of AEs; 65% of patients in the iptacopan 10 mg BID (twice daily) group, 68% in 50 mg BID, 55% in 100 mg BID, 54% in iptacopan 200 mg BID and 64% in placebo groups reported at least one AE up to Day 90
- All treatment emergent AEs to Day 90 were mild (92%) or moderate (8%); the most common AEs were: headache, back pain, diarrhea, nasopharyngitis, and vomiting with no dose response or difference from placebo for any of these
- No study drug–related serious AEs and no deaths were reported during the study
- Overall, there were no serious infections and no infections reported to be caused by encapsulated bacteria

Conclusions

- This is the first study to report the safety and efficacy of selective alternative pathway (AP) inhibition in IgAN
- Inhibition of AP activation with iptacopan for 90 days was associated with a significant dose–dependent reduction in urine protein–to–creatinine ratio (UPCR) and a trend to estimated glomerular filtration rate (eGFR) stabilization
  - After 90 days, patients treated with iptacopan 200 mg BID experienced 23% reduction in proteinuria versus placebo
- Iptacopan treatment was well tolerated and resulted in inhibition of various biomarkers of AP activity
- These results suggest that iptacopan may reduce proteinuria and stabilize kidney function in patients with IgAN and support further evaluation of iptacopan in the ongoing Phase 3 APPLAUSE–IgAN trial[11] (NCT04578834; currently recruiting)

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Disclosures:

JB and VP are co-chairs of the Steering Committee for LNP023 trials in IgAN; BR, HZ, NK, BM, DVR and HT are members of the Steering Committee for LNP023 trials in IgAN; HZ has received funds from Janssen; BM is a national leader for ASCEND–ND and –D trials (GSK), NeflgArd trial (Calliditas), DUPLEX and PROTECT trials (Retrophin); MM, AC, WW and OP are employees of the study sponsor (Novartis).

This scientific information may include data/information on investigational uses of compounds/drugs that have not yet been approved by regulatory authorities.

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