Novartis Investor Relations

# Iptacopan (LNP023) update

**Investor presentation**
**June 22, 2021**

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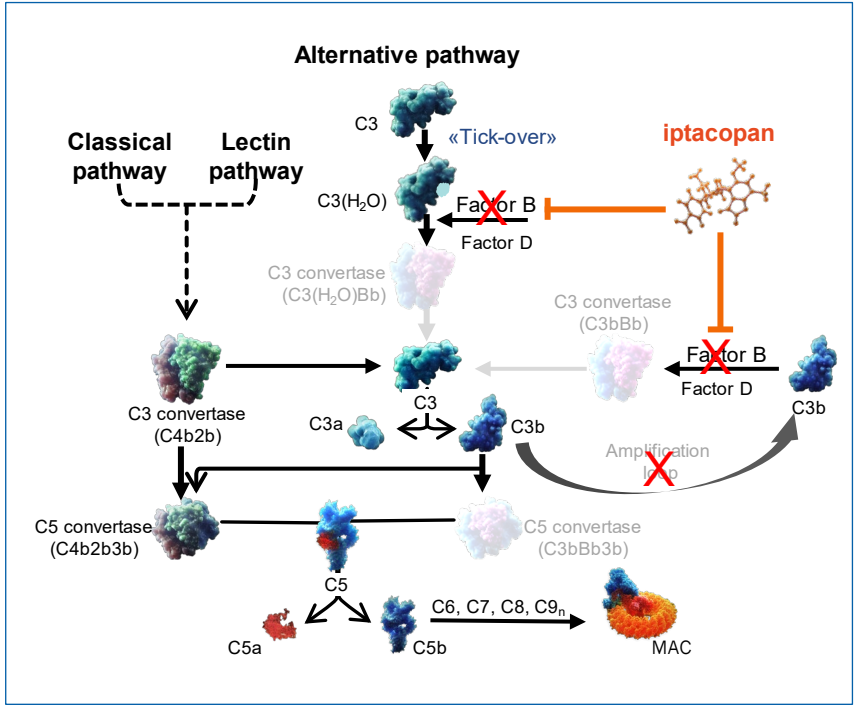
# Iptacopan could become a potentially preferred treatment option for several diseases with high unmet need – a pipeline in a pill

- The complement system is a foundational component of the innate immune system; dysregulation and/or overactivation of the cascade leads to and characterizes several diseases
- Iptacopan development program covers several nephrology and hematology indications that currently have limited (PNH[1], aHUS[2], LN[3]) or no approved treatments (IgAN[4], C3G[5], CAD[6], iMN[7])
- Positive Ph2 data in IgA nephropathy (IgAN) and C3 glomerulopathy (C3G) presented at ERA-EDTA 2021
- Positive Ph2 results for paroxysmal nocturnal hemoglobinuria (PNH) presented at ICKSH 2021 and EHA 2021
- Regulatory designations granted: PRIME for C3G, Breakthrough for PNH, and five orphan drug designations
- Ph3s ongoing in PNH, IgAN and expected to start in C3G and aHUS in coming months; iMN Ph2 ongoing
- First filings expected 2023; multi-billion potential if efficacy and safety confirmed across multiple indications

1. PNH = paroxysmal nocturnal hemoglobinuria 2. aHUS = atypical hemolytic uremic syndrome 3. LN = Lupus nephritis 4. IgAN = IgA nephropathy 5. C3G = C3 glomerulopathy
6. CAD = cold agglutinin disease 7. iMN = idiopathic membranous nephropathy

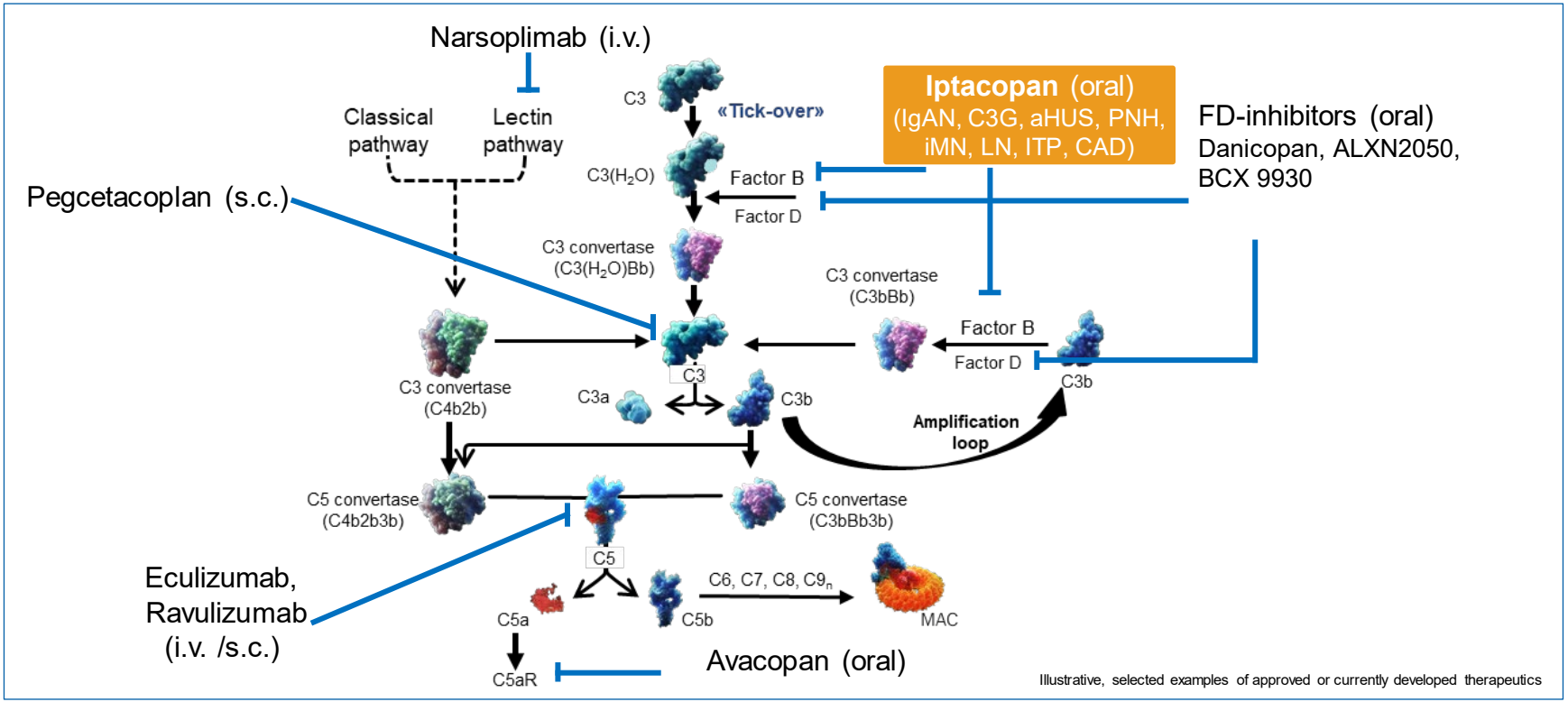
# Iptacopan is an oral, potent, selective factor B inhibitor...

- Dysregulation of the complement pathway is associated with a range of rare kidney and hematological diseases
- **Iptacopan (LNP023)** is an **oral,** first-in-class, **potent** and selective small-molecule **inhibitor of factor B (FB)**
- **Iptacopan binds to FB to suppress the activity of C3 convertase** and thus signaling from the alternative complement pathway (AP) and activation of the amplification loop
- **This prevents downstream generation of the C5 convertase complex**, opsonization, and formation of C3a and C5a anaphylatoxins and membrane attack complex (MAC)
- **Direct classical and lectin pathway signaling remains intact**, resulting in a potentially lower meningococcal infection risk in vaccinated patients compared to terminal complement pathway inhibitors



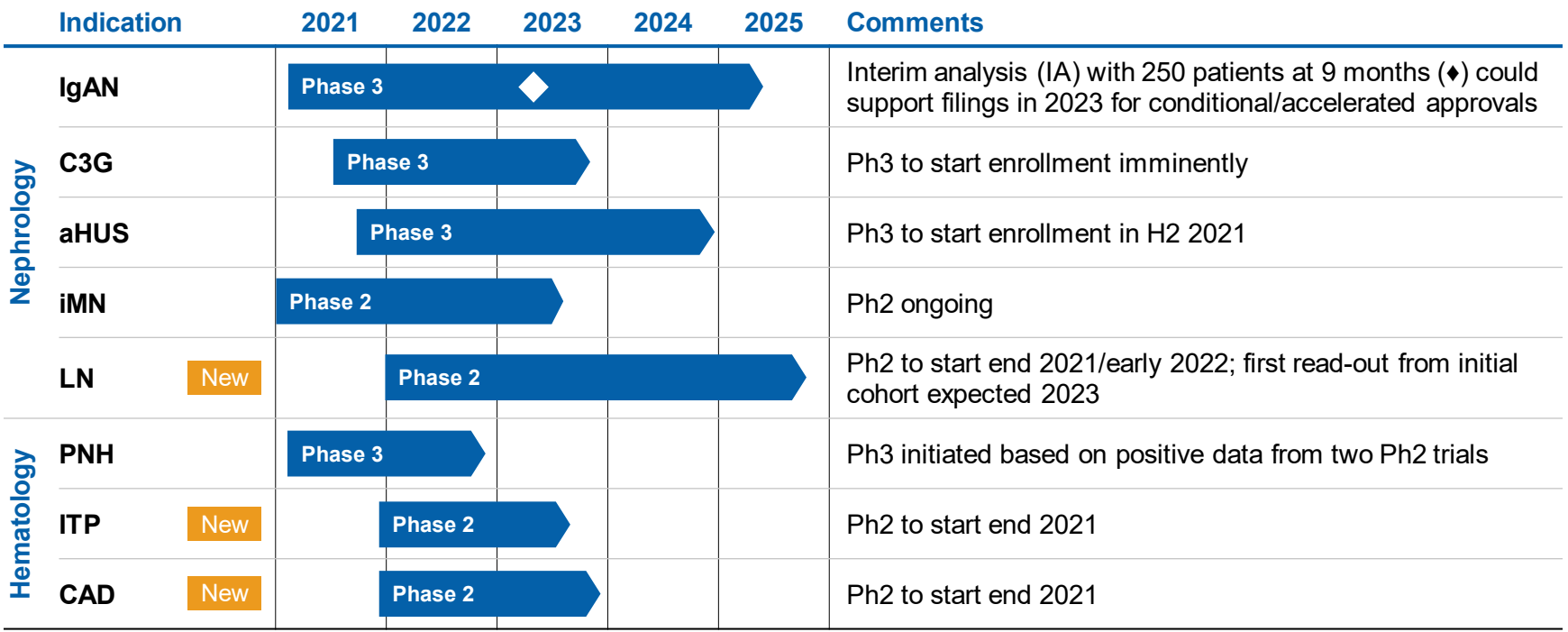

Schubart A et al. Proc Natl Acad Sci U S A 2019;116(16):7926-7931.

# ... with a promising profile enabling its broad development...




Illustrative, selected examples of approved or currently developed therapeutics

# … across both nephrology and hematology




IgAN = IgA nephropathy C3G = C3 glomerulopathy aHUS = atypical hemolytic uremic syndrome iMN = idiopathic membranous nephropathy LN = Lupus nephritis PNH = paroxysmal nocturnal hemoglobinuria
ITP = immune thrombocytopenic purpura CAD = cold agglutinin disease



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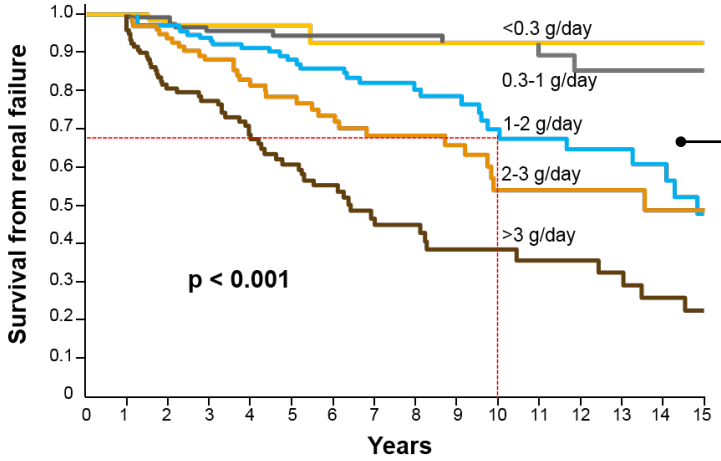
# In IgA nephropathy, iptacopan could potentially delay the need for dialysis and/or transplant

## TA[3]-proteinuria: the strongest clinical predictor for IgAN kidney function decline[2]




- **Most common primary glomerulonephritis,** most common cause of kidney failure in young adult Caucasians[1]
- **Prevalence:** US: ~185k; EU5: ~32-51k; China: ~1m; Japan: ~130k
- **Standard of care (SoC):** currently no approved therapies, focus on supportive care
- **Proteinuria** ≥1g/day is the strongest risk factor for poor prognosis in IgAN: ~30% of patients with proteinuria 1-2 g/day progress to kidney failure within 10 years
- **Proteinuria reduction is an important clinical goal in IgAN** and a relevant endpoint for accelerated registration pathways by FDA and other authorities
- **Activation of the alternative pathway (AP)** is present in almost **90% of biopsies**
- By targeting the AP, iptacopan has the potential to slow disease progression and **delay the need for dialysis and/or transplant**

1. Nair R, Walker PD. Kidney Int 2006;69:1455-83 2. Reich HN et al. J Am Soc Nephrol 2007;18:3177–183. 3. TA = time averaged

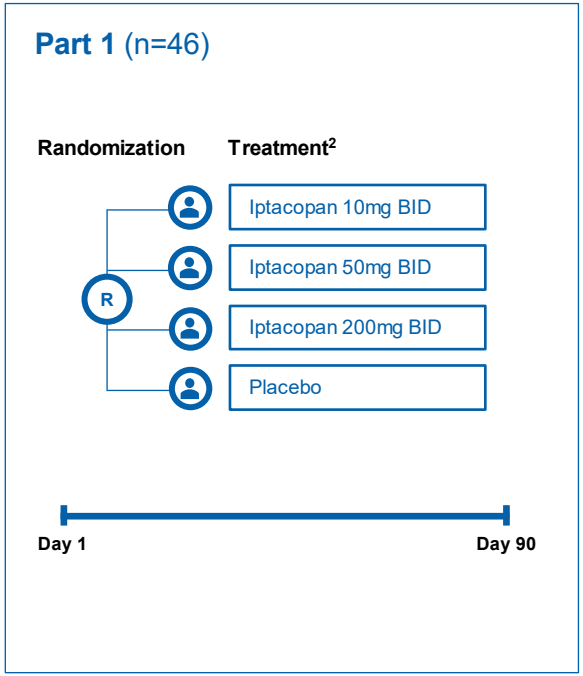
# IgAN Ph2 study robustly designed for rapid development...

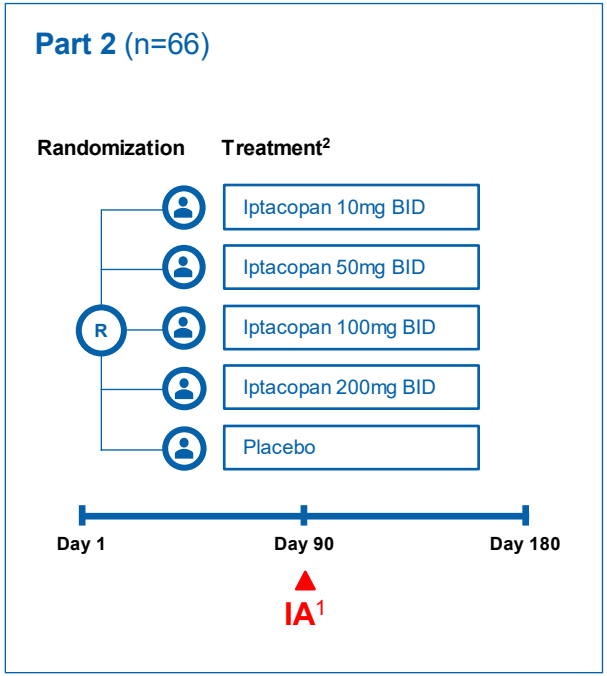
**Population**
**Biopsy-confirmed IgAN** patients at risk of progression with elevated proteinuria (UPCR ≥0.75g/g) despite being on stable background therapy[5]

**Study design**
Adaptive, seamless, **double-blind, placebo-controlled, dose-ranging**

**Primary objective**
**Dose response** on the reduction in proteinuria vs. placebo after 90 days

**Secondary objectives**
Safety and tolerability, eGFR[3], and biomarkers reflecting activity of AP[4]

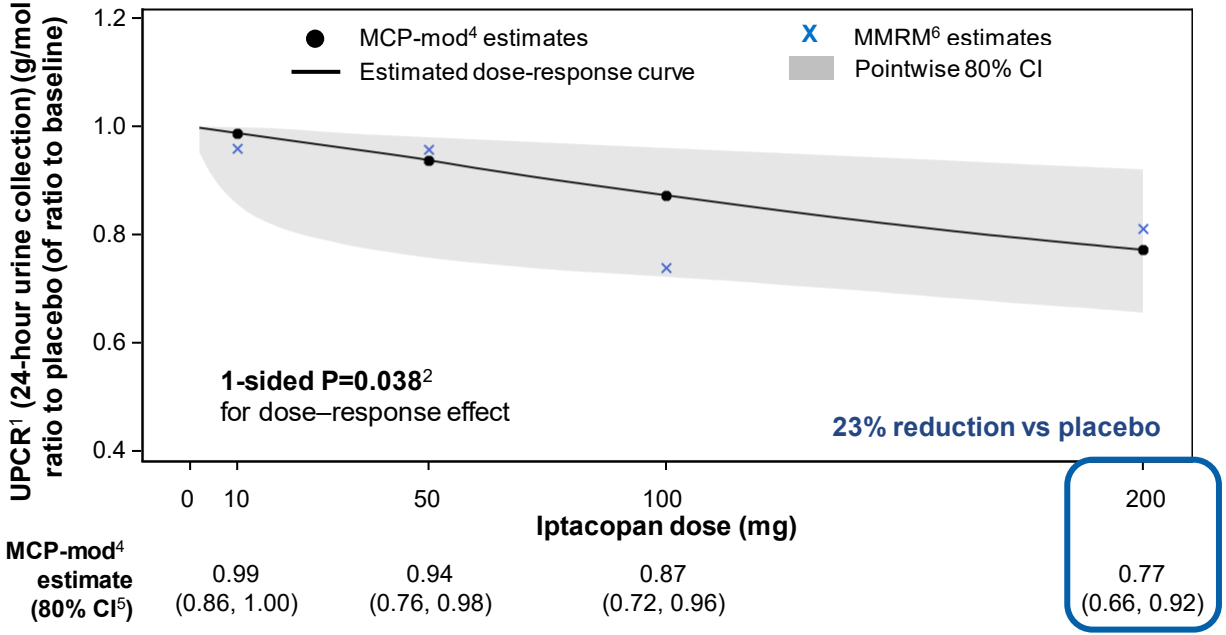



1. IA = interim analysis: analysis includes patients pooled from parts 1 and 2 of the study (n=112) 2. BID = twice daily dose of ACEi or ARB therapy for the individual, antihypertensive therapy or diuretics for at least 90 days before dosing 3. estimated glomerular filtration rate 4. AP = alternative pathway 5. Supportive care including a maximally tolerated

# … showed 200mg BID[3] led to a clinically meaningful proteinuria reduction of 23% at Day 90…

Primary endpoint data presented at ERA-EDTA 2021

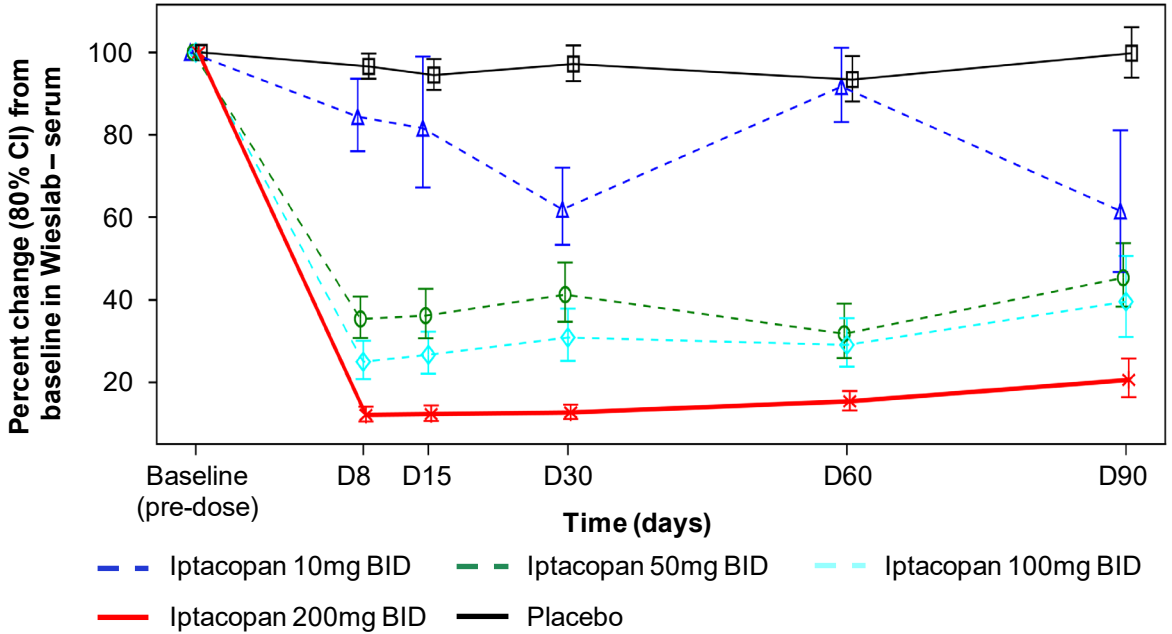



- Statistically **significant effect of dose-response in proteinuria reduction**[8] by iptacopan versus placebo at 90 days
- **Iptacopan 200mg BID**[3] **led to a 23% reduction** (80% CI: 8%, 34%)
- Treatment with **iptacopan** showed encouraging trend to **early stabilization of renal function (eGFR**[7]**)**
- **Well tolerated;** no serious infections

1. UPCR = Urine protein to creatinine ratio 2. Multiplicity-adjusted P-value; analysis adjusted for baseline UPCR (24-hour) and ancestry 3. BID = twice daily 4. MCP-mod = Multiple Comparison Procedure – Modelling
5. CI = confidence interval 6. MMRM = mixed model repeated measurements 7. eGFR = estimated glomerular filtration rate 8. 24-hour UPCR

# … with the 200mg BID delivering rapid, sustained, near complete inhibition of the alternative complement pathway…

Data presented at ERA-EDTA 2021




**Iptacopan**

- **Dose-dependent reduction** of AP activation measured by serum Wieslab assay
- **Rapid** - Day 8 onwards
- Also reduced other complement biomarkers, including plasma Bb and urinary sC5b-9

. BID = twice daily CI = confidence interval AP – alternative complement pathway

# … providing the basis to initiate the APPLAUSE-IgAN Ph3 study

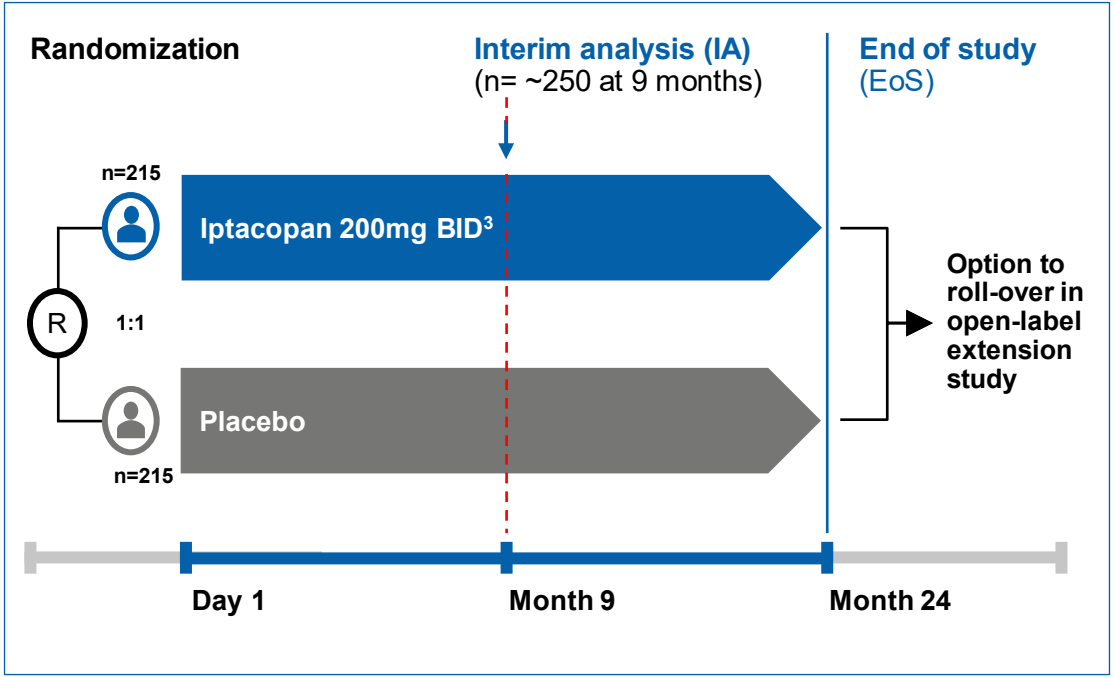
## Population

**Biopsy-confirmed IgAN** patients **at risk of progression** with elevated proteinuria (UPCR[2] ≥1g/g) **despite being on stable background therapy**[1]

## Primary objectives

**IA: Assess superiority of iptacopan** vs. placebo in reduction of proteinuria[2] at 9 months; **to support regulatory submission for accelerated/conditional approval**

**EoS: Assess superiority of iptacopan** vs. placebo in **slowing progression of IgAN** measured by annualized total slope of eGFR decline over 24 months




1. Including at least maximally tolerated dose of ACEi/ARB for at least 90 days 2. UPCR (urine protein-to-creatinine ratio) from 24-h urine collection 3. BID = twice daily

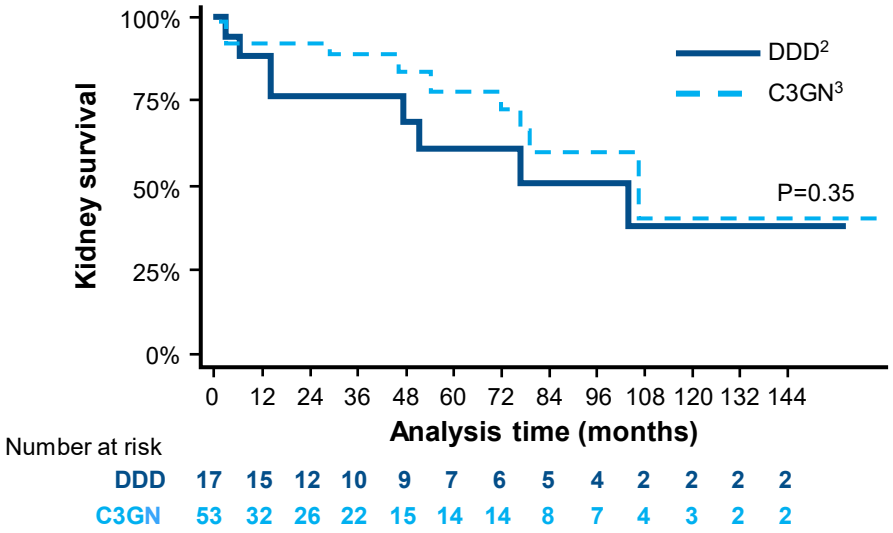
# Robust Ph2 data demonstrate clinically meaningful effect. Ph3 initiated to support worldwide regulatory filings

- First study to report safety and efficacy of an alternative complement pathway inhibitor in IgAN
- **Robust Ph2 design provides confidence** iptacopan has the potential to deliver a clinically meaningful effect
  - Randomized, double-blind and placebo-controlled study throughout the 90 days study period
  - 112 patients randomized to three (part 1) or four (part 2) different doses of iptacopan or placebo
- **Primary study objective met**: dose-dependent reduction in 24h UPCR at 90 days when compared to placebo
  - 23% UPCR reduction considered clinically meaningful; already observed after 90 days of treatment
  - Early trend of renal function stabilization (measured by eGFR)
  - Strong and dose-dependent inhibition of biomarkers of alternative complement pathway activity
  - Iptacopan treatment well tolerated at all doses
- **Ph3 APPLAUSE-IgAN is ongoing** globally to support iptacopan filings worldwide
- **Potential first oral targeted anti-complement therapy in IgAN** to delay dialysis and/or transplant

UPCR = Urine protein to creatinine ratio  eGFR = estimated glomerular filtration rate

# Iptacopan has potential to be disease modifying, delaying or preventing need for dialysis and/or kidney transplant in C3G

## K-M analysis of kidney survival[1] by C3G subtype[4]




- **C3G** is an **ultra-rare**, severe form of primary glomerulonephritis and is commonly diagnosed in adolescents and young adults
- **Prevalence**: US: ~10k; EU5: ~1.5-2.5k; China: ~32k; Japan: ~3.2k
- There are currently **no approved therapies**
- **~50%** patients develop **kidney failure within 10 years** of diagnosis
- **Post-transplantation recurrence** and allograft loss **is common** (50% in DDD[2], 75% in C3GN[3])
- Characterized by complement dysregulation and complement C3 deposition in the kidney
- In C3G, iptacopan has the potential to be disease modifying and to **delay, or even prevent, the need for dialysis and/or transplant**

1. End-stage kidney disease (ESKD) free renal survival 2. Dense Deposit Disease 3. C3 glomerulonephritis 4. Medjeral-Thomas et al. Clin J Am Soc Nephrol. 2014;9(1):46-53

# Iptacopan Ph2 provides data on patients with both native and transplanted kidneys...

## Population

**Cohort A**: **Biopsy-confirmed C3G** patients[1], with **native kidneys** and reduced serum C3 levels
Interim data available

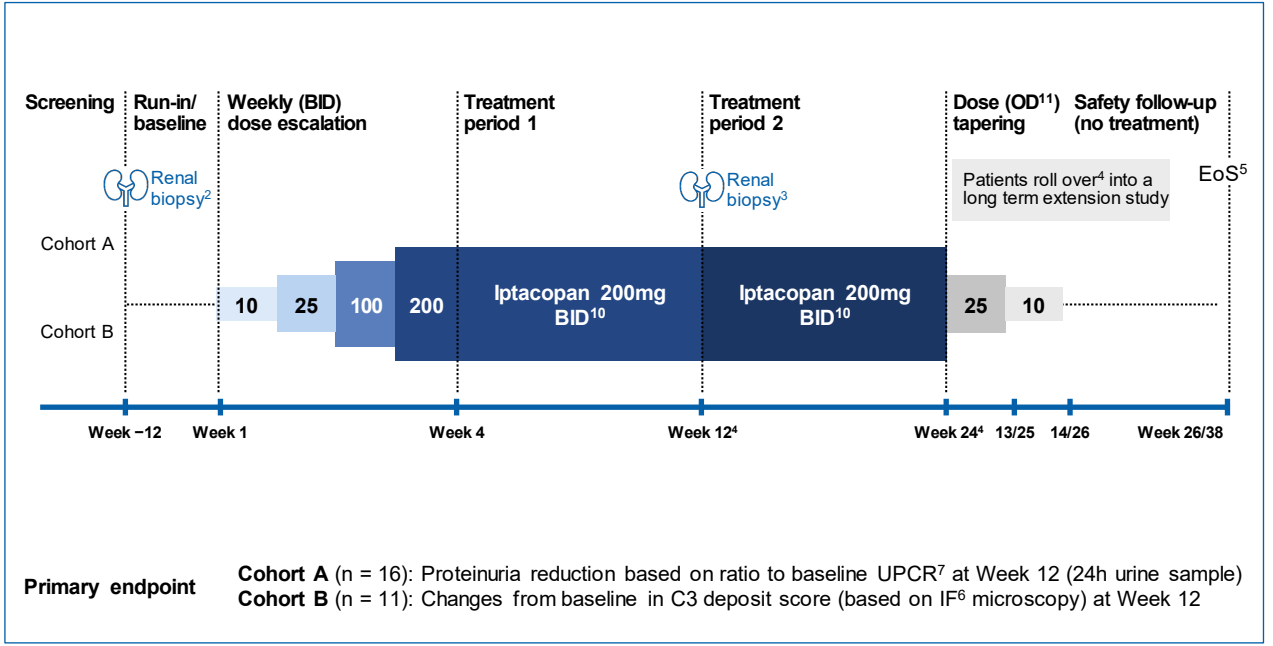
**Cohort B:** patients[1] **with C3G recurrence** following kidney transplantation
Data expected in Q3 2021

## Primary objective (Cohort A)

**Reduction in proteinuria** at Week 12 measured as ratio to baseline of UPCR[7]

## Secondary objectives

eGFR[8], and biomarkers reflecting activity of AP[9], safety and tolerability

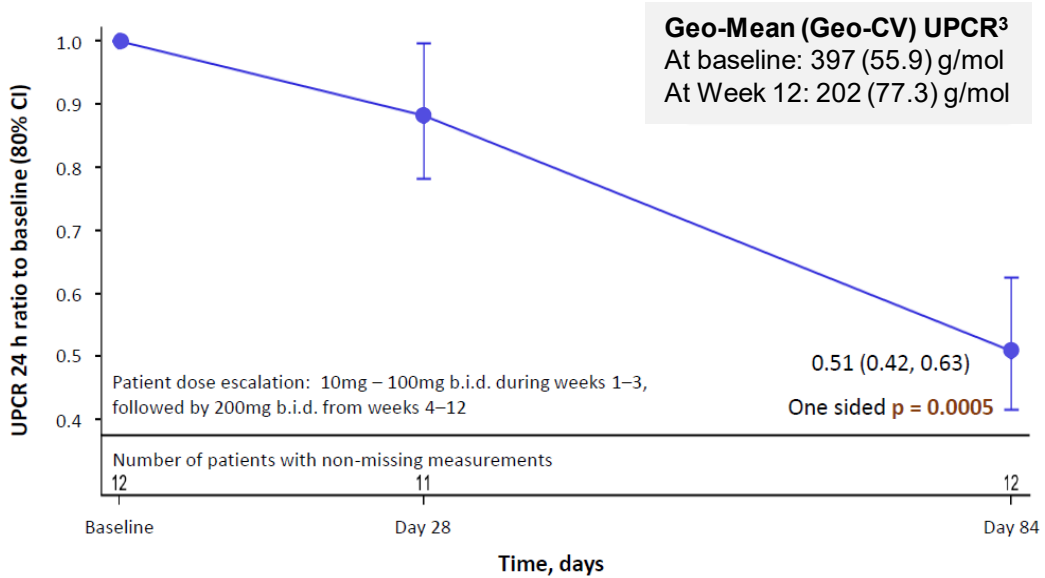



1. Patients aged ≥18 years 2. Not required for Cohort A unless most recent biopsy >12 months old 3. Optional for Cohort A 4. Patient may roll over into a separate extension study at Week 12 5. EOS = end of study
6.IF = immunofluorescence 7. UPCR = Urine protein to creatinine ratio 8. eGFR = estimated glomerular filtration rate 9. AP = alternative complement pathway 10. BID = twice daily 11. OD = once daily

# … showing clinically meaningful 49% reduction in proteinuria…

IA data on primary endpoint presented at ASN 2020

## UPCR[3] (24h urine collection) vs. baseline over time[1]



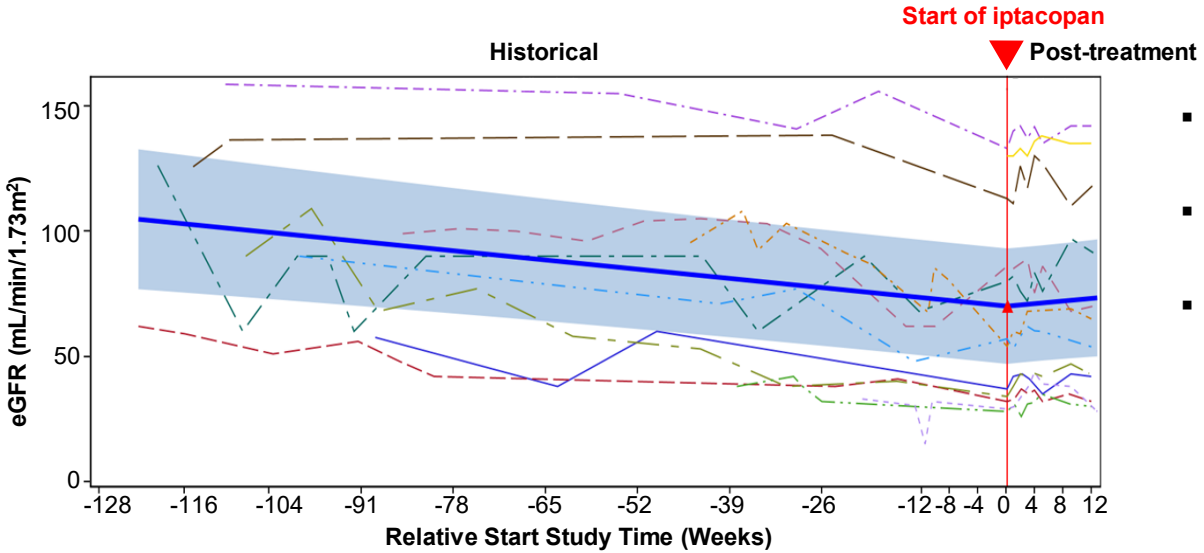

- **Significant and clinically meaningful reduction** in proteinuria of **49%** from baseline
- Already at **3 months** there are signs of **stabilization of kidney function** (eGFR[4])
- Well tolerated with no unexpected or new safety findings
- ERA-EDTA 2021: new retrospective observational cohort study data: longitudinal change in proteinuria strongly associated with kidney failure risk in C3G[2]

1. Note: all patients from cohort A (with native kidney) 2. Caravaca-Fontan, Nephrol Dial Transplant 2021 Mar 29;gfab075. 3. UPCR = Urine protein to creatinine ratio 4. eGFR = estimated glomerular filtration rate

# … with improvements in trajectory of renal function decline compared to historical patients' trend

Data presented at ERA-EDTA 2021

## Mean eGFR[1] slope and 95% CI[2] indicated by bold blue line and surrounding shadowed area




- Iptacopan treatment leads to **stabilization of renal function**
- Patients experienced deterioration in renal function historically
- Iptacopan's estimated effect corresponds to a mean predicted eGFR preservation of 6.4 mL/min/1.73m² over 12 weeks (p=0.0459)

Individual patient eGFR slopes (n=12) for up to 2 years prior to and following commencement of 12-week course of iptacopan

1. eGFR = estimated glomerular filtration rate 2. CI = confidence interval



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# Ph2 C3G data formed basis to initiate Ph3 APPEAR-C3G to support regulatory submission

## Population

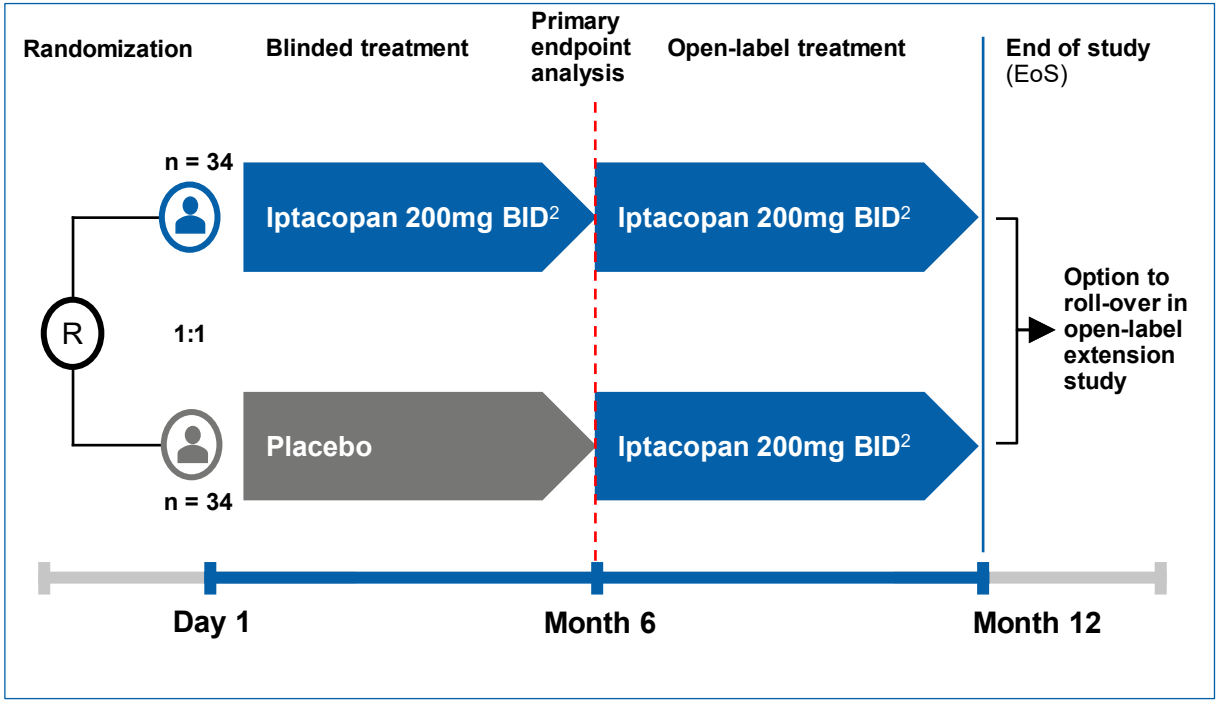
Adult patients with **biopsy-confirmed C3G and native kidney**. Proteinuria ≥1g/g (24h UPCR[1])

## Primary objective

**Proteinuria** reduction at 6 months

## Secondary objectives

eGFR[3], proportion achieving a composite renal endpoint, reduction in glomerular inflammation, safety and tolerability




1. UPCR = urinary protein to creatinine ratio 2. BID = twice a day 3. eGFR = estimated glomerular filtration rate

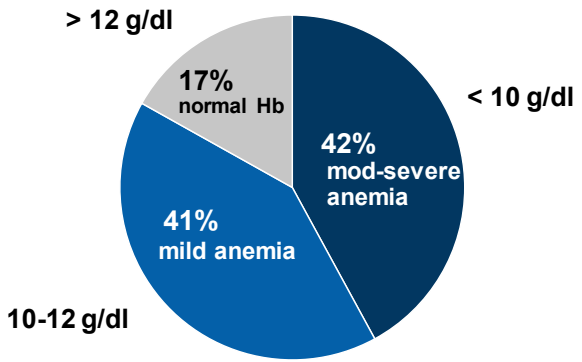
# Strong Ph2 data demonstrate clinically meaningful effect. Ph3 to be initiated to support worldwide regulatory filings

- **Clinically meaningful reduction in 24h UPCR of 49% after 12 weeks** and **stabilization of renal function**
  - Beneficial effects on proteinuria reduction and eGFR were seen very fast and sustained
  - Rapid increases in serum C3 levels and reductions in markers of complement activity provide mechanistic support
  - Favorable safety and tolerability profile
- New data presented at ERA-EDTA 2021 show **statistically significant and clinically important improvements by iptacopan in eGFR slope** when compared to pre-treatment period, suggesting that iptacopan may slow progression to, or potentially even prevent development of, kidney failure in patients with C3G
- Final Ph2 results, including from cohort B in patients with recurrent C3G after kidney transplant expected in Q3 2021 and planned to be presented at an upcoming congress
- Double-blind, placebo-controlled **Ph3 APPEAR-C3G** study projected **to start enrollment imminently**
- **Potential to become first targeted and evidence-based treatment in C3G**

UPCR = Urine protein to creatinine ratio  eGFR = estimated glomerular filtration rate

# Iptacopan has the potential to be the first oral anti-complement mono-therapy in patients with PNH

## Hematological response to eculizumab[1]




- **Paroxysmal nocturnal hemoglobinuria** (PNH) is a **rare, life-threatening blood disorder caused** by an acquired mutation in hematopoietic stem cells that leads to absence of complement-regulatory proteins
- **Prevalence**: WW 7-16 cases/million; US 5-6k[2]
- **Many patients remain anemic and transfusion dependent** despite eculizumab treatment
  - C3-mediated **extravascular hemolysis not addressed** by anti-C5
  - ~40% remain **anemic** (Hb[3] <10g/dl) of which ~50% are transfusion dependent[1]
- By specifically targeting the complement pathway proximally, **iptacopan could address both intra- and extravascular hemolysis** and thereby address the remaining unmet need in PNH
- Interim Ph2 data already showed that iptacopan provides clinical benefits as add-on to eculizumab in patients with residual hemolysis

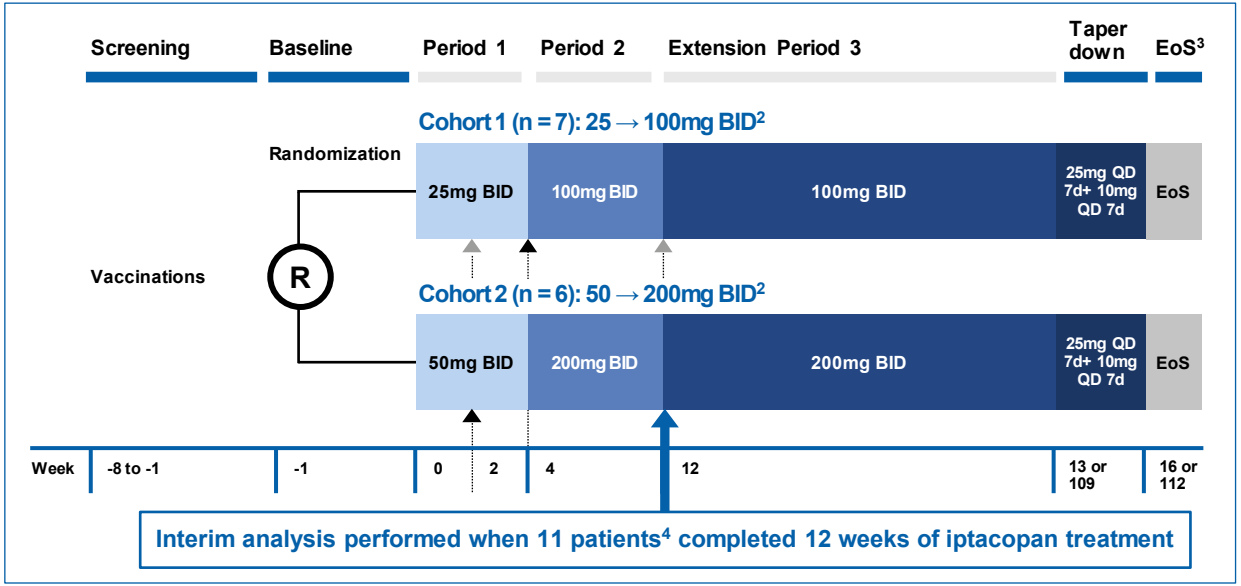
1. Blood (2019) 134 (Supplement_1): 3517 2. Petropoulou AD 2010 3. Hb = Hemoglobin

# Iptacopan Ph2 study in patients with PNH who are anti-C5 treatment naive

**Primary objective:**
Reduction of **PNH-associated hemolysis** (LDH[1] levels at week 12)

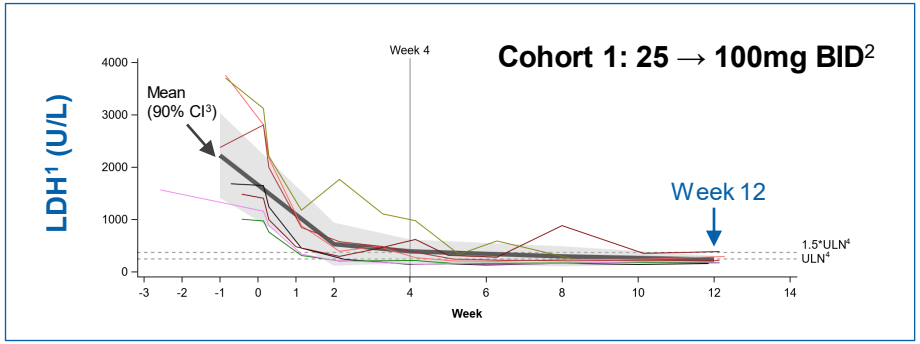
**Secondary objectives:**
Dose-response, markers of intravascular and extravascular hemolysis (incl. Hb), markers associated with risk of thrombosis, safety and tolerability, pharmacokinetics

**Key exclusion criteria:**
Complement inhibition within prior 3 months, history of splenectomy




1. LDH = Lactate dehydrogenase 2. BID = Twice a day (QD = Once a day) 3. EoS = End of study 4. One patient in Cohort 1 started study drug taper prior to cutoff and discontinued after cutoff by patient preference, due to worsening of pre-existing neutropenia, one patient in Cohort 2 discontinued after 2 days of dosing due to non-severe AE of headache

# Ph2 PNH study met primary endpoint of reduction in LDH[1] at week 12...

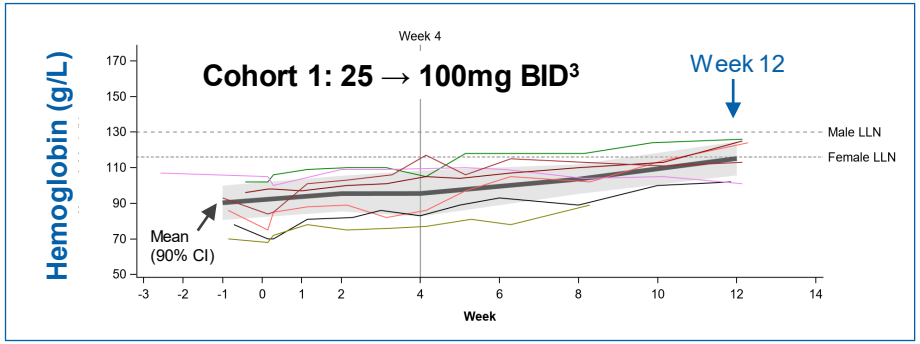


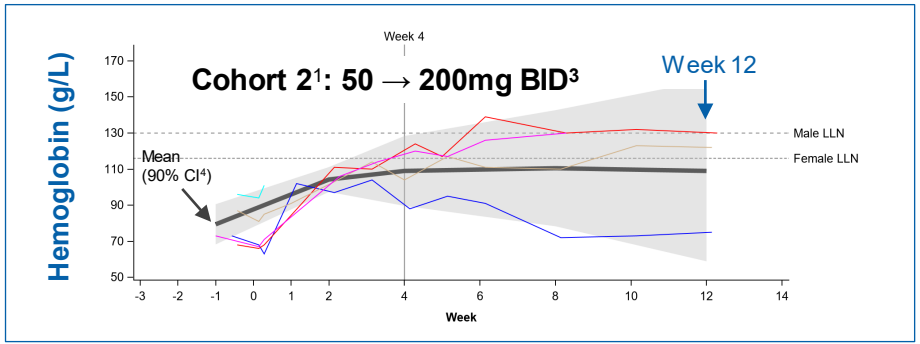

New data (anti-C5 naive) presented at EHA 2021

- **Patients** in both cohorts **met the primary endpoint** of reducing LDH[1] levels by ≥60% at Week 12
- After week 4, iptacopan achieved mean LDH reductions of 80-90%
- LDH reduction was **rapid and durable**, less variability observed in the higher dose cohort
- Markers of intra- and extravascular hemolysis normalized in the majority of patients

1. LDH = Lactate dehydrogenase 2. BID = Twice a day 3. CI = Confidence interval 4. ULN = Upper limit of normal

# ... with clinically meaningful increases in hemoglobin observed in all patients




New data (anti-C5 naive) presented at EHA 2021

All patients experienced **rapid, durable increase** in hemoglobin

All patients except one **remained transfusion-free** until Week 12

- One patient in cohort 2 (blue line) got one red blood cell (RBC) transfusion on study Day 3
- This patient (blue line) had pre-existing MDS[2], requiring 13 RBC transfusions during the year prior to study entry

1. One patient in Cohort 2 was excluded for Hb analyses due to an RBC transfusion that occurred between screening and baseline, raising Hb from 71 to 110 g/L 2. MDS = Myelodysplastic syndrome 3. BID = twice a day CI = confidence interval

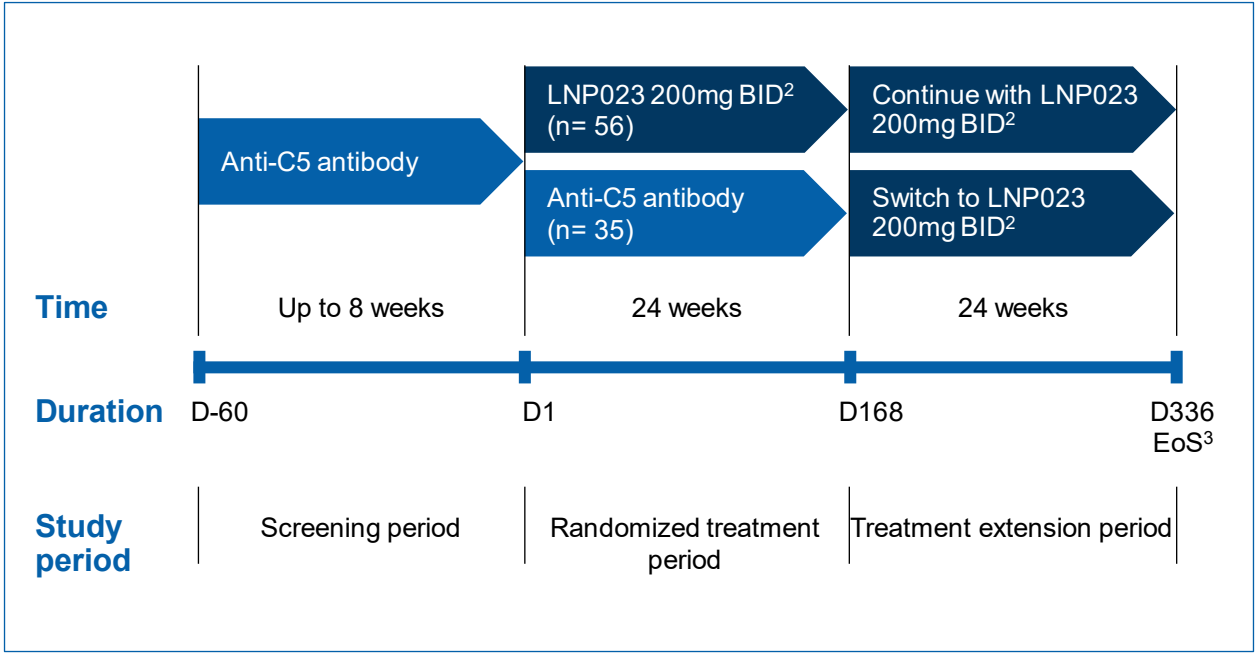
# Ph2 data provide basis for iptacopan Ph3 APPLY-PNH

**Population** (n ~91)

Adult PNH patients (Hb <10g/dL) on a stable regimen of anti-C5 therapy 6 months prior to randomization

**Primary endpoints**

- Proportion of patients achieving increase in Hb ≥2g/dL from baseline in the absence of RBC[1] transfusion
- Proportion of patients achieving Hb ≥12g/dL in the absence of RBC[1] transfusion




1. RBC = Red Blood Cell 2. BID = twice a day 3. EoS = end of study

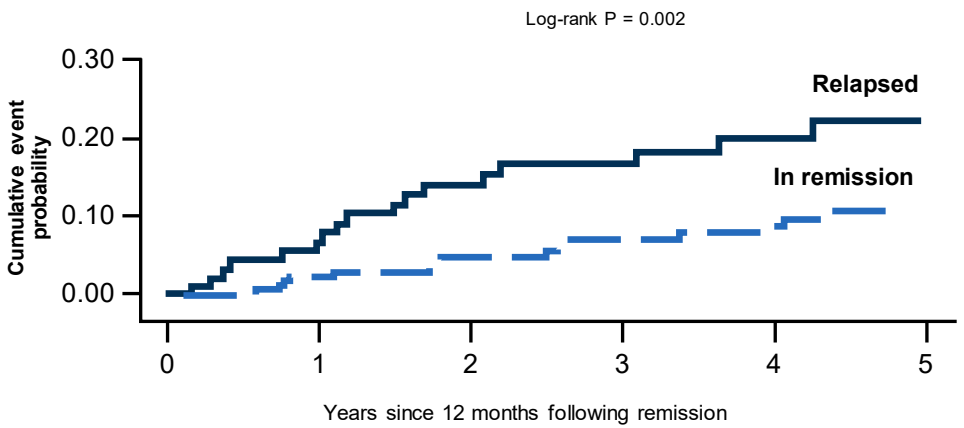
# Iptacopan has the potential to become the first oral anti-complement mono-therapy in patients with PNH

- Interim analysis (EBMT 2020) showed iptacopan provided **clinical benefits as add-on** to eculizumab in PNH patients with residual hemolysis
  - Marked reduction of hemolytic markers and transfusion-free improvement of hemoglobin in the majority of patients
  - Well tolerated with most common AE[1]s being headache, insomnia, rhinitis and rhinorrhea
  - Clinical benefits persisted upon discontinuation of eculizumab
- New data (EHA 2021) show **clinically important benefits of monotherapy iptacopan** in anti-C5 treatment naive PNH patients, including normalization of markers of intra- and extravascular hemolysis; resulting in a rapid and durable, transfusion-free improvement of hemoglobin levels in the majority of patients, with a favorable safety profile
- **Ph3 APPLY-PNH** study to assess **superiority of iptacopan vs. anti-C5 therapy** in patients with residual anemia despite standard of care treatment is **ongoing to support filings as of 2023**
- Iptacopan could become the first **oral** anti-complement mono-therapy in PNH offering significant convenience to patients along a potential superior benefit/risk

1. AE = adverse event

# Iptacopan could improve nephrotic syndrome and remission rates in patients with idiopathic Membranous Nephropathy

## Development of ESKD[1] or 50% reduction in renal function in patients with remission of MN vs. relapse[2,3,4]

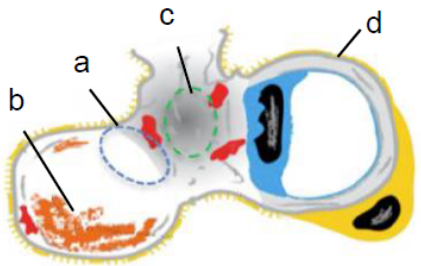



- **Idiopathic Membranous Nephropathy** (iMN) is a rare autoimmune glomerular disease and the most common cause of nephrotic syndrome in non-diabetic adults
- **Prevalence**: US: ~80k; EU5: ~82k; China: ~422k; Japan: ~32k
- **There are currently no approved therapies**
- **30-40%** of patients develop **kidney failure within 5-15 years** of diagnosis
- **Relapses** after remission **are common** (15-30% of patients)
- Complement pathway activation has been shown in kidney biopsies
- In iMN, iptacopan has the potential to **rapidly improve nephrotic syndrome and remission rates**

1. ESKD = End-stage kidney disease. 2. Cattran DC et al. J Am Soc Nephrol 28: 995–1003, 2017. 3. Lai WL, et al. J Formos Med Assoc. 2015;114(2):102–111. 4. Keri KC, et al. Postgrad Med J. 2019;95(1119):23–31

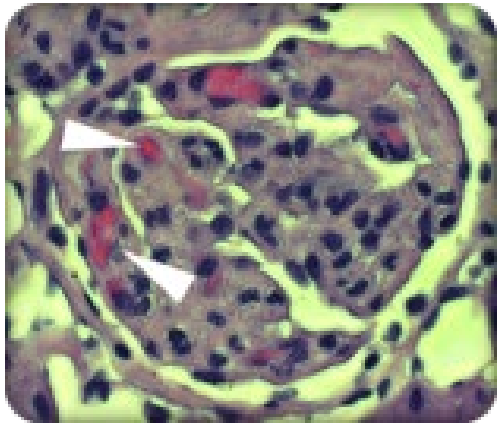
# Iptacopan has the potential to become first oral anti-complement therapy in patients with atypical Hemolytic Uremic Syndrome

## Glomerular changes in aHUS[8]




aHUS arises from an initial EC[1] injury. Defective complement control on endothelial surfaces results in cell lysis, **(a)** loss of EC[1], **(b)** followed by thrombus formation, **(c)** loss of mesangial cells and mesangiolysis. **(d)** In the chronic or repair phase, the newly formed EC[1] produces new extracellular matrix, leading to double contours/GBM[2] thickening

## Kidney biopsy showing TMA



Fibrin thrombi and red blood cell fragments present in the capillary loops (white arrowheads)[7]

- **Atypical Hemolytic Uremic Syndrome** (aHUS) is a life-threatening, progressive, rare form of thrombotic microangiopathy (TMA) often affecting children[5]
- **Prevalence**: US <10k
- **>50% of patients need dialysis** and/or develop more permanent renal damage within 12 months following the first episode of aHUS[6]
- **Unmet need** remains despite current SoC[4] with C5 inhibitors such as patient burden
- Associated with dysregulation of the alternative pathway
- **Iptacopan** has potential to become the **first oral** anti-complement therapy with a **strong benefit/risk** profile

1. EC = endothelial cell 2. GBM = glomerular basement membrane. 3. TMA = thrombotic microangiopathy 4. SoC = standard of care 5. Goodship THJ et al. Kidney Int 2017;91:539–51. 6. Fremeaux-Bacchi V et al. Clin J Am Soc Nephrol 2013;8:554–621. 7. Dixon BP, Gruppo RA. Pediatr Clin N Am 2018;65:509–25 8. Zipfel PF, et al. J Am Soc Nephrol. 2020;31(2):241–256.

# Iptacopan may have the potential to delay dialysis and/or transplant in patients with Lupus Nephritis (LN)

## Patient population

- Inflammation of the kidneys associated with proteinuria, hematuria, impaired kidney function and high blood pressure
- Affects up to 40% of adults (~90% women of childbearing age) and 80% of children with systemic lupus erythematosus (SLE); major cause of morbidity and mortality[1]
- Remission achieved in only 30–50% of patients; 10-20% of patients develop kidney failure within 10 years of diagnosis[1]
- Major ethnic disparities: Less frequent and severe for Caucasians; highly prevalent in African/Caribbean patients, Hispanic and Asian patients accounting for ~28-52% of the LN population

## Scientific rationale for iptacopan

- Strong complement activation in SLE[5]
- In LN, deposition of nucleic acid-containing material in the glomeruli triggers the engagement of complement, activation of kidney stromal cells and recruitment of circulating pro-inflammatory cells
- Significantly decreased plasma C3 and increased Bb, C3a, C5a, and MAC found in active LN
- Reduced levels of C3 and C4 in plasma (overconsumption)

## Standard of care

- Induction with high dose corticosteroids + immunosuppressants (oral MMF[2] or cyclophosphamide/CNIs[3]), followed by lower doses as maintenance therapy; off-label rituximab used for refractory disease
- High unmet need for convenient and safe therapies with rapid nephron protection and durable CRR[4] >20%, even after two novel entrants in 2020 (belimumab, voclosporin)

## Expected milestones

- Ph2 to start end 2021 / early 2022
- First read-out from initial cohort expected 2023
- Filing expected ≥2025

1. Maria NI, Davidson A. Protecting the kidney in systemic lupus erythematosus: from diagnosis to therapy. Nature Reviews Rheumatology. 2020;16:255–267 2. MMF = mycophenolate mofetil 3. CNI = Calcineurin inhibitor
4. CRR = complete renal response 5. systemic lupus erythematosus

# Initiating Ph2 iptacopan study in Q4 2021 in patients with Immune Thrombocytopenic Purpura (ITP)

## Patient population

- Autoimmune thrombocytopenia (= platelets <100 k/µL) with increased risk of bleeding
- Annual incidence of ~3-10/ 100,000 and increasing with age
- Typical time of diagnosis during early adulthood (20-40y)
- Usually presents acutely with signs and symptoms of bleeding (petechiae, bruising, mucosal bleeding)

## Scientific rationale for iptacopan

- Excessive platelet destruction in the spleen and liver and insufficient platelet production in the bone marrow, resulting in low platelet counts
- Evidence of complement involvement and/or reduced serum levels of complement factors in 30-50% of ITP patients
- Degree of platelet destruction / disease severity correlates with level of complement activation

## Standard of care

- Steroids and/or IVIG[1] in acute first-line therapy
- In persistent / chronic ITP: TPO-RAs[2] and/or rituximab as 2nd line and splenectomy and/or fostamatinib as 3rd line
- Continued unmet medical needs exist particularly for durable remissions in relapsed / refractory patients (~30% of population)

## Expected milestones

- Cohort in hematology basket study
- Ph2 start in Q4 2021 with first results expected 2023
- Filing projected ≥2025

1. IVIG = Intravenous immunoglobulin 2. TPO-RAs = thrombopoietin receptor agonists

# Initiating Ph2 iptacopan study in Q4 2021 in patients with Cold Agglutinin Disease (CAD)

## Patient population

- Auto-immune hemolytic anemia, often triggered by cold temperatures or viral infections
- Prevalence of 1-9 / million
- More women than men affected; median age at diagnosis is 72 years and median age at the onset of symptoms 65 years
- Reduced quality of life due to anemia; symptoms include fatigue, dizziness, tachycardia, dyspnea, abdominal pain, acrocyanosis

## Scientific rationale for iptacopan

- IgM autoantibody-mediated disease
- Anemia primarily caused by extravascular hemolysis in spleen / liver and which is largely complement-dependent through C3 fragments deposition on RBCs[1]

## Standard of care

- No approved therapy
- Plasma apheresis; steroids and rituximab used off-label
- Sutimlimab (anti-C1 mAb) Ph3 positive; approval pending
- Iptacopan has potential for first-in-class oral complement pathway inhibitor in CAD

## Expected milestones

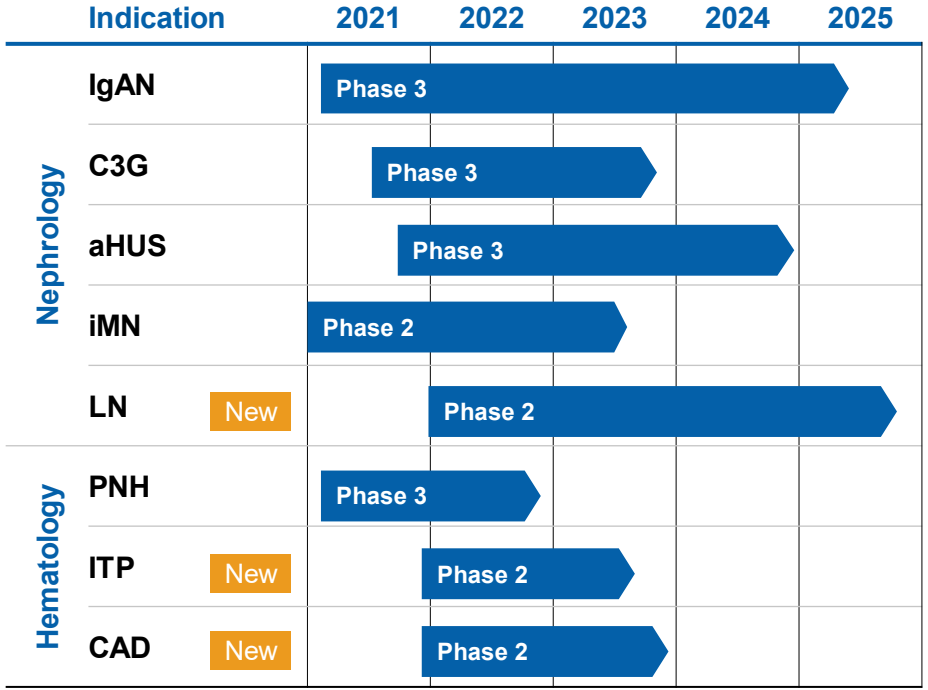
- Cohort in hematology basket study
- Phase 2 start in Q4 2021, with first results expected 2023
- Filing projected ≥2025

1. RBC = red blood cells

# Iptacopan in parallel development across several nephrology and hematology diseases, with global multi-blockbuster potential

## Market potential

| Indication | US prevalence thousands |
|---|---|
| **Nephrology** | |
| IgAN | ~185 |
| C3G | <10 |
| aHUS | <10 |
| iMN | ~80 |
| LN | ~100 |
| **Hematology** | |
| PNH | <10 |
| ITP | ~100 |
| CAD | <10 |




IgAN = IgA nephropathy C3G = C3 glomerulopathy aHUS = atypical hemolytic uremic syndrome iMN = idiopathic membranous nephrpopathy LN = lupus nephritis PNH = paroxysmal nocturnal hemoglobinuria ITP = Immune thrombocytopenic purpura CAD = Cold agglutinin disease



NOVARTIS | Reimagining Medicine

# Novartis is making significant efforts to prepare for a successful launch of iptacopan...

1. **Partnering with patient organizations**: Elevating the “voice of the patient” to raise awareness of high burden of illness and unmet need across the different diseases

2. **Real world data generation**: Working with key registries across the world to demonstrate the potential value of iptacopan to the overall healthcare system

3. **Patient journey mapping**: Identifying key clinical and non-clinical implementation barriers that need to be removed to ensure optimal patient outcomes

4. **Medical education and evidence generation**: Establish a strong scientific “share of voice” at congresses to highlight the unmet need, build innovative partnerships with healthcare system stakeholders and ensure a robust evidence base for future implementation in clinical practice

# … which has the potential to become first-in-class for several rare complement driven diseases with high unmet need

Complement driven diseases are **rare and often progressive diseases**

Many of these diseases **affect young patients, significantly impacting their QoL** and even leading to premature death

Iptacopan could **delay the progression or control the manifestations of these rare diseases**, thus improving QoL for patients and easing the overall burden on healthcare systems

In renal diseases, our aspiration is to “extend dialysis-free life”

For many of these diseases[1], **there are no approved therapies** and **some** current treatment options show **limited efficacy/ significant side effects**

For others[2], a need exists for options to **better control the disease and ease the burden** on patients and the overall healthcare system

Iptacopan is a **first-in-class oral** Factor B inhibitor that targets some of the **key drivers of these complement driven diseases**

QoL = quality of life 1. IgAN, C3G, CAD, iMN 2. PNH, aHUS, LN



NOVARTIS | Reimagining Medicine

# Iptacopan is a pipeline in a single molecule, potentially addressing several diseases with high unmet need

- Pursued complement-driven diseases are rare and affect mostly young patients with no or limited evidence-based and approved treatment options
- Iptacopan is a **first in class, oral, potent and selective Factor B inhibitor** of the alternative complement pathway, which is postulated to play a key role in the underlying pathophysiology of the indications in scope
- **Positive efficacy results** along with a favorable safety profile from **four Ph2 studies in three indications**
- Due to its targeted MoA, iptacopan leaves the direct classical and lectin pathway signaling intact, resulting in a potentially lower meningococcal infections risk in vaccinated patients when compared to terminal complement pathway inhibitors such as anti-C5s
- **First filings expected 2023** to support outlook with multi-billion potential based on a differentiated profile addressing key unmet needs