# Health Technology Briefing
# March 2023

# Iptacopan for treating complement 3 glomerulopathy

| Company/Developer | Novartis Pharmaceuticals UK Ltd |
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☒ New Active Substance ☐ Significant Licence Extension (SLE)

| NIHRIO ID: 27442 | NICE TSID: 10435 | UKPS ID: 662369 |
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## Licensing and Market Availability Plans

Currently in phase III clinical trials.

## Summary

Iptacopan is in development for the treatment of patients with complement 3 glomerulopathy (C3G) which is a rare disease. C3 is a blood protein that plays a key role in the normal immunity. The damaging build-up of the C3 protein in kidneys of patients with C3 glomerulopathy mostly results from dysregulation of the alternative complement pathway which is part of the body's immune system. The build-up of this C3 protein damages the kidneys and can lead to a life-threatening condition which prevents the kidneys from filtering fluids and waste products from the body.

Iptacopan is a first-in-class, orally administered, small-molecule inhibitor (a type of protein) that blocks another protein called factor B, which is involved in the production of alternative pathway C3 convertase. By blocking factor B and hence activity of alternative pathway C3 convertase, iptacopan is expected to reduce the formation of downstream complexes that result in inflammation and injury to the kidney. If licensed, iptacopan will offer a novel treatment option for patients with C3G.

## Proposed Indication

Treatment of patients with C3 Glomerulopathy (C3G).[1]

## Technology

### Description

Iptacopan (LNP023) is an oral, first-in-class, potent, and selective inhibitor of factor B, a key component of the alternative pathway (AP).[2] Factor B is a key serine protease of the alternative pathway (AP) of the complement cascade.[3] It is involved in the production of alternative pathway C3 convertase. Consequently, iptacopan-mediated inhibition of FB suppresses C3 convertase activity, blocking the cleavage of C3 and activation of the amplification loop.[2]

Iptacopan is currently in clinical development for C3G in adults. In the phase III trial (NCT04817618), 200mg iptacopan is administered orally twice a day.[4]

### Key Innovation

C3G is a devastating disease that has poor prognosis, with a 30% risk of end stage renal disease at two years.[5,6] People can end up facing life-altering and often exhausting kidney dialysis or transplantation. Unfortunately, no treatment is universally effective or curative and there are currently no disease-specific treatments available.[7]

Results from the final analysis of the Phase II clinical trial, NCT03832114, show that Iptacopan significantly reduces proteinuria and C3 deposit scores in native and transplanted kidneys of C3G patients. If licensed, iptacopan would offer a novel treatment option for adult patients with C3G.[8]

### Regulatory & Development Status

Iptacopan does not currently have marketing authorisation in the EU/UK for any indication.

Iptacopan for the treatment of C3G has the following designation/awards.[9-12]

- An orphan drug designation in the EU in December 2018 for the treatment of C3G
- A PRIME designation by the EMA in October 2020 for the treatment of C3G.
- Innovative Licensing and Access Pathway (ILAP) by the MHRA in October 2021 for the treatment of C3G
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Iptacopan is also in Phase III/II clinical development for:[13]

- Other kidney diseases such as Lupus Nephritis and Primary IgA Nephropathy
- Paroxysmal Nocturnal Haemoglobinuria

## Patient Group

### Disease Area and Clinical Need

C3 glomerulopathy is a kidney condition characterised by abnormal deposits of protein C3 within glomeruli. It is caused by dysregulation of the alternative complement system pathway. The signs and symptoms of C3G can include high levels of protein in the urine (proteinuria), blood in the urine (haematuria), reduced amounts of urine, low levels of protein in the blood, swelling in many areas of the

body (oedema), high blood pressure and fatigue.[14] Affected individuals may have particularly low levels of C3 protein in the blood. There are two major forms of C3G: dense deposit disease (DDD) and C3 glomerulonephritis (C3GN). Although the two disorders cause similar kidney problems, the features of dense deposit disease tend to appear earlier than those of C3 glomerulonephritis, usually in adolescence.[14] The renal prognosis in C3G is poor, with a 30% risk of kidney failure at 2 years. After kidney transplantation, the risk of recurrence in the transplanted kidney is over 70%, with more than a 50% chance of graft loss.[5]

C3G is rare. Each year there are 1 to 2 people per million of the UK population who have C3 glomerulopathy.[15] The population likely to be eligible to receive Iptacopan could not be estimated from available published sources.

## Recommended Treatment Options

There are currently no National Institute for Health and Care Excellence (NICE) recommended treatments for C3G.

- Use of eculizumab to treat people with C3G is off-label.[5]
- The kidney Disease: Improving Global Outcomes (KDIGO) guideline recommends treatment with ACE inhibitors or ARBs, and for patients with moderate to severe disease the addition of mycophenolate mofetil (MMF) plus glucocorticoids. Enrolment in a clinical trial should also be considered.[16]

## Clinical Trial Information

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| Trial | **APPEAR-C3G;** NCT04817618 . EudraCT: 2020-004589-21 A Multicentre, Randomized, Double-blind, Parallel Group, Placebo-controlled Study to Evaluate the Efficacy and Safety of Iptacopan (LNP023) in Complement 3 Glomerulopathy.<br>**Phase: III** Recruiting<br>**Location(s): 8** EU countries, UK, USA, and other countries<br>**Primary completion date:** August 2023 |
| Trial Design | Randomised, Parallel assignment, triple-masked, placebo controlled |
| Population | N=68 (estimated); male and female patients with C3G; aged 18 to 60years. |
| Intervention(s) | Iptacopan 200mg orally twice daily. |
| Comparator(s) | Matched placebo |
| Outcome(s) | Primary outcome:<br>• Log-transformed ratio to baseline in UPCR (sampled from a 24-hour urine collection). [ Time Frame: 6 months (double-blind)].<br>To demonstrate the superiority of iptacopan compared to placebo in reducing proteinuria.<br>See trial records for full list of other outcomes. |
| Results (efficacy) | - |
| Results (safety) | - |

| Clinical Trial Information | |
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| Trial | NCT03955445. EudraCT 2018-004253-24 An Open-label, Non-randomized Extension Study to Evaluate the Long-term Efficacy, Safety and Tolerability of LNP023 in Subjects with C3 Glomerulopathy.<br>**Phase:** II -Recruiting<br>**Location(s):** 4 EU countries UK and USA<br>**Primary completion date:** October 2024 |
| Trial Design | Non-Randomised, open label, single group assignment |
| Population | N=95 (estimated); patients with C3G who have completed the Phase 2 study NCT03832114 (CLNP023X2202) trial: aged 18years and older. |
| Intervention(s) | Iptacopan capsule |
| Comparator(s) | No comparator |
| Outcome(s) | Primary outcome measure:<br>• Number of participants with composite renal response [ Time Frame: 9-months visit]<br><br>See trial record for full list of other outcomes. |
| Results (efficacy) | - |
| Results (safety) | - |

| Clinical Trial Information | |
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| Trial | NCT03832114. An Open-label, Non-randomized Study on Efficacy, Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of LNP023 in Two Patient Populations with C3 Glomerulopathy.<br>**Phase:** II Completed<br>**Location(s):** 4 EU countries, UK, and USA<br>**Completion date:** April 2021 |
| Trial Design | Non-randomised, open-label, single group |
| Population | N=27 (N=16 native kidney patients and N=11 patients with C3G recurrence following kidney transplantation); male and female patients with C3G; aged 18 years to 65 years.[8] |
| Intervention(s) | Increasing doses of Iptacopan up to 200 mg. |
| Comparator(s) | No comparator |
| Outcome(s) | The primary outcome:<br>• Cohort A: Change from Baseline in Urine Protein to Creatinine Concentration Ratio (UPCR) [ Time Frame: Week 12]<br>• Cohort B: Change from Baseline in C3 Deposit [ Time Frame: Week 12]<br><br>See trial record for full list of other outcomes. |

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| Results (efficacy) | 12 weeks treatment with Iptacopan 200mg twice daily resulted in statistically significant and clinically important reduction of proteinuria in patients with native kidney C3G (UPCR-45% vs baseline) and a significant reduction in C3 deposit score in follow-up kidney biopsies in patients with post-transplant recurrent C3G.[8] Additionally, both cohorts of this Phase II study showed a profound and sustained inhibition of alternative complement pathway activity and normalization of serum C3 levels over 12 weeks. In combined data from both cohorts, kidney function remained stable after 12 weeks, as assessed by Estimated Glomerular Filtration Rate (eGFR) (average increase of 1.04 mL/min compared to baseline).[8] Long-term treatment (12 months) with iptacopan results in further proteinuria reduction and eGFR improvement beyond that previously reported following 12weeks treatment in native C3G. Stable eGFR was seen in recurrent C3G, with stable increases in serum C3 levels found in both cohorts.[17] |
| Results (safety) | Iptacopan was generally well-tolerated, and most AEs were of mild severity in both cohorts.[17] |

## Estimated Cost

The cost of iptacopan is not yet known.

## Relevant Guidance

### NICE Guidance

- NICE Evidence Summary. C3 glomerulopathy in the native kidney: eculizumab ESUOM49. December 2015.

### NHS England (Policy/Commissioning) Guidance

- NHS England Service Specifications; Assessment And Preparation For Renal Replacement Therapy (including establishing dialysis access) A06/S/e.
- NHS England Service Specifications; Adult Kidney Transplant Service. 16079/S.
- NHS England Specialised Commissioning Team: Eculizumab for the treatment of recurrence of C3 glomerulopathy post-kidney transplant (all ages).

### Other Guidance

KDIGO 2021; Clinical Practice Guideline for Management of Glomerular Disease.[16]

## Additional Information

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