Alternative complement pathway inhibition with iptacopan to arrest disease progression in C3 Glomerulopathy (APPEAR-C3G)

Richard JH Smith [1], David G Kavanagh[2], Ronda Tawfik[3], Angelo J Trapani[3], Yaqin Wang[3], Nicholas Webb[4], Marina Vivarelli[5], Andrew S Bomback[6]

1. University of Iowa Molecular Otolaryngology and Renal Research Laboratories, Iowa City, IA, United States
2. National Renal Complement Therapeutics Centre, Newcastle-upon-Tyne, United Kingdom
3. Novartis Pharmaceuticals Corp, East Hanover, NJ, United States
4. Novartis Pharma AG, Basel, Basel-Stadt, Switzerland
5. IRCCS Ospedale Pediatrico Bambino Gesu, Rome, Italy
6. Department of Medicine, Division of Nephrology, Columbia University Medical Center, New York, NY, United States

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

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Disclosures and acknowledgements

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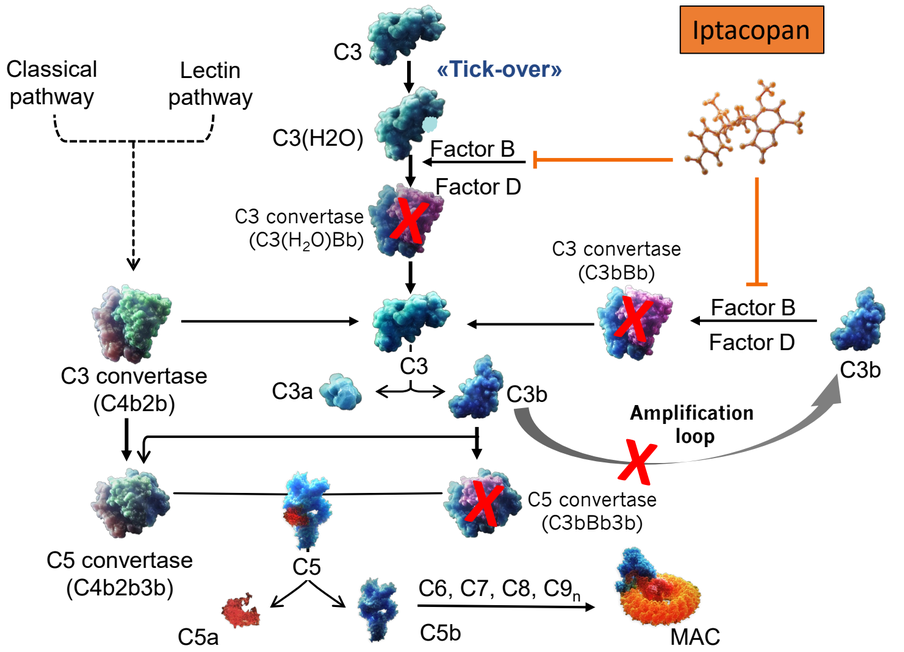
Introduction

APPEAR-C3G

- **C3 glomerulopathy (C3G)** is a rare kidney disease caused by dysregulation of the alternative complement pathway (AP)[1]
- The AP acts as an amplification loop for all complement pathways and is important for defence against infections
- Unlike the classical and lectin pathways, the AP is constantly active at low levels in a process called ‘tick over’[2]
- Currently, there are no approved therapeutic agents for C3G
- Iptacopan (LNP023) is an oral, highly potent, and selective small-molecule inhibitor of complement Factor B
- Factor B is one of the key positive regulators of the AP[3]
- By inhibiting Factor B, iptacopan reduces AP activity, thus reducing complement-mediated damage and inflammation[3]

Alternative Pathway



References

1. Smith RJH, et al. Nat Rev Nephrol. 2019;15(3):129–143
2. Lachmann, PJ, et al. The FASEB Journal. 2018;32:123–129.
3. Schubart A, et al. Proc Natl Acad Sci U S A. 2019;116(16):7926–7931

Abbreviations

AP, alternative complement pathway; C3G, C3 glomerulopathy

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Study aim and patients

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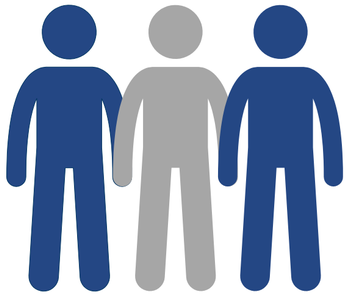
- Multicenter, randomized, double-blind, parallel group, placebo-controlled study

To **evaluate** the **efficacy** and **safety** of **iptacopan** in **patients with C3G and native kidney**



Adult patients aged 18–60 years (n~68) with biopsy-confirmed C3G and proteinuria (≥1g/g based on 24h urine collection)

References

https://clinicaltrials.gov/ct2/show/NCT04817618 (Accessed 09 Sep 2021)

Abbreviations

C3G, C3 glomerulopathy; n, number of patients

Study Design

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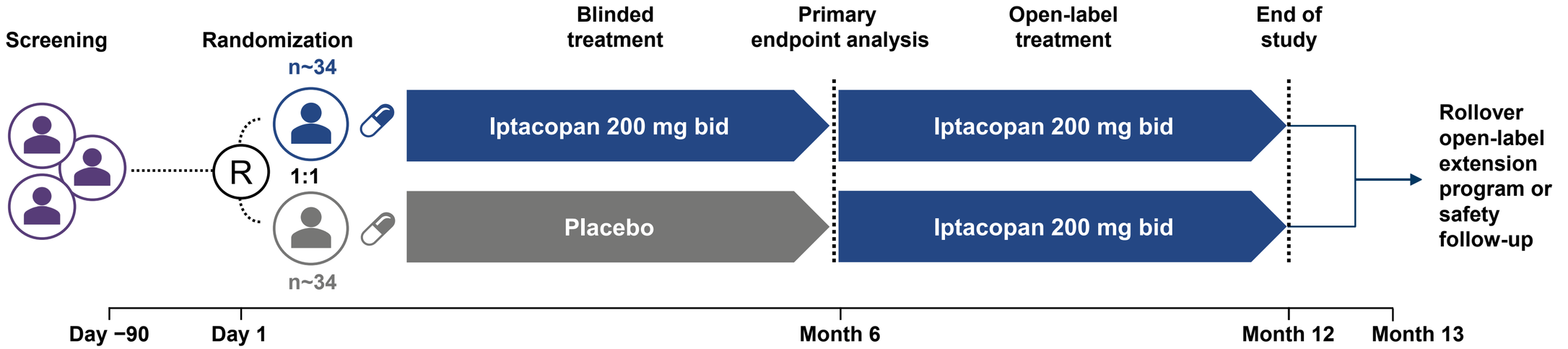
- A **placebo-controlled** Phase 3 study of iptacopan monotherapy in patients with C3 glomerulopathy
- The study treatment phase comprises a 6-month blinded period and a 6-month open-label period



Study design status	• Actively enrolling • Estimated study completion: August 2023

Patients will be stratified by corticosteroid or mycophenolic acid treatment at randomization

References

https://clinicaltrials.gov/ct2/show/NCT04817618 (Accessed 09 Sep 2021)

Abbreviations

C3G, C3 glomerulopathy; bid, twice daily

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Primary and secondary objectives

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Primary Objectives

Double-blind period

- To demonstrate the superiority of iptacopan versus placebo on proteinuria (UPCR) reduction at 6 months

Open-label period

- To assess the effect of iptacopan on proteinuria (UPCR) from baseline at 12 months for both treatment arms and from 6 months to 12 months for placebo arm

Secondary Objectives

- To demonstrate the superiority of iptacopan versus placebo on improvement from baseline in eGFR and responder rate of a 2-component composite renal endpoint* at 6 months
- To assess the effect of iptacopan versus placebo on reduction of glomerular inflammation in the kidney and improvement of patient-reported fatigue† at 6 months
- To evaluate the safety and tolerability of iptacopan versus placebo during the 6-month double-blind period
- To assess the effect of iptacopan on the following, from baseline at 12 months for both treatment arms and from 6 months to 12 months for placebo arm:
  - Responder rate of a 2-component composite renal endpoint*
  - Reduction of glomerular inflammation in the kidney
  - Improvement of patient-reported fatigue†
- To evaluate the safety and tolerability of iptacopan during the 6-month open-label period and entire 12-month treatment period

*Stable or improved eGFR from baseline [≤15% reduction] and a ≥50% reduction from baseline in UPCR

†Using FACIT–Fatigue score

References

https://clinicaltrials.gov/ct2/show/NCT04817618 (Accessed 09 Sep 2021)

Abbreviations

C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; UPCR, urine protein:creatinine ratio

Key exploratory objectives

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Double-blind period

- To evaluate the effect of iptacopan versus placebo on:
  - Serum C3 levels
  - Glomerular C3 deposition
  - Serum and plasma complement biomarkers
  - Health related quality of life
  - Proteinuria (assessed by UPCR)
  - eGFR
  - Biomarkers of kidney damage
  - UACR
  - Incidence of hematuria
  - FACIT-Fatigue
- To evaluate PK parameters of iptacopan
- To evaluate the following in both treatment arms:
  - Relationships between changes in C3, proteinuria and renal histopathology
  - Relationships between changes in complement biomarkers and C3G progression

Open-label period

- To assess the longer-term effects of iptacopan on renal function, complement biomarkers, glomerular C3 deposition and chronicity, health-related quality of life, incidence of hematuria, and biomarkers of kidney damage
- To evaluate PK parameters of iptacopan

References

https://clinicaltrials.gov/ct2/show/NCT04817618 (Accessed 09 Sep 2021)

Abbreviations

C3, complement protein 3; C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; FACIT, functional assessment of chronic illness therapy; PK, pharmacokinetics; UACR, urine albumin to creatinine ratio; UPCR, urine protein to creatinine concentration ratio.

Key inclusion and exclusion criteria

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Inclusion¶

- Aged ≥18 years and ≤60 years
- Biopsy-confirmed diagnosis of C3G
- Reduced C3 (<0.85 X LLN)
- UPCR ≥1.0 g/g
- eGFR¥ or measured GFR ≥30 mL/min/1.73 m^2
- On maximally recommended or tolerated dose of ACEi or ARB for ≥90 days
- Vaccination against *Neisseria meningitides*, *Streptococcus pneumoniae* and *Haemophilus influenzae*

Exclusion

- Organ transplant, including kidney
- Rapidly progressive crescentic GN
- Renal biopsy with interstitial fibrosis/tubular atrophy >50%
- MGUS
- Liver disease, infection or injury
- Evidence of urinary obstruction or difficulty in voiding
- Use of complement inhibitors within 6 months prior to screening or use of immunosuppressants (except mycophenolic acid), cyclophosphamide or systemic corticosteroids at a dose >7.5 mg/day (or equivalent for a similar medication) within 90 days of study drug administration

¶Other protocol-defined inclusion/exclusion criteria may apply

¥Using the CKD-EPI formula for ≥18 years

References

https://clinicaltrials.gov/ct2/show/NCT04817618 (Accessed 09 Sep 2021)

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; LLN, lower limit of normal; MGUS, monoclonal gammopathy of undetermined significance; UPCR, urine protein:creatinine ratio

APPEAR-C3G Phase 3 trial

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Statistical analysis

- The primary analysis will be carried out at the time the last participant has completed the 6-month randomized treatment period
- The log ratio to baseline in UPCR, change from baseline in eGFR, and change from baseline in fatigue total score will be assessed using a mixed model for repeated measures (MMRM)
- The change from baseline to month 6 in the histology total activity score will be analyzed using an analysis of covariance (ANCOVA) model
- A logistic regression model will be used to assess the probability of meeting the composite renal endpoint

Abbreviations

eGFR, estimated glomerular filtration rate; MMRM, mixed model for repeated measures; UPCR, urine protein:creatinine ratio

APPEAR-C3G Phase 3 trial

APPEAR-C3G

Aim

This pivotal Phase 3 study in C3G aims to establish the safety and clinical benefits of alternative pathway inhibition with iptacopan by using various functional, biomarker and histopathological assessments

Current status:

-Actively enrolling

-Estimated study completion: August 2023

Scan the QR Code

For further details on the trial, please scan the QR code

Abbreviations

C3G, C3 glomerulopathy; QR, quick response