MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION

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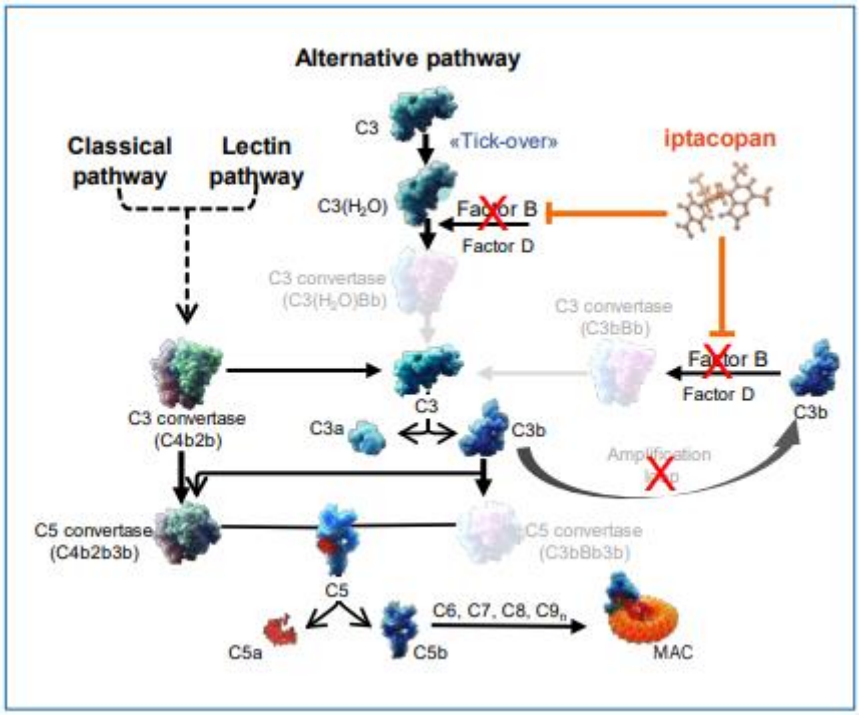
IPTACOPAN FOR THE TREATMENT OF C3 GLOMERULOPATHY

KEYWORDS: Iptacopan, LNP023, C3 Glomerulopathy

SUMMARY OF TECHNOLOGY

Iptacopan is an investigational and first-in-class factor B (FB) inhibitor of the alternative complement pathway (AP). Iptacopan binds to FB and prevents the formation of the AP C3-convertase (C3bBb). This limits the cleavage of C3 to the active fragment C3b. Iptacopan is given orally 200 mg twice a day. Iptacopan is one of the key drivers of complement-driven renal diseases (CDRDs) and it has the potential to become the first targeted therapy to delay progression to dialysis in C3 glomerulopathy (C3G). Iptacopan is currently in development for several CDRDs where significant unmet needs exist, including C3G, IgA nephropathy (IgAN), atypical haemolytic uraemic syndrome (aHUS), and idiopathic membranous nephropathy (iMN), as well as the blood disorder paroxysmal nocturnal hemoglobinuria (PNH).[1]



The phase II trials results showed the potential for iptacopan to provide the first targeted treatment for people living with C3G. Based on the positive results, iptacopan has received European Medicines Agency (EMA) PRIME designation for C3G and orphan drug designations from the U.S. Food and Drug Administration (FDA) and EMA

in C3G and PNH.[2] The phase III APPEAR-C3G was initiated and targeted to be completed by 2023.[3]

INNOVATIVENESS

Novel, completely new	✔
Incremental improvement of the existing technology	
New indication of an existing technology	

DISEASE BURDEN

C3 glomerulopathy is an ultra-rare, severe form of primary glomerulonephritis and is commonly diagnosed in adolescents and young adults. C3 glomerulopathy is characterised histopathologically by an accumulation of the C3 component of complement in renal tissue and results in kidney malfunctions. The presentation of C3G ranges from asymptomatic haematuria and proteinuria to an acute presentation with the classic signs and symptoms of glomerulonephritis. The common symptoms include low protein levels in the blood, proteinuria, lower amounts of urine and blood in the urine. Approximately 50% of affected individuals enter end-stage renal disease ten years after being diagnosed.[4]

In the United States, the incidence of C3G is estimated to be between 1 case per 1,000,000 and 2 - 3 cases per 1,000,000 based on an analysis of C3G registry data. The prevalence might be as low as 5 cases per 1,000,000 in the United States. Data derived from four European studies provide estimates of 0.2 - 1.0 cases per 1,000,000 of the population.[4] However, in Malaysia, there is no retrieval data on incidence or prevalence of C3G.

There are currently no approved therapies. Clinical trials are underway to test the efficacy of several first-generation drugs that target the alternative complement pathway.[4]

CURRENT OPTIONS FOR PATIENTS

There is no approved treatment available currently.

POTENTIAL IMPACT OF TECHNOLOGY

Based on retrieval evidence up to 21 April 2022, one cohort study was included in this review.

a. Clinical Impact

A phase II, open-label, two cohorts, non-randomised study was conducted to evaluate the efficacy, safety and pharmacokinetics of iptacopan in two groups of patients; those with C3G (cohort A) and patients who have undergone kidney transplantation and have subsequent C3G recurrence in the transplanted organ (cohort B). The primary endpoint for cohort A was a reduction in proteinuria [as measured by 24-hour urinary protein to creatine ratio (UPCR 24h)] from baseline to week 12. The primary endpoint for cohort B was a change in C3 deposit score (based on immunofluorescence microscopy) from kidney biopsy from baseline to week 12. On completion of the study, all patients had the option to receive ongoing iptacopan in a long-term extension study.[1]

A total of 16 patients in cohort A showed a 45% reduction in proteinuria compared to baseline, as measured by UPCR 24h (p=0.0003). A total of seven patients in cohort B showed a reduction in C3 protein deposits compared to baseline, as measured by C3 deposit score (based on immunofluorescence microscopy) from kidney biopsy (p=0.0313).[1]

Both cohorts in this phase II study showed strong and sustained inhibition of alternative complement pathway activity and normalisation of serum C3 levels over 12 weeks. In combined data from both cohorts, kidney function remained stable after 12 weeks, as assessed by the estimated glomerular filtration rate (eGFR, average increase of 1.04 mL/min compared to baseline).[1]

b. Cost
There was no retrieval data on the cost of iptacopan.

c. Organisational
There was no organisational issue identified.

d. Societal/ethical
There was no societal or ethical issue identified.

e. Safety
Iptacopan showed a favourable safety and tolerability profile with no serious adverse events suspected to be related to the drug.

In conclusion, iptacopan could be a viable treatment option for those with C3 glomerulopathy. However, the results of phase III study are important to evaluate the effectiveness and safety of iptacopan in patients with native kidney C3G.

EVIDENCE

- Novartis. Novartis iptacopan meets primary endpoints in Phase II study in rare kidney disease C3 glomerulopathy (C3G). Available at: https://www.novartis.us/news/media-releases/novartis-iptacopan-meets-primary-endpoints-phase-ii-study-rare-kidney-disease-c3 [Assessed on 8 April 2022]

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2. Novartis. Novartis investigational oral therapy iptacopan (LNP023) receives FDA Breakthrough Therapy Designation for PNH and Rare Pediatric Disease Designation for C3G. Available at: https://www.novartis.com/news/media-releases/novartis-investigational-oral-therapy-iptacopan-lnp023-receives-fda-breakthrough-therapy-designation-pnh-and-rare-pediatric-disease-designation-c3g [Assessed on 8 April 2022]
3. Novartis. Study of Efficacy and Safety of Iptacopan in Patients with C3 Glomerulopathy. Available at: https://www.recruiting-trials.novartis.com/clinicaltrials/study/nct04817618 [Assessed on 8 April 2022]
4. Smith RJH, Appel GB, Blom AM et al. C3 glomerulopathy - understanding a rare complement-driven renal disease. Nat Rev Nephrol. 2019; 15(3):129-143.

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