27 February 2025
EMA/96410/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fabhalta

International non-proprietary name: Iptacopan

Procedure No. EMEA/H/C/005764/II/0001

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACEi	Angiotensin-converting enzyme inhibitor
AESI	Adverse event of special interest
aHUS	Atypical hemolytic uremic syndrome
AP	Alternative pathway
ARB	Angiotensin II receptor blocker
aRMM	additional risk minimization measure
C3G	Complement 3 Glomerulopathy
C3G-HI	Complement 3 Glomerulopathy-Histologic Index
C3GN	Complement c 3 glomerulonephritis
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
CKD	Chronic kidney disease
CKD-Epi	Chronic kidney disease-Epidemiology collaboration
CMKD	Complement mediated kidney diseases
COVID-19	Coronavirus disease of 2019
CPK	Creatine phosphokinase
CS	Corticosteroids
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DBP	Diastolic blood pressure
DDD	Dense deposit disease
DKD	Diabetic kidney disease
eGFR	estimated glomerular filtration rate
EU	European Union
EoPh2	End of Phase 2
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full analysis set
FB	Factor B
FDA	Food and Drug Administration
FMV	First morning void
FU	Follow up
GCP	Good clinical practice
GLOSEN	Spanish Arm for the Study of Glomerular Disease
HA	Health Authority
HR	Hazard ratio
IA	Interim analysis
IC-MPGN	Immune complex mediated-membranoproliferative glomerulonephritis
IF	Immunofluorescence
IFTA	Interstitial fibrosis and tubular atrophy
IgA	Immunoglobulin A
IgAN	IgA nephropathy
IPIG	International PNH Interest Group
J2R	Jump to reference
KDIGO	Kidney Disease Improving Global Outcomes
MAC	Membrane attack complex
MAD	Multiple Ascending Dose
MAR	Missing at random

MeDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
MPGN	Membranoproliferative glomerulonephritis
MPA	Mycophenolic acid
OATP	Organic anion transporting polypeptides
OR	Odds ratio
PD	Pharmacodynamics
PFDD	Patient-focused drug development
P-gp	P-glycoprotein
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PNH	Paroxysmal nocturnal hemoglobinuria
PopPK	Population Pharmacokinetic
PYs	Patient-years
RPGN	Rapid Progressive glomerulonephritis
RRT	Renal replacement therapy
SAD	Single Ascending Dose
SBP	Systolic blood pressure
SAF	Safety analysis set
SCP	Summary of Clinical Pharmacology
SE	Standard Error
SOC	System organ class
SRI	Severe renal impairment
TEAE	Treatment emergent adverse event
UK	United Kingdom
UPCR	Urinary protein creatinine ratio
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 2 July 2024 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include, in combination with a renin-angiotensin system (RAS) inhibitor, the treatment of adult patients with complement 3 glomerulopathy (C3G) for Fabhalta, based on interim analysis results from study CLNP023B12301 (APPEAR-C3G) and supported by additional evidence of efficacy and safety data from Phase II study CLNP023X2202 (X2202) and Phase IIIb study CLNP023B12001B (C3G-REP). APPEAR-C3G is a Phase 3, multicenter, randomized, double-blind, parallel arm, placebo-controlled study to evaluate the efficacy and safety of iptacopan in patients with C3G. The study included a 6-month blinded, placebo-controlled period, followed by a 6-month period in which all patients receive open-label iptacopan (total study duration of 12 months). As a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8 and 5.1 of the SmPC are being updated. The Annex II and Package Leaflet are updated in accordance. Version 2.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

The variation requested amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Fabhalta, was designated as an orphan medicinal product EU/3/18/2104 on 14 December 2018. Fabhalta was designated as an orphan medicinal product in the following indication: Treatment of C3 glomerulopathy

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0222/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-002705-PIP01-19-M02 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised

orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The MAH received Protocol Assistance from the CHMP on 15 November 2018 (EMEA/H/SA/3968/1/2018/III) and 25 February 2021 (EMEA/H/SA/3968/1/FU/1/2020/PA/PR/II). The Protocol Assistance pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Janet Koenig

Timetable	Actual dates
Submission date	2 July 2024
Start of procedure:	20 July 2024
CHMP Rapporteur Assessment Report	16 September 2024
PRAC Rapporteur Assessment Report	20 September 2024
PRAC members comments	23 September 2024
Updated PRAC Rapporteur Assessment Report	26 September 2024
PRAC Outcome	3 October 2024
CHMP members comments	7 October 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 October 2024
Request for supplementary information (RSI)	17 October 2024
CHMP Rapporteur Assessment Report	9 January 2025
PRAC Rapporteur Assessment Report	7 January 2025
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	13 January 2025
PRAC Outcome	16 January 2025
CHMP members comments	20 January 2025
Updated CHMP Rapporteur Assessment Report	23 January 2025
Request for supplementary information (RSI)	30 January 2025
CHMP Rapporteur Assessment Report	12 February 2025
PRAC Rapporteur Assessment Report	12 February 2025
CHMP members comments	17 February 2025
PRAC members comments	17 February 2025
Updated CHMP Rapporteur Assessment Report	21 February 2025
Updated PRAC Rapporteur Assessment Report	n/a
Opinion	27 February 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Complement 3 Glomerulopathy (C3G) is an ultra-rare (incidence 1-2 per 1 million people) complement-mediated kidney disease caused by dysregulation of the complement alternative pathway (AP) in plasma and in the glomerular microenvironment, resulting in accumulation of complement proteins such as C3 in the glomeruli.

Claimed therapeutic indication

Fabhalta is indicated for the treatment of adult patients with complement 3 glomerulopathy (C3G) in combination with a renin-angiotensin system (RAS) inhibitor, or in patients who are RAS-inhibitor intolerant, or for whom a RAS inhibitor is contraindicated (see section 5.1).

Epidemiology

Please also refer to paragraph "Disease or condition" above.

Due to its rarity and relatively recent new disease classification, there is limited availability of long-term natural history data for C3G. The available literature indicates that C3G affects predominantly patients under the age of 40 years and 30-40% of C3G patients are diagnosed under 18 years of age (Servais et al 2012, Medjeral-Thomas et al 2014, Bomback et al 2018, Chauvet et al 2022, Lomax-Browne et al 2022). The overall prognosis of C3G is poor. Up to 50% of adult patients progress to kidney failure within 10 years of diagnosis (Smith et al 2019).

Biologic features

The AP dysregulation is mediated by acquired autoantibodies and/or genetic variants inducing overstimulation of the AP while subsequent deposition of complement proteins and their cleavage products results in proliferative glomerulonephritis and capillary-wall remodelling of the glomerulus with the formation of double contours. These structural changes lead to progressive loss of kidney function and ultimately, kidney failure.

Based on findings seen only under electron microscopy, C3G is classified into two slightly distinct histopathologic entities, namely C3 glomerulonephritis (C3GN) and dense deposit disease (DDD). C3G that develops in the patient's native kidneys is referred to as native C3G whereas, when it reoccurs in a patient post-kidney transplantation, it is called recurrent C3G.

The long-term outcomes of DDD and C3GN are similarly poor: most recent series report no significant difference in risk of and time to kidney failure (Medjeral-Thomas et al 2014, Bomback et al 2018).

Clinical presentation, diagnosis

Patients often present with haematuria (presence of blood in urine), sub-nephrotic or nephrotic range proteinuria, arterial hypertension, peripheral oedema, loss of appetite, sleep problems, and fatigue. These symptoms are frequently accompanied by low serum C3 levels and/or elevated sC5b-9 levels, which reflect over-activation of the AP and terminal complement pathway, respectively.

Management

While kidney transplantation is a treatment option for younger patients with kidney failure, persistent AP dysregulation also results in recurrence of C3G in 55-85% of kidney transplant recipients. C3G recurrence is fast, with reported time to recurrence of 14 to 28 months post-transplantation (Smith et al 2019, Heiderscheit et al 2022, Caravaca-Fontan et al 2023a). Graft loss is common (≥50%) and occurs at a median of 4-6 years post-transplantation (Zand et al 2014, Regunathan-Shenk et al 2019, Halfon et al 2022, Caravaca-Fontan et al 2023a).

The disease mechanism, clinical course and risk of kidney failure is similar in both C3G and recurrent C3G, with dysregulation of the AP being central to the pathophysiology of the disease, as evidenced by histological changes on light microscopy, C3-dominant deposition on immunofluorescence staining, as well as by common biomarker profiles (Zand et al 2014, Salvadori and Bertoni 2016).

2.1.2. About the product

Iptacopan is a proximal complement inhibitor that targets the Factor B to selectively inhibit the complement AP while leaving the direct signalling from the complement lectin and classical pathways intact. Inhibition of Factor B prevents activation of the AP-mediated C3 convertase, thus preventing opsonisation of cells with C3 fragments, formation of C3a and C5a anaphylatoxins, and downstream generation of the C5 convertase and the membrane attack complex (MAC; C5b-9) (Schubart et al 2019). Iptacopan blocks the very first step of the underlying mechanism of C3G, namely the inhibition of the C3 convertase overactivation.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

EMA granted PRIME designation for iptacopan in C3 Glomerulopathy indication (LNP023/C3G - EMA/PRIME/20/035; EMA/CHMP/566570/2020) in September 2020.

Scientific advice:

On 30th September 2020, the Applicant requested SA (EMA/H/SA/3968/FU/1/2020/PA/PR/II). Key questions dealt with the design of the phase 3 study (patient eligibility criteria, primary and secondary endpoints, estimands and analysis method, applicability of phase 3 results to a broad C3G population including patients with lower baseline proteinuria levels, higher serum C3 levels, and recurrent C3G after kidney transplantation).

It was agreed by CHMP, to include adolescents and adults with histologically confirmed C3G. CHMP recommended a standardised, centralised diagnostic approach to assess patho-histology of renal biopsy samples. The Applicant pointed out, that the qualifying biopsy will be based on local assessment, while the two biopsies to assess the histological secondary endpoint are planned to be centrally rated by a review committee of three experts. This approach was accepted by CHMP.

Stratification according to sub-entities of C3G (DDD/ C3GN) was issued within the discussion meeting; it was accepted by CHMP that disease features of C3GN and DDD can be addressed without the need of stratification.

Overall, the Applicant pursues a claim including a broad population of patients with C3G. The selection of patients with substantial proteinuria (UPCR>1.0g/g) was accepted by CHMP as an enrichment strategy. In this context, the CHMP emphasized that this endpoint needs to be supported by data from other endpoints. It remains to be established at the time of MAA whether and how the results from patients with UPCR>1.0g/g can be extrapolated to patients with lower UPCR. Likewise, the selection of patients with low baseline C3 should be justified in the MA dossier, as about a third of patients with C3G do not present with low C3 (Ito et al., 2017). Third, extrapolation to patients with recurrent C3G after kidney transplantation needs further exploration. While it was generally agreed by CHMP, that iptacopan should be effective in native and recurrent C3G, specific issues like DDI with concomitant immunosuppressive therapy need to be addressed in the MA dossier.

The primary endpoint of UPCR reduction from baseline to six month was discussed. Proteinuria reduction is expected to go along with some improvement in eGFR. To this end, it was recommended to collect retrospective data on eGFR slopes before randomisation in the phase 3 study, as such allowing for a comparison of slope data before and on treatment. In addition, it was recommended to evaluate eGFR change from baseline as a secondary endpoint. In general, a double blind treatment period of six month might be too short to have a discernible effect on eGFR. However, recruitment and feasibility issues in the context of a longer double-blind period as highlighted by the Applicant in the discussion meeting were acknowledged by CHMP.

The proposed composite response endpoint (proteinuria reduction and less than 15% decline in eGFR) was seen critically by CHMP, as a 15% decline in eGFR might indicate clinical worsening and cannot plainly be counted as treatment success within the response endpoint. It was recommended to split this endpoint into two separate components. Further, acceptability of the 15% criterion should be further elucidated through sensitivity analyses using a range of lower thresholds.

Fatigue assessment using the FACIT score was accepted as key secondary endpoint. It was emphasized by CHMP, that data on this patient reported outcome are only valid from the double-blind period. The proposal to use an anchor-based approach to support a minimum clinically relevant difference for this measure in C3G patients has been found acceptable in this ultra-rare condition.

The proposed estimand strategy including the definition of intercurrent events (other complement inhibitor pathway treatment, rescue therapy, renal replacement therapy), as well as the proposed stratification factor „immunosuppressive therapy" were accepted. A subgroup analysis per subtype (DDD, C3GN) was recommended.

In general, the recommendations given in the SA have been followed in the APPEAR study design. The requested analysis of eGFR slope data before (=without treatment) and after randomisation (=on treatment) in the APPEAR study was performed which is highly endorsed.

2.1.4. General comments on compliance with GCP

During Assessment no issue of GCP non-compliance arose.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Table 1: Summary of main study results

Substance (INN/Invented Name): Iptacopan			
CAS-number (if available): 2447007-60-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log Dow (pH 5): 0.12 log Dow (pH 7): 0.3 log Dow (pH 9): 0.085	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log D_{ow}	(pH 7): 0.3	not B
	BCF	L/kg_{ww}	B/vB/not B
Persistence	DT50	$DT_{50\ Total\ System}$ (12 °C) 14.5 d	not P
Toxicity	NOEC fish	0.85 mg/L	not T
PBT-statement:	The compound is considered to be not PBT, nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PECsurfacewater, refined with overall PEC for both indications	0.0274 (refined by Prevalences)	µg/L	≥ 0.01 threshold: Y
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption Soil 1 = type clay Soil 2 = type loam Soil 3 = type sandy loam Sludge 1 = ARA Birs Sludge 2 = ARA ProRheno Kommunale	OECD 106	$K_{oc,\ soil\ 1}$ = 522 L/kg_{oc} $K_{oc,\ soil\ 2}$ = 3209 L/kg_{oc} $K_{oc,\ soil\ 3}$ = 785 L/kg_{oc} $K_{oc,\ sludge\ 1}$ = 73 L/kg_{oc} $K_{oc,\ sludge\ 2}$ = 30 L/kg_{oc}	
Ready Biodegradability Test	OECD 301 B	6 %/ 28 d not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = silt loam Sediment 2 = loamy sand (USDA)	OECD 308	$DT_{50,\ water}$ = 3.1/ 3.4 d $DT_{50,\ sediment}$ = 36.1/30.3 d $DT_{50,\ whole\ system}$ = 5.7/6.8 d % shifting to sediment = 36.9% (d14:14,8%parent + 22,1%NER) 2 TPs > 10% in water <u>TPs:</u> $DT_{50,\ water}$ M3: increasing TP $DT_{50,\ water}$ M9: 42.9 d (20°C) $DT_{50,\ water}$ M9: 91.5 d (12°C)	<u>M3:</u> 4-(4-ethoxy-2-piperidy)benzoic acid <u>M9:</u> 4-(4-ethoxy-1-pentadeca-trienoyl-2-piperidyl)benzoic acid **The active substance forms two very persistent transformation**

					products >10% in water
Phase IIa Effect studies					
Study type	**Test protocol**	**Result**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata*	OECD 201	NOErC	92000	µg/L	growth rate
Daphnia magna, Reproduction Test	OECD 211	NOEC	8300	µg/L	
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	850	µg/L	weight
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC (3h)	920000	µg/L	total respiration
Phase IIb Studies					
Sediment dwelling organism/ *Chironomus riparius*	OECD 218	NOEC	544.64	mg/kg_{dw}	

2.2.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

The applicant provided an Environmental Risk Assessment (ERA) in accordance with the respective EMA guidance (EMEA/CHMP/SWP/4447/00, corr. 2).

Phase I of the ERA showed that the predicted environmental concentration in surface water (PECsurfacewater) after refinement for prevalences is 0.0274 µg/L and therefore higher than the threshold value of 0.01 µg/L. Thus, a Phase II ERA was triggered. The outcome of the Phase II-Tier A risk assessment indicates no noteworthy risk potential for surface waters, groundwater and microorganisms in sewage treatment plants and the outcome of the Phase II-Tier B risk assessment indicates that iptacopan does not constitute a risk to sediment compartments. The active substance does form two very persistent transformation products in water but the PBT screening of iptacopan detected no potential PBT properties. Overall, the new indication leads to a significant increase in environmental exposure further to the use of iptacopan however, considering the above data, iptacopan is not expected to pose a risk to the environment.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application leads to a significant increase in environmental exposure further to the use of iptacopan. However, considering the above data, iptacopan is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Overview of studies supporting clinical efficacy

Study, Status	Study design, population	Treatment duration	No. patients enrolled/ Treatments
Primary efficacy			
APPEAR-C3G[1] Completed, Data cut-off date 06-May-2024 (last participant last visit for the adult cohort)	Phase 3 multicenter, randomized, double-blind, parallel arm, placebo-controlled study in patients with biopsy confirmed C3G and native kidneys	12 months planned: 6 months randomized treatment period 6 months open label iptacopan extension period	Adults N=74: n=38, iptacopan 200 mg b.i.d. in randomized treatment period n=36, placebo in randomized treatment period N=73 in open-label iptacopan 200 mg b.i.d treatment period
Supportive efficacy			
Study X2202 *Completed* LPLV: 23-Apr-2021	Phase 2 open-label, non-randomized study on efficacy, PK, PD, safety, and tolerability of iptacopan in 2 patient populations with C3G (Cohort A: C3G; Cohort B: recurrent C3G)	Cohort A: 12 weeks Cohort B: 12 weeks	N=27 (Cohort A: n=16; Cohort B: n=11) Iptacopan 200 mg b.i.d. after a 4-week dose escalation phase on 10 mg b.i.d. (Week 1), 25 mg b.i.d. (week 2), 100 mg b.i.d. (Week 3) and 200 mg b.i.d. (Week 4 and beyond)
Study B12001B C3G rollover extension study *Ongoing* Data cut-off date: 01-Oct-2023	Phase 3b open-label, non-randomized extension study of iptacopan in patients with C3G or recurrent C3G	Up to 66 months; up to 33 months* of follow-up presented within SCE (ongoing study)	N=61 **APPEAR-C3G: n=35 Study X2202: n=26 Cohort A: n=16 Cohort B: n=10 Iptacopan 200 mg b.i.d.

[1] APPEAR-C3G includes an on-going adolescent arm which is not presented in this dossier as patients are on-going and blinded.

* For patients in Study B12001B, data is pooled by parent study and the total number of months of follow-up from the parent and extension studies (Study X2202 + Study B12001B) is used in efficacy.

** Data for patients from APPEAR-C3G continuing in Study B12001B are not presented separately in this report due to the limited amount of data available as of the data cut-off. This data is however included in the analysis of the change in eGFR slope for all C3G patients.

2.3.2. Pharmacokinetics

Iptacopan clinical pharmacology studies in healthy participants including details of SAD/MAD, food effect studies, human mass-balance study, Japanese ethnic sensitivity study, DDI study with CYP2C8 inhibitor, OATP inhibitor as well as P-gp substrate and OATP substrate, hepatic impairment study and QTcF study were included and assessed within the authorisation procedure of iptacopan for treatment of paroxysmal nocturnal haemoglobinuria. A phase 2 study evaluating PK in patients with C3G and recurrent C3G post-kidney transplantation (study X2202) was already included and assessed within this procedure. A summary of pivotal PK findings from this and other studies can be found in the subsequent Table 2.

Table 2: Summary of pivotal PK findings

Study Number	Popu-lation	N	Study Day	Cmax (ng/mL)	Ctrough Cmin[#] (ng/mL)	Tmax (hr)	AUCtau (hr*ng/mL)
X2101	HV	6	14	4120±1090 (26.3%)	1350±156 (11.5%)	2.02 (0.750-3.00)	25600±4300 (16.8%)
X2201	PNH	10	29	3500±1340 (38.2%)	1190±433 (36.5%)	2.00 (1.00 - 2.00)	24400±8720 (35.7%)
X2202 cohort A	C3G	15	28	3600±1230 (34.2%)	1480±653 (44.0%)	2.00 (1.00-4.00)	26900±10900 (40.5%)
X2202 cohort B	C3G	9	28	4700±2200 (46.8%)	2180±1610 (73.9%)	2.00 (1.00-4.00)	37700±22000 (58.5%)
X2203	IGAN	24	30	4940±1770 (35.9%)	2200±964 (43.7%)	2.00 (0.500 - 4.00)	37100±13500 (36.4%)
X2204	PNH	5	57	4520±1520 (33.6%)	1510±416 (27.5%)[#]	2.00 (1.00 - 4.13)	33300 ± 8830 (26.5%)
C12301	PNH	38	28	5182.9±2696.08 (52%)	2058.1± 856.24 (44.2%)	Not estimated	Not estimated
C12302	PNH	58	28	3942.2±1677.34 (42.5%)	1474.4±510.33 (34.6%)[$]	Not estimated	Not estimated

Study X2202 cohort A: Non-transplanted C3G patients with reduced C3 serum levels, Study X2202 cohort B: Patients who have undergone kidney transplant and have C3G recurrence

#=Cmin, Statistics are Mean±SD (CV%), For Tmax, statistics are Median (Min-Max), [$]trough level is iptacopan concentration at 0 hr

PK results are taken following at least 14 days of 200 mg b.i.d. dosing, although a lower dose level may have been administered prior to starting the 200 mg dose (see study-specific designs)

New PK data from study APPEAR-C3G and the open-label extension study B12001B in patients with C3G are in accordance with these findings, please see the following Table 3 and Table 4.

Table 3: Summary statistics of mean iptacopan pre-dose trough concentrations in participants in the double-blind and open-label treatment periods of Phase 3 Study APPEAR-C3G

	Day 30	Day 180	Day 210	Day 360
n	32	28	31	32
Mean concentration (ng/mL) (SD)	1590 (865)	2130 (1580)	1720 (887)	1890 (1150)
CV% mean	54.3	74.1	51.7	60.8

CV% = coefficient of variation (%) = (sd/mean)*100

Table 4: Summary statistics of mean pre-dose trough iptacopan concentrations in the roll-over extension study B12001B for participants from Study X2202 Cohort A (C3G) and Cohort B (recurrent C3G)

	Day 84		Day 174		Day 264		Day 354	
	Cohort A	Cohort B	Cohort A	Cohort B	Cohort A	Cohort B	Cohort A	Cohort B
n	16	8	15	8	13	7	13	8

	Day 84		Day 174		Day 264		Day 354	
	Cohort A	Cohort B	Cohort A	Cohort B	Cohort A	Cohort B	Cohort A	Cohort B
Mean concentration (ng/mL) (SD)	1640 (802)	2030 (1050)	1600 (722)	2480 (1830)	1760 (805)	2850 (1650)	1600 (594)	2520 (1480)
CV% mean	49.0	51.7	45.2	73.9	45.7	58.0	37.1	58.8

CV% = coefficient of variation (%) = (sd/mean) *100

PK in patients with renal impairment, more likely with C3G than with PNH was also already determined, primarily by a PopPK approach. The minor, clinically not relevant, increase of iptacopan plasma concentration determined with renal impairment might account, at least in part, for the differences seen in the Table 3 and Table 4 above (X2202 cohort B).

The PK results were already included in the SmPC of Fabhalta and no respective changes are suggested in this variation procedure.

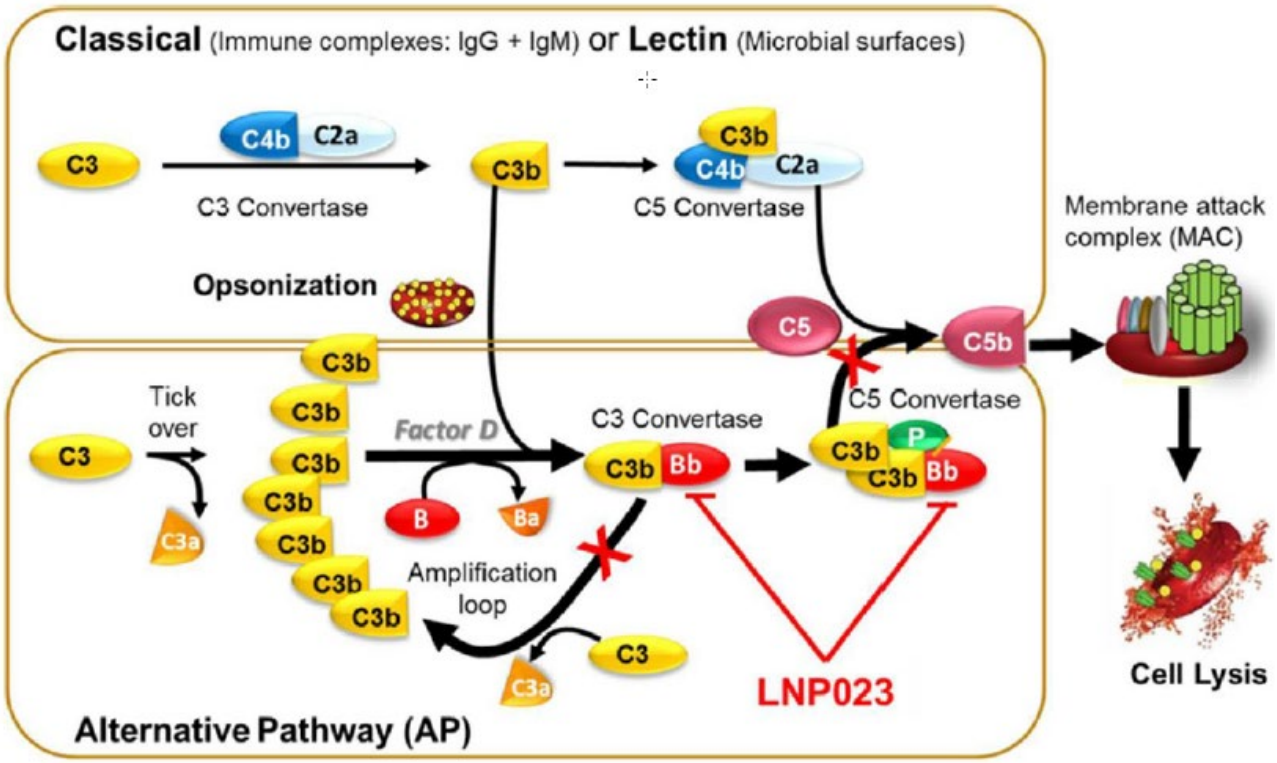
2.3.3. Pharmacodynamics

Mechanism of action

Iptacopan is a proximal complement inhibitor that specifically binds to Factor B (FB), a protease of the alternative complement pathway (AP) and a catalytic component of the C3 and C5 convertase complexes. Inhibition of FB prevents activation of the AP/amplification loop as well as subsequent production of the anaphylatoxins C3a and C5a, opsonization of cells with C3 fragments and formation of the membrane attack complex (MAC). In detail, after binding to C3b or C3(H2O), FB is activated through proteolytic cleavage by Factor D (FD) to generate C3bBb, the C3 convertase containing the FB catalytic subunit (Bb). Iptacopan binds to the active site of Bb as well as to latent FB with nanomolar affinity and blocks cleavage of C3 by the C3 convertase of the AP. The studies conducted for evaluating the interaction of iptacopan and Factor B were described in the EPAR of the initial MAA.

An overview of complement activation is provided in the Figure 1 below.

Figure 1: Overview of the complement system with the site of action of iptacopan (LNP023)



Primary and secondary pharmacology

Most pharmacodynamic (PD) parameters were obtained in the phase 2 study X2202. Key parameters such as Wieslab assay and plasma levels of Factor Bb, C3 and sC5b-9 were also determined in the phase 3 study APPEAR-C3G.

Study X2202

The purpose of this study was to assess the clinical efficacy, pharmacodynamics, safety, tolerability and pharmacokinetics of LNP023 in patients with C3G and to evaluate the effect of different doses of LNP023 on complement biomarkers to drive dose selection for a Phase III study.

Study design

The study was a non-confirmatory, open-label, two Cohort, single-arm, non-randomized study evaluating the efficacy, safety, tolerability, pharmacokinetics, pharmacodynamics and dose/biomarker relation of LNP023 in two patient populations:

- Non-transplanted C3G patients with reduced C3 serum levels (<0.90 x lower limit of the lab normal range), enrolled in Cohort A
- Patients who have undergone kidney transplant and have C3G recurrence, enrolled in Cohort B. Cohort B started in parallel to Cohort A

The only difference between Cohort A and B designs is due to the collection of biopsies at baseline and at Week 12. For the baseline evaluation of the C3 deposit score an optional biopsy not older than 3 months before screening visit could be collected for Cohort A. While a mandatory biopsy not older than 3 months before screening should be performed for Cohort B.

The screening period lasted up to 60 days and was divided into a screening visit and a run-in period. Patients who met the eligibility criteria at screening were admitted to baseline evaluations.

The baseline period consisted of 30 days and included two visits. Patients during baseline period were under stable doses of supportive therapy (antihypertensive and antiproteinuric therapy, e.g. angiotensin converting enzyme inhibitors, angiotensin II receptor blockers (ACEi/ARB), mycophenolate mofetil (MMF), systemic corticosteroids as per KDIGO guidelines).

Two treatment periods followed the baseline evaluation.

Treatment period 1 consisted of 12 weeks and was divided as

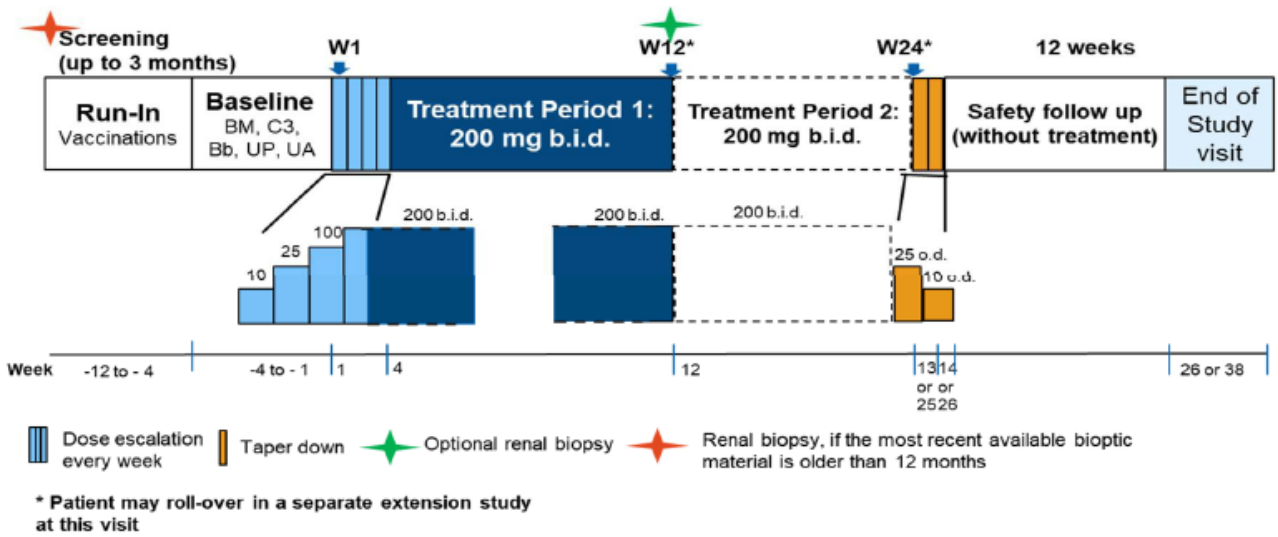
- Day 1 - Day 28 (Weeks 1-4) was a dose-escalation phase.
- Day 29 - Day 84 (Weeks 5-12), the dose of 200 mg b.i.d. was continued for additional 8 weeks for a total duration of 9 weeks.

Treatment period 2 was a non-mandatory treatment extension of 12 weeks.

Following the completion of Treatment period 1 or 2, if the investigator deemed it beneficial to continue treatment, the patient could roll-over to the extension study.

The study design is graphically summarised below.

Figure 2: Cohort A study design Note. The design for Cohort B was identical except that the renal biopsies were not optional)



The most important inclusion criteria are listed below. Note that in Cohort A elevated urinary protein excretion and reduced serum C3 was required for inclusion, besides biopsy, whereas in Cohort B only biopsy was required for confirming C3G.

Cohort A

- Patients (females and males ≥18 years) had C3G as confirmed by renal biopsy within twelve months prior to enrollment (confirmation by the Investigator is required).
- C3G patients with reduced C3 at screening (defined as less than 0.90 x lower limit of the lab normal ranges) were eligible for this study.
- eGFR (using the CKD-EPI formula) ≥30 mL/min per 1.73 m2 for patients on a maximum recommended or maximum tolerated dose of an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB).

- UPCR ≥ 100 mg/mmol sampled from first morning void (or ≥ 1 g/24h total urinary protein excretion from a 24h urinary collection during run-in) at run-in (Visit 20) or at baseline (Visit 30).

Cohort B

- Patients (females and males ≥18 years) had C3G recurrence after transplantation as confirmed by renal biopsy after transplantation within twelve months prior to enrolment (confirmation by the Investigator is required).
- Estimated GFR (using the CKD-EPI formula) ≥30 mL/min per 1.73 m2.
- Normal or elevated urinary protein excretion at screening or at baseline (Visit 30).

The primary endpoint of the study was reduction of UPCR in Cohort A and was histological improvement in Cohort B; see Table 5 below.

Table 5: Primary objectives and endpoints

Objectives	**Endpoints**
Cohort A: To evaluate the efficacy of LNP023 in reducing proteinuria at Week 12	Ratio to baseline of Urine Protein to Creatinine concentration Ratio (UPCR) derived from 24h urine collection.
Cohort B: To assess histopathological changes in kidney biopsies at Week 12	Change from baseline in C3 Deposit Score (based on immunofluorescence microscopy).

Furthermore, secondary and exploratory endpoints were defined. In summary, the following PD parameters were determined in Study X2202:

Renal Parameters

The pharmacodynamic effect of LNP023 was assessed by analysing the following renal parameters:

- UA, UACR, UP, UPCR, serum creatinine, creatinine clearance, eGFR, hematuria
- Ratio to baseline of UPCR and UACR derived from 24-h urine collection

Complement pathway biomarkers

Soluble complement biomarkers in the blood were evaluated as potential pharmacodynamics and mode-of-action markers. These included:

- Circulating fragment of factor B (Bb)
- C3

Exploratory complement pathway biomarkers

Soluble complement biomarkers in circulation and in urine were explored as potential pharmacodynamics and mode-of-action markers. They included:

- Factor B
- sC5b-9

Study participants

The demographic and baseline characteristics of Cohort A and B differed from each other in many aspects. Most salient examples are shown in the Table 6 below. This will be discussed in the context of the respective parameter when its change from baseline is presented.

Table 6: Demographics and baseline characteristics (Safety analysis set)

		Cohort A	**Cohort B**
		N=16	**N=11**
UPCR 24hr (g/mol)	n	16	9
	Mean (SD)	454.0 (242.16)	112.3 (178.05)
	Geo-mean	401.9	36.2
	CV% geo-mean	53.64	310.78
	Median	391	24
	Range	199 - 1019	9 - 445
eGFR (ml/min/1.73m2)	n	16	11
	Mean (SD)	70.1 (35.10)	52.2 (17.29)
	Geo-mean	61.8	49.4
	CV% geo-mean	57.32	37.71
	Median	65	59
	Range	28 - 134	27 - 74
Urine albumin (UA) 24h (mg/day)	n	16	11
	Mean (SD)	4663.1 (2330.53)	1070.0 (2482.74)
	Geo-mean	4164.7	88.1
	CV% geo-mean	52.39	1377.81
	Median	4277	38
	Range	1777 - 9030	8 - 8020
UACR 24hr (g/mol)	n	16	10
	Mean (SD)	378.2 (193.81)	78.8 (148.87)
	Geo-mean	338.4	9.8
	CV% geo-mean	50.50	1208.7
	Median	307	7
	Range	178-811	1-374
Urine protein (UP) 24h (mg/day)	n	16	11

	Mean (SD)	5574.9 (2853.59)	1350.0 (2913.96)
	Geo-mean	4945.2	283.4
	CV% geo-mean	54.27	378.15
	Median	5221	180
	Range	2170 - 11339	58 - 9550
Serum creatinine (µmol/L)	n	16	11
	Mean (SD)	134.0 (60.64)	152.2 (40.52)
	Geo-mean	122.1	147.1
	CV% geo-mean	46.71	28.42
	Median	115	142
	Range	62 - 271	94 - 205
Creatinine clearance	n	16	11
(mL/min)	Mean (SD)	78.9 (43.02)	58.5 (27.83)
	Geo-mean	69.9	52.9
	CV% geo-mean	52.98	50.16
	Median	66	58
	Range	29 - 184	27 - 122
C3 Deposit Score	n	1	10
	Mean (SD)	12.00	4.15 (3.816)
	Median	12.0	3.0
	Range	12.0 - 12.0	0.0 - 12.0
DDD present – n(%)	No	14 (88)	7 (64)
	Yes	2 (13)	3 (27)

Laboratory methods

The MAH has submitted bioanalytical reports including validation reports for the assays used to determine the complement-related parameters. All assays were based on commercial kits, and the MAH performed control experiments to ensure that the assays properly work in the MAH's hands. Not all determinations were satisfactory, i.e. fulfilled the applicant's acceptance criteria. The respective samples were excluded from further analysis.

The Wieslab assay was already described in the original MAA of Fabhalta. It was commercially obtained from Svar Life Science. Selectivity of the assay for the AP was obtained by using an AP-specific activator, LPS, and by conducting the assay in the presence of Mg^{2+} and in the absence of Ca^{2+} (i.e. by adding EGTA). The readout was formation of the sC5b-9 complex, which was detected by an antibody recognising a neo-antigen on this complex.

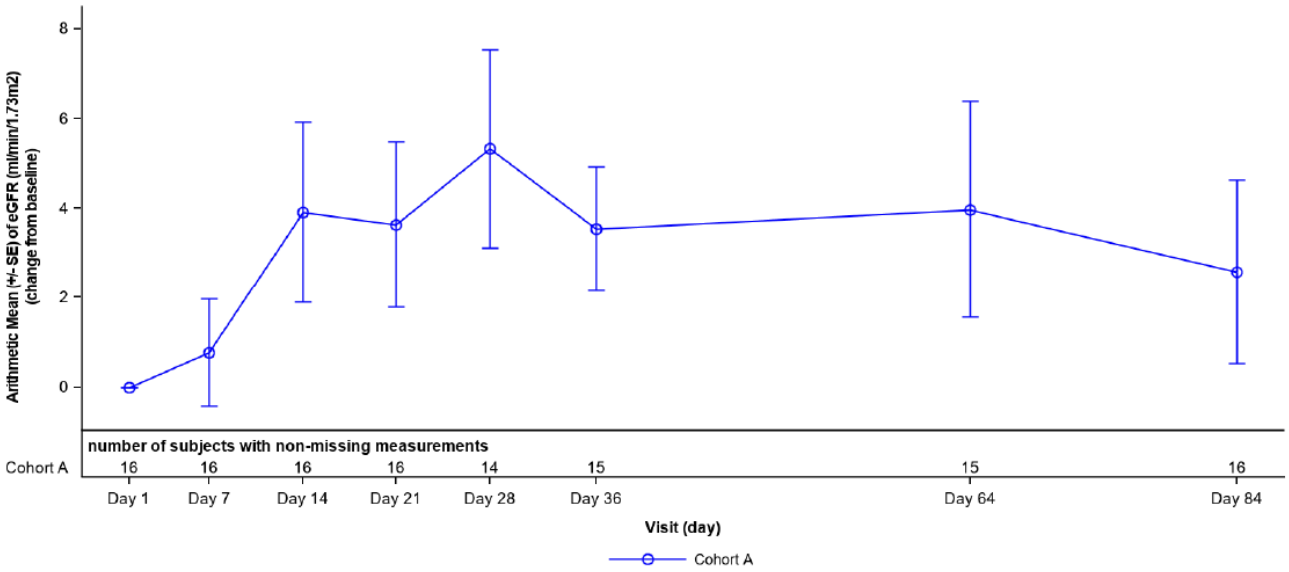
The other complement factors and complement-related proteins were quantified by antigen-based methods, often using an ELISA format or magnetic beads with fluorescence detection.

Laboratory results

eGFR

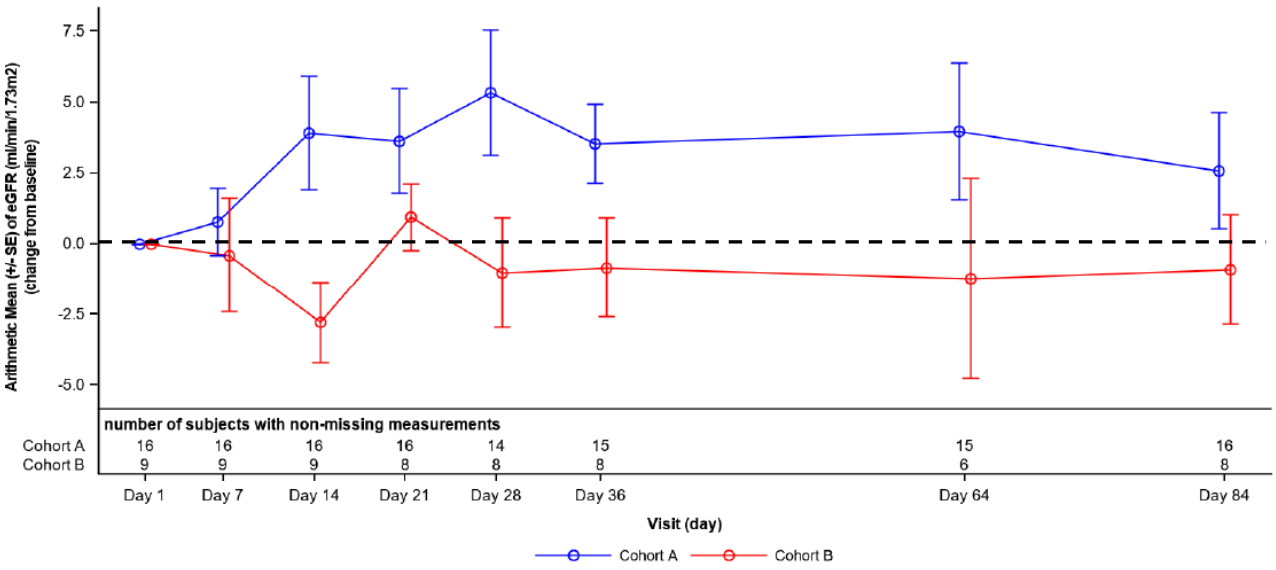
In Cohort A (subjects with native kidney), there was an eGFR increase from baseline after initiation of iptacopan, see Figure 3 below. The eGFR increased by around 5 ml/min/1.73m2 from baseline to Day 28. Thereafter, eGFR decreased again but remained above baseline, by around 2.5 ml/min/1.73m2, at study end. The reason for this (in part transient) eGFR increase is not known.

Figure 3: Parameter: eGFR (ml/min/1.73m2) (change from baseline); Mean (+/- SE)



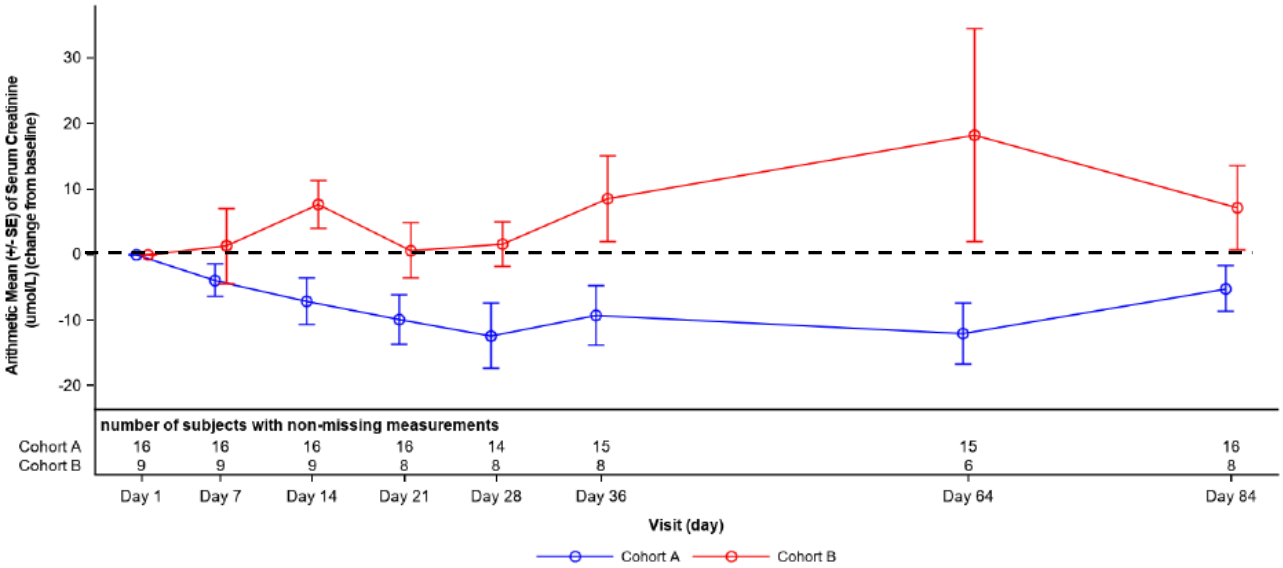
In Cohort B (Figure 4 below, red line), the eGFR changes over time followed a different pattern compared to Cohort A (blue line in the Figure 4; different scale of the y-axis compared to the Figure 3 above). Except for a dip at Day 14 by around 2.5 ml/min/1.73m2, eGFR largely remained unchanged over time in Cohort B. It is unclear whether the dip at Day 14 is a true biological effect or whether it is due to random fluctuation.

Figure 4: Parameter: eGFR (ml/min/1.73m2) (change from baseline); Mean (+/- SE)



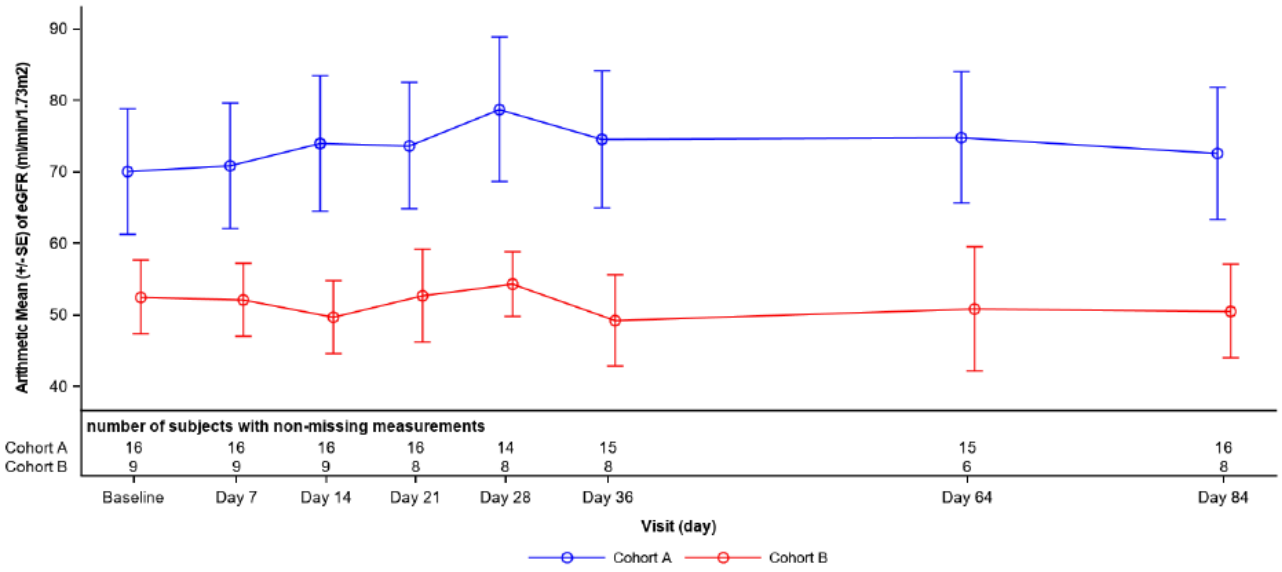
Since eGFR is calculated from serum creatinine, the time-course of the latter is displayed in the Figure 5 below. In line with the eGFR results, serum creatinine showed an in part transient decline in Cohort A and no major change in Cohort B up to Day 28. After Day 28 in Cohort B, the variability (SE) became high, which prevents firm conclusions.

Figure 5: Parameter: Serum Creatinine (umol/L) (change from baseline); Mean (+/- SE)



The above Figure 4 and Figure 5 depict eGFR changes from baseline. The absolute values are given in the following Figure 6. Baseline eGFR was higher in Cohort A than in Cohort B (70 vs. 52 ml/min/1.73m2). This difference remained fairly consistent for the period shown (up to Day 84, i.e. 12 weeks).

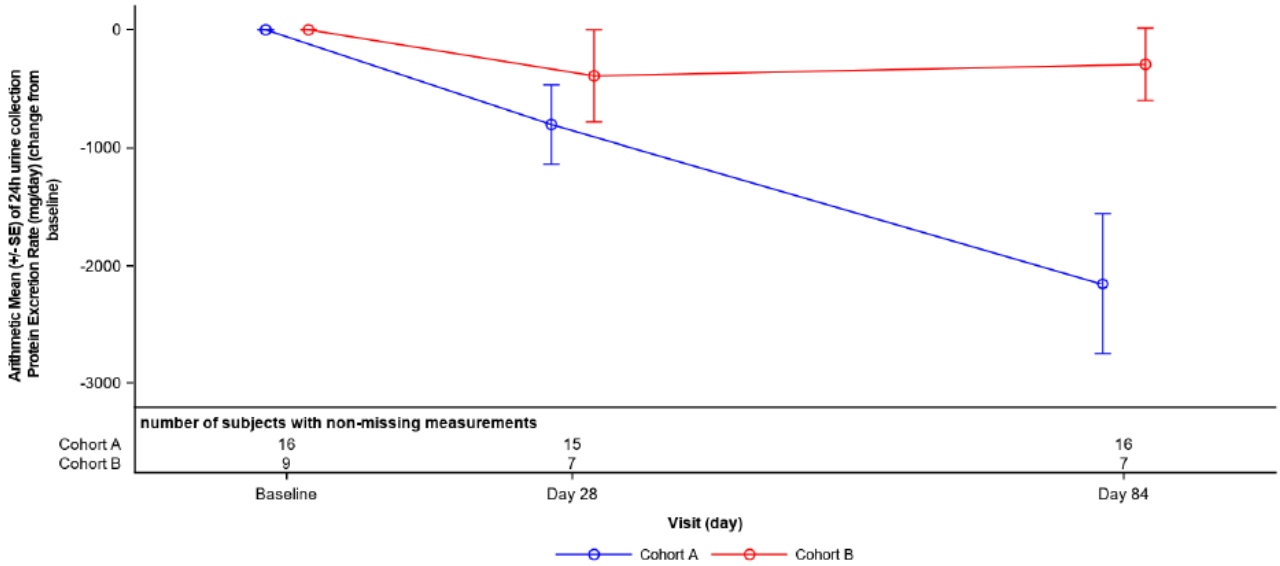
Figure 6: Parameter: eGFR (ml/min/1.73m2)



Protein excretion/UPCR

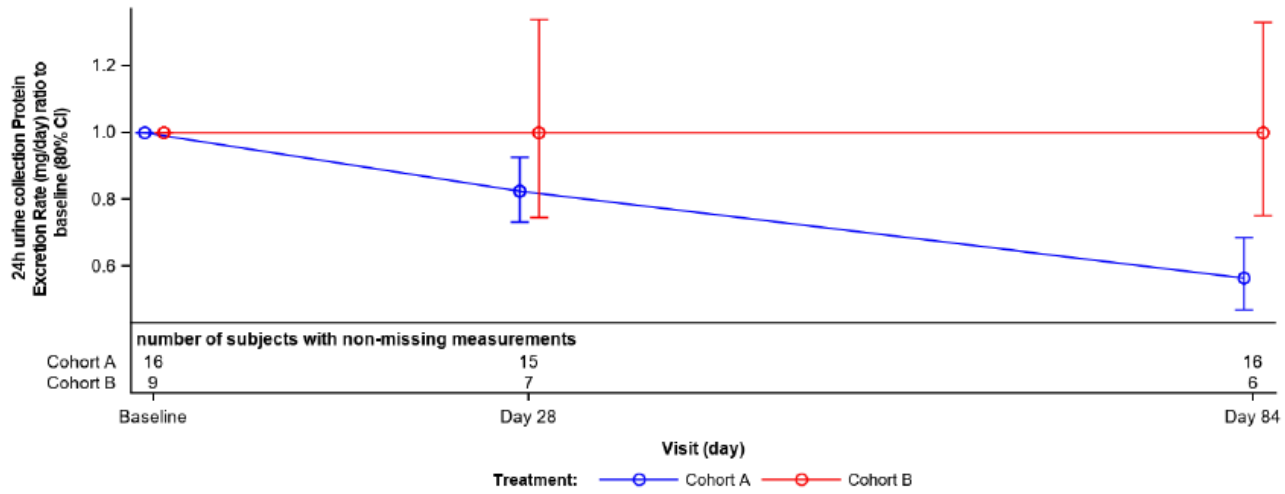
The daily protein excretion rate, measured in urine collected over 24 hours, is shown in the Figure 7 below. Note that the arithmetic means are shown; in other figures on protein excretion the geometric mean is used (is indicated in the respective figures). There was a steady decline in 24 h protein excreting in Cohort A and no major change in Cohort B.

Figure 7: Arithmetic mean (+/-SE) Parameter: 24h urine collection Protein Excretion Rate (mg/day) (change from baseline)



When using the geometric mean of 24 h protein excretion, there is clearly no change over time in Cohort B, whereas there still is a steady decline in Cohort A. However, there is high variability (large 80% CI) in Cohort B. This is due to the fact that changes were observed in only one patient as discussed further below.

Figure 8: Adjusted geometric mean (80% CI) of ratio to baseline for urine protein (UP) 24h by LNP023 dose over time; Parameter: 24h urine collection Protein Excretion Rate (mg/day)

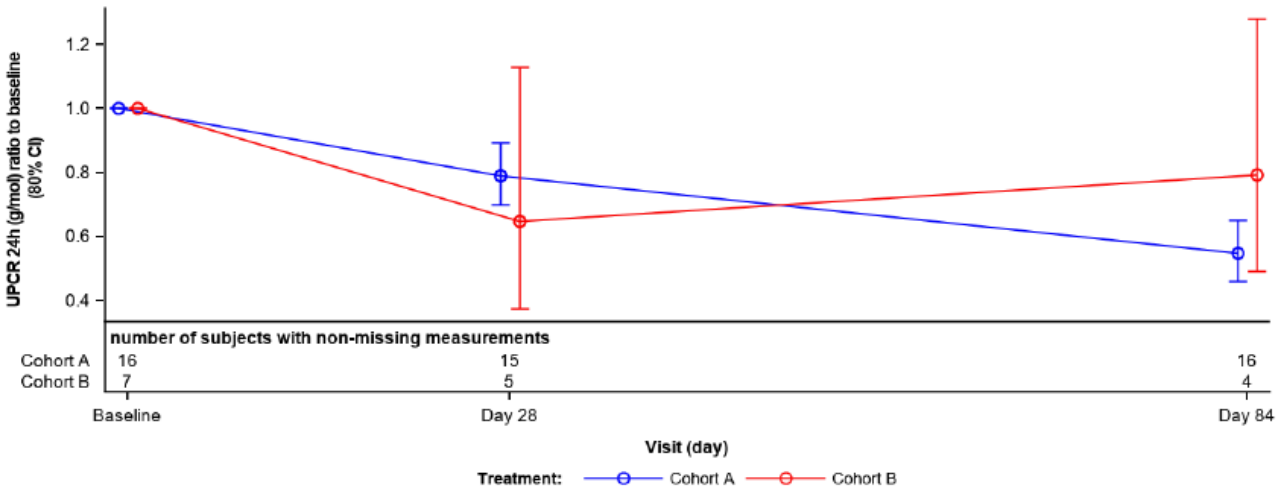


Individual patient data on the development of protein excretion over time show that in Cohort A the decline was rather consistent across all participants except for one subject who showed a clear increase in protein excretion.

In Cohort B (Figure 9 below), it is remarkable that all but one subjects had a very low protein excretion at baseline. Only one subject had a marked protein excretion at baseline, which declined by around 60% at Day 84.

Regarding UPCR (geometric mean), there was again a steady decline over time in Cohort A. In Cohort B, the picture was inconsistent, and there was a high variability (large 80% CI).

Figure 9: Adjusted geometric mean (80% CI) of log ratio to baseline for UPCR (24h urine collection) over time; Parameter: UPCR 24h (g/mol)



Factor B and Factor Bb

In Study X2202, the plasma level of Factor B increased from baseline up to Day 15 in both cohorts. The active Factor B, i.e. Factor Bb, decreased simultaneously (see the following two figures)

Figure 10: Parameter: Plasma Complement Factor B (ng/mL)

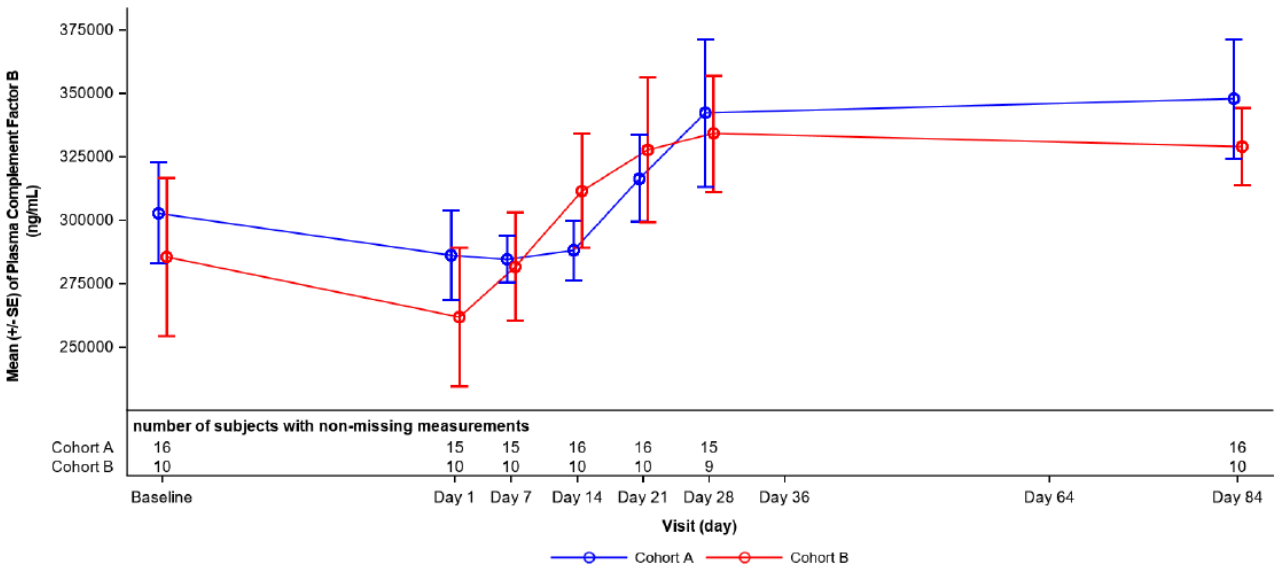
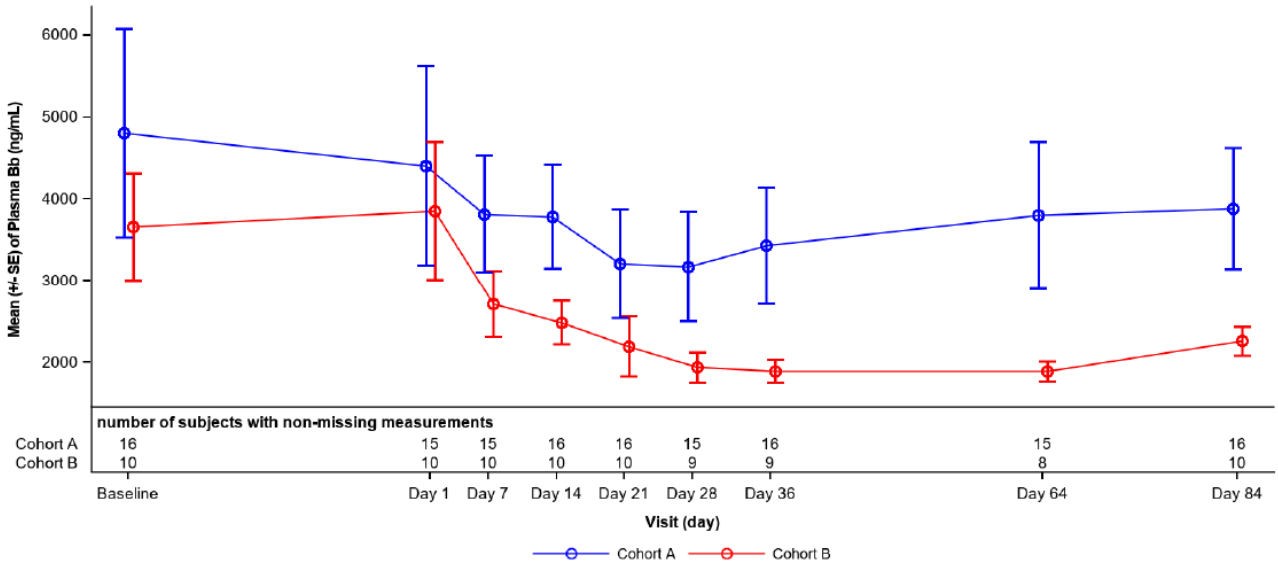
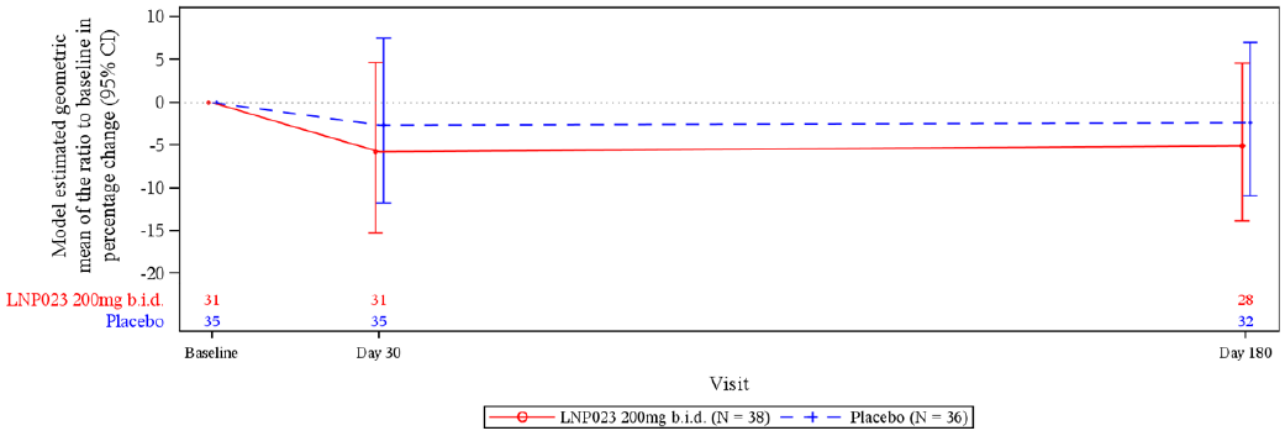


Figure 11: Parameter: Plasma Bb (ng/mL)



Also in the phase 3 study APPEAR-C3G an initial (mild) decrease in Factor Bb in plasma was observed. The factor remained below baseline throughout the study, see Figure 12 below.

Figure 12: Model estimated geometric mean of the ratio to baseline in percentage change (95% CI) of plasma Bb up to month 6 by treatment group (Full analysis set) (APPEAR-C3G)



Upon treatment with iptacopan, the plasma level of complement factor C3 increased from baseline and compared to placebo in the studies X2202 and APPEAR-C3G, see the following two figures. This consistent increase reflects a decrease in complement activity since less Factor C3 is cleaved and activated to Factor C3b.

Figure 13: Parameter: Serum Complement C3 (g/L) (change from baseline)

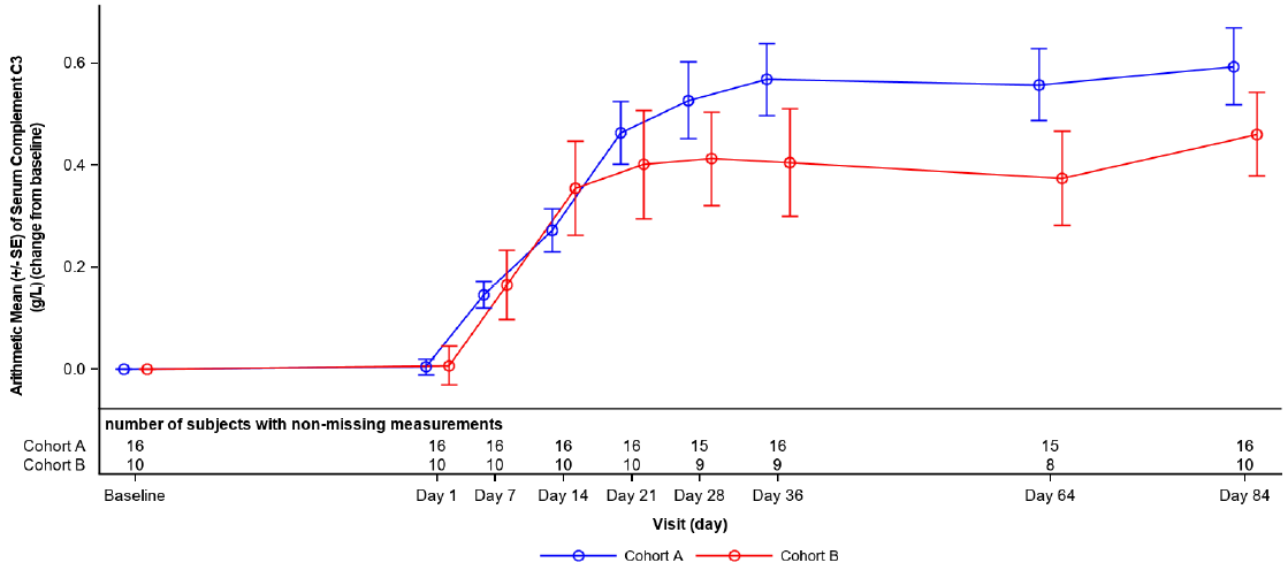
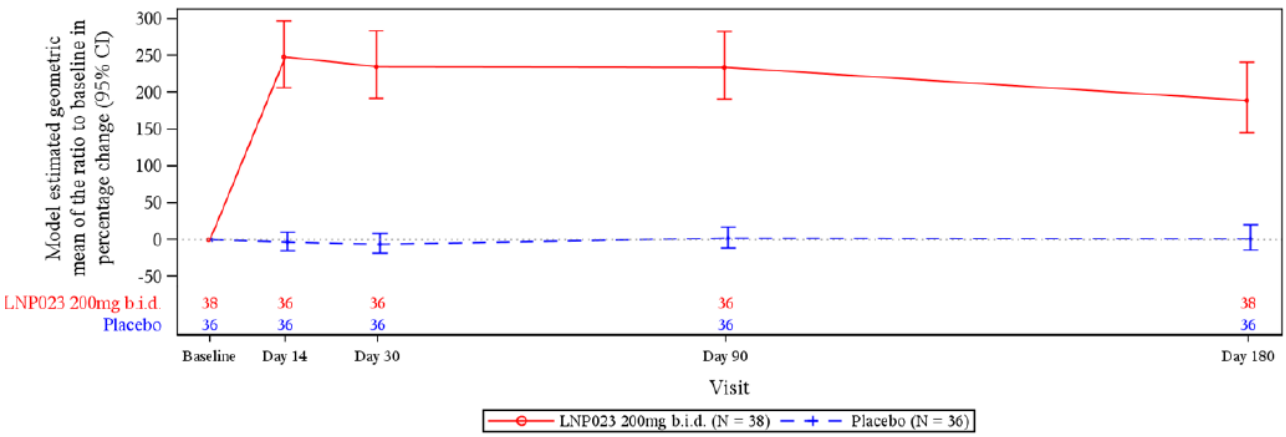


Figure 14: Model estimated geometric mean of the ratio to baseline in percentage change (95% CI) of serum complement C3 up to month 6 by treatment group (Full analysis set) (APPEAR-C3G)



sC5b-9

The effector structure of the complement system, the membrane attack complex (MAC), was quantitatively determined by measuring sC5-9, i.e., the soluble complex of complement factors C5b to 9. In line with the expected effect of iptacopan, the plasma sC5b-9 level sharply decreased from baseline and compared to placebo in studies X2202 and APPEAR-C3G, see the following two figures. Notably, there was hardly effect of iptacopan on sC5b-9 in Cohort B (transplanted patients) of Study X2202 which questions the disease activity in these subjects.

According to the MAH, the observed difference between the two cohorts in Study X2202 (i.e. markedly stronger iptacopan effect in Cohort A than in Cohort B) is consistent with intravascular activation of the AP in C3G disease. Plasma sC5b-9 levels in patients with recurrent C3G (Cohort B) are more comparable to healthy participants and therefore minimal iptacopan effect on this biomarker was observed. One hypothesis is that concomitant immunosuppressant drugs in recurrent C3G patients (kidney transplant patients) inhibit to some degree sC5b-9 production at baseline.

Figure 15: Study X2202, Parameter: Plasma SC5b-9 (ng/mL)

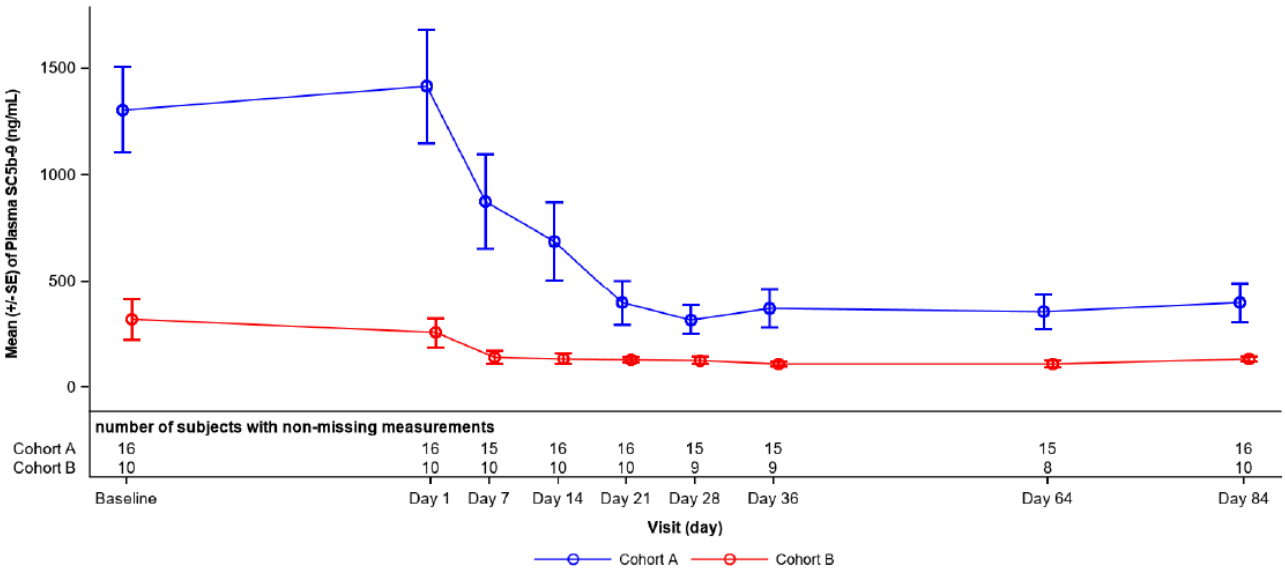
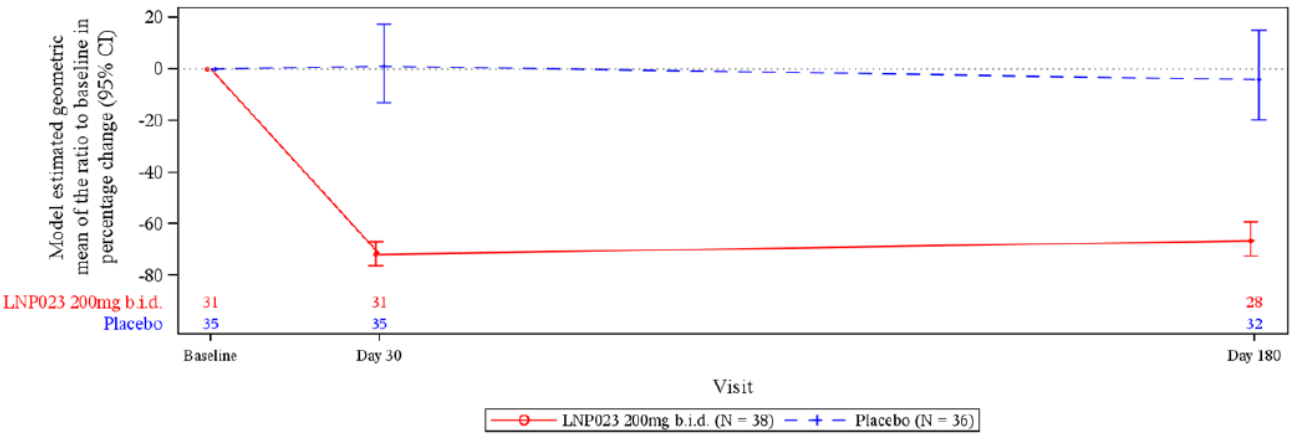


Figure 16: Model estimated geometric mean of the ratio to baseline in percentage change (95% CI) of plasma sC5b-9 up to month 6 by treatment group (Full analysis set) (APPEAR-C3G)



Wieslab assay

The Wieslab assay measures the extent to which the complement system in the plasma can be activated, in this case via the AP. For performing the assay, AP is started *ex vivo* (i.e. in patient plasma) by adding LPS (lipopolysachharide); the resulting complement activation is quantified by measuring formed sC5b-9. With iptacopan treatment, the responsiveness of the AP to LPS stimulation becomes down regulated over time and compared to placebo (see the following two figures). Notably, in Study X2202 (Figure 17 below) the decrease was more pronounced in Cohort B since the baseline was higher. It can be assumed that in Cohort A, with higher disease activity, part of the complement factors is consumed by permanent activation (as indicated by higher levels of spontaneously formed sC5b-9, see above) so that LPS can activate a lower amount of complement factors.

Figure 17: Parameter: Serum WIESLAB (iu)

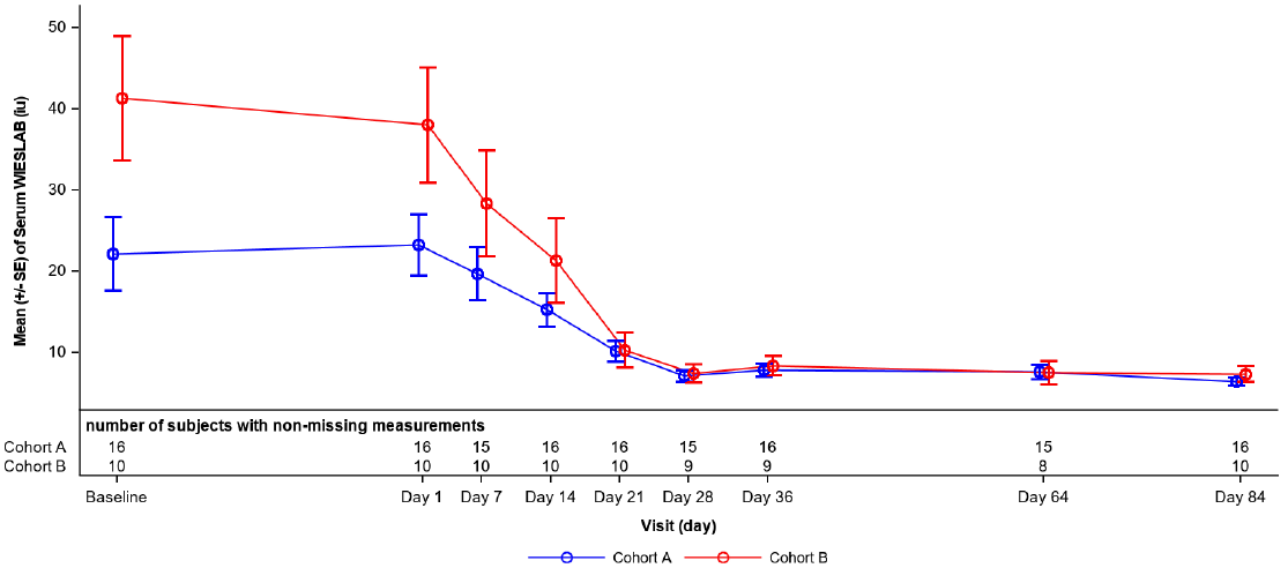
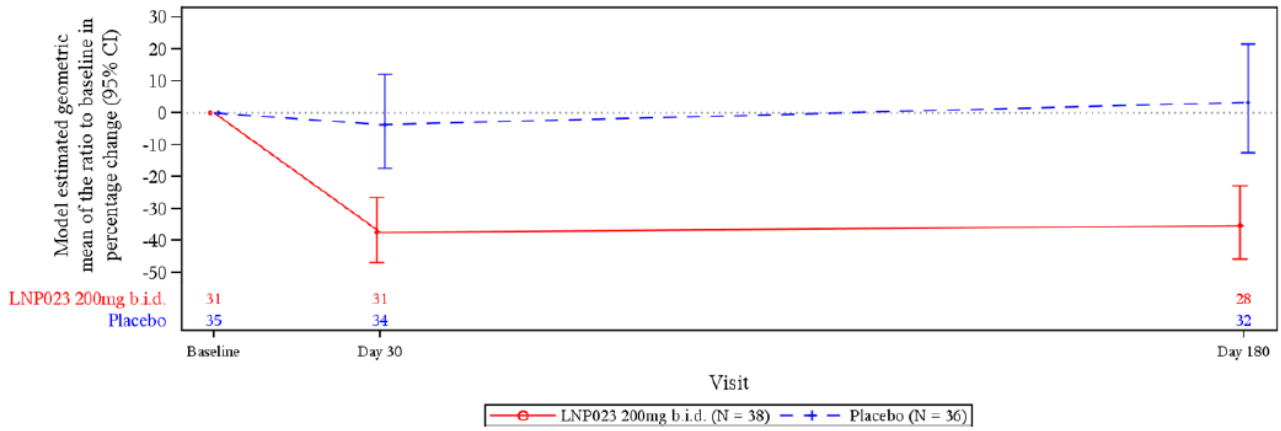


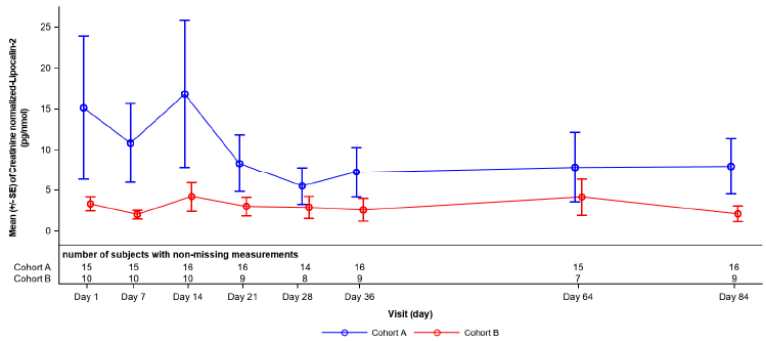
Figure 18: Model estimated geometric mean of the ratio to baseline in percentage change (95% CI) of serum Wieslab up to month 6 by treatment group (Full analysis set) (APPEAR-C3G)



Selected urine parameters

In order to assess disease activity, the MAH also measured several inflammation markers and renal function parameters in blood and urine such as lipocalin; see Figure 19 below for data from urine. All values were normalised to creatinine. Overall, no major changes were seen in Cohort B. In Cohort A, a mild decline from baseline was observed. According to the MAH, this may indicate a positive effect of iptacopan on kidney inflammation, glomerular damage and tubular function.

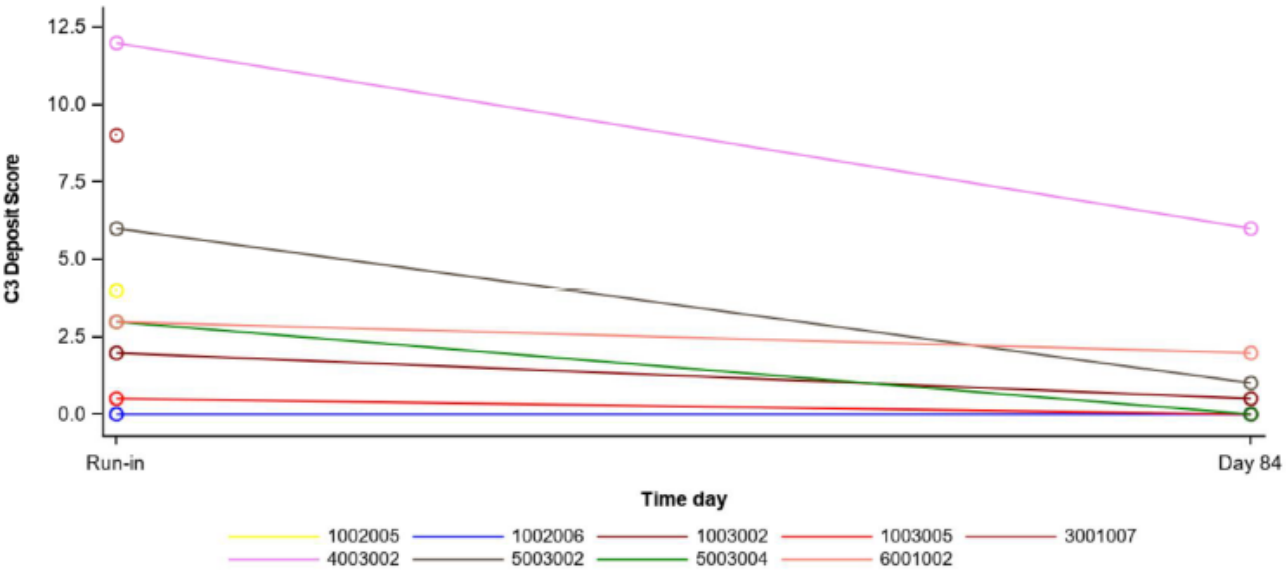
Figure 19: Creatinine normalized-Lipocalin-2 (pg/nmol)



Histological scores

The ***C3 Deposit Score*** is based on C3 immunofluorescence in renal biopsies collected at run-in and Week 12. The score varies from 0 to 3 graded intensity values for C3 deposition for the mesangial and capillary location. The score for each location (mesangial and capillary) was multiplied with a factor of 1 for segmental and a factor of 2 for global extend. The total score ranges from 0 to 12.

Figure 20: Individual summary plots for C3 Deposit Score - Cohort B (PD analysis set 1)



The ***disease activity score*** uses as baseline biopsy/bioptic material collected/made available at run-in. This score provided an idea of the extent of a given lesion. A post-hoc analysis was conducted by considering the number of glomeruli with global sclerosis in deriving the total scores to get a proportion of the function that could be effectively recovered.

The ***disease chronicity score*** uses as baseline the biopsy/bioptic material collected at run-in. A certain pattern could not be observed with the broad variability at baseline (i.e., values ranging from 0 to 159).

The disease activity score revealed a very low value at baseline in all but two subjects of Cohort B. These two subjects had a rather high score at baseline that markedly declined during treatment with iptacopan. The disease chronicity score revealed a less consistent picture. Again, most patients had a low score at baseline. Four subjects had higher scores at baseline. During iptacopan treatment, the score slightly increased in most patients; two subjects revealed a decrease.

2.3.4. PK/PD modelling

PopPK modelling and a PBPK modelling were assessed in the initial MAA of iptacopan. As the PBPK model was considered not qualified to inform dosing in patients with organ impairment the Applicant submitted an updated population PK modelling report including the APPEAR-C3G data following request of the CHMP. The conclusions were consistent with the original popPK analysis, with minor numerical differences of the covariate effects. High shrinkage was observed for BSV on Tlag and BSV on ka. Additionally, the covariate "indication" (disease) that was retained in the sensitivity analysis of the original popPK model was removed from the updated sensitivity analysis, as the inclusion of this covariate was an artefact of the small C3G sample size (n=27) in the original popPK data pool. This was considered acceptable by the CHMP.

2.3.5. Discussion on clinical pharmacology

The pharmacokinetics of iptacopan was assessed within the initial MAA of iptacopan for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria. This already included PK in patients with C3G. In this extension of indication application, no new PK findings were submitted.

The primary action of iptacopan is binding to complement factor Bb (and to the Bb domain of Factor B) and inhibiting its biological activity. *In vitro* studies for describing this interaction were already submitted with the initial MAA. By inhibiting Factor Bb, less Factor C3b is formed and thereby the complement activation via the AP is reduced. This can be exploited for treatment of complement-dependent diseases such as C3G, the subject of this extension of indication, or paroxysmal nocturnal haemoglobinuria (PNH), the subject of the initial MAA. By inhibiting only the AP of complement activation, the extent of resulting immune suppression can be limited.

C3G often is induced by so-called nephritic factors, autoantibodies against certain complement factors. A frequent target of these autoantibodies is complement factor C3; in this case, the autoantibody is called C3Nef. C3Nef was frequently found in the participants of the iptacopan trials and stabilises the complex between the factors C3b and Bb, which together form active C3 convertase. Thereby C3Nef could interfere with the action of iptacopan, which binds to Bb to inhibit C3 convertase. Therefore, the MAH provided a separate analysis of eight C3Nef-positive (C3Nef+) patients in the iptacopan group of APPEAR-C3G. It turned out that there was no difference between C3Nef+ and all subjects in respect to serum C3 and sC5b-9. For 24h-UPCR, a stronger reduction from baseline was observed in the C3Nef+ subgroup compared to all iptacopan-treated subjects (-69.4% in C3Nef+ patients vs. -39.7% overall at Day 90). The reason for the difference in UPCR reduction is not known, but the results of the analysis clearly demonstrate that presence of C3Nef does not negatively affect the efficacy of iptacopan.

In this application, PD was mainly covered by Study X2202 in which several parameters of complement activation and inflammation were determined in blood and urine of the participants. Key parameters were also determined in the pivotal study APPEAR-C3G. In the latter, placebo control is available whereas in X2202 only changes from baseline can be evaluated due to the lack of a control group. Study X2202 included a group of patients with native kidney (Cohort A) and a group with transplanted kidney (Cohort B), in which C3G has occurred again (recurrent C3G). Overall, the activity of C3G in Cohort B appeared rather low. In particular, urine protein excretion and histological C3G activity score were nearly normal in most Cohort B subjects, and plasma sC5b-9 level was low. Furthermore, mean eGFR in Cohort B was in the range as expected for a transplanted kidney according to published literature. The MAH explained that most subjects of Cohort B were in an early stage of recurrent C3G, diagnosed by histological detection of C3 deposits in renal biopsy. Clinical or laboratory findings were largely absent in this stage besides a reduction of serum C3 in most subjects. This means for the use of iptacopan in clinical practice that the diagnosis of recurrent C3G may rely on histological findings to make early treatment possible. This is now

included in Sections 4.2 with reference to 5.1 (description of study *X2202)* of the SmPC. Biopsies routinely taken after transplant can be used for this purpose. When the suspicion of recurrent C3G first comes from clinical features, it should be confirmed by biopsy.

In Cohort A, all complement parameters responded to iptacopan as expected and as already described in the initial MAA. Factor C3 in plasma increased since inhibition of Factor Bb by iptacopan prevents it cleavage. The plasma level effector complex of the complement system for membrane attack, sC5b-9 decreased. In the longer term, a down-regulation of the complement AP was observed, reflected by a mild increase in Factor B level, a mild decrease in Factor Bb and a decreased complement activity in the Wieslab assay. The *ex-vivo* Wieslab assay measures sC5b-9 formation in plasma after initiating the AP by LPS. The same effects were seen in the iptacopan group Study APPEAR-C3G whereas no changes from baseline were observed in the placebo group. The applicant proposed the below text for inclusion in 5.1 of the SmPC which was considered acceptable by the CHMP:

"In patients with C3G, the mean serum C3 level increased by 249% compared to baseline at day 14 of iptacopan treatment, reflecting inhibition of pathological C3 cleavage. The plasma soluble C5b-9 and urine soluble C5b-9 decreased from baseline by 71.8% and 92.1%, respectively, on the first observation at day 30 of treatment with iptacopan 200 mg twice daily. The effect was sustained over the observation period of 12 months. A reduction of glomerular C3 deposition at 6 months was also observed based on C3 deposit score change."

It was shown that iptacopan leads to an immediate increase of eGFR after initiation of treatment. In Study X2202, the highest magnitude of the increase was around 5 ml/min/1.73m2 at Day 24; at Day 84, eGFR was still around 2.5 ml/min/1.73m2 above baseline. The short-term changes most likely do not reflect changes in disease activity. Although the changes are small, they may confound the interpretation of eGFR changes over time as an efficacy parameter since in the iptacopan C3G studies, the eGFR changes over time considered related to disease progression were also small. For distinguishing reversible functional effects from effects of disease progression the MAH identified three subjects who at least temporarily discontinued iptacopan while eGFR data are available for this time. No relevant changes in eGFR were observed. This indicated that the eGFR increase after treatment start is not due to any haemodynamic changes in the kidney but most like is a consequence of reduced inflammation. Iptacopan inhibits complement activity in the glomeruli and thereby reduces cellular damage and inflammation. This can improve glomerular function.

In Cohort A, iptacopan also induced reduction in urine protein excretion and UPCR, the primary objective. This is further discussed in the efficacy section.

2.3.6. Conclusions on clinical pharmacology

No new PK findings were submitted. The measured PD parameters were well in line with the expected mode of action of iptacopan and the pharmacological profile supports the use of iptacopan in patients with C3G. The sections 4.2 and 5.1 of the SmPC were updated accordingly.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

The iptacopan 200 mg bid dose was selected based on the available PK/PD efficacy and safety data from the Phase 1 first in human study (FIH) [Study LNP023X2101] and the Phase 2 study in C3G [Study

CLNP023X2202]. This dose has also been approved for the treatment of adult patients with PNH based on studies CLNP023X2201 and CLNP023X2204 (please refer to the EPAR of the initial MA).

Based on healthy participant studies, near maximal iptacopan inhibition of biomarkers of the alternative pathway (Wieslab, plasma Bb, plasma sC5b-9) was observed at 2 hours after the first dose. Pharmacodynamic steady state occurs in the first 2-3 days of bid dosing and pharmacokinetic steady state occurs after approximately 5-7 days of bid dosing. Healthy participants and patients with PNH, IgAN and C3G had similar complement biomarker responses to iptacopan treatment.

In the Phase 2 Study X2202 in C3G (described in detail in this report as supportive study), the dose of iptacopan was titrated to 10, 25, 100 and 200 mg bid. The doses below 200 mg were administered for one week in which iptacopan steady state would be achieved. The 200 mg bid dose of iptacopan, administered for 9 weeks, produced maximum changes in complement biomarkers that are associated with C3G disease pathophysiology.

Exposure-response modelling of blood complement biomarkers (serum Wieslab assay, plasma Bb and plasma sC5b9) indicated that 200 mg bid was the dose level expected to achieve Ctrough above EC90 of all three primary alternative pathway biomarkers in the majority of C3G patients (≥82%) (see Pop PK).

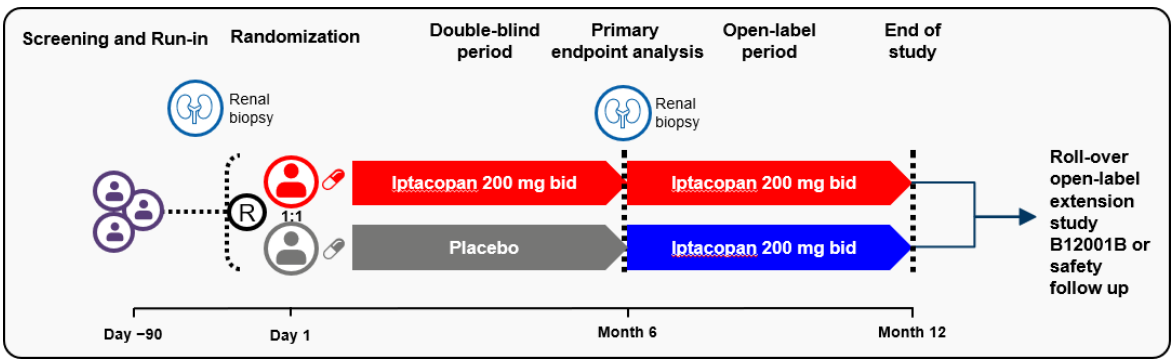
2.4.2. Main study

APPEAR-C3G

A multicenter, randomized, double-blind, parallel group, placebo-controlled study to evaluate the efficacy and safety of iptacopan (LNP023) in complement 3 glomerulopathy.

APPEAR-C3G is an ongoing phase 3, multicenter, randomized, double-blind, parallel group, placebo-controlled study in participants with C3G. The study includes a 180-day blinded (6 months), placebo-controlled period, followed by a 180-day period in which all subjects receive open-label iptacopan (for a total of 12 months). Participants who have completed the 12 months treatment period on study drug will be eligible to continue to receive iptacopan in the single-arm open-label extension study B12001B.

Figure 21: Study design of Phase 3 study APPEAR-C3G



Methods

Study participants

Main inclusion criteria

Key inclusion criteria for the study population were as below:

- Male and female participants age ≥ 18 and ≤ 60 years at Screening
- Diagnosis of C3G as confirmed by kidney biopsy within 12 months prior to enrollment
- Prior to randomization, all participants must have been on a maximally recommended or tolerated dose of an ACEI or ARB for at least 90 days. The doses of other antiproteinuric medications including MPAs, corticosteroids, SGLT2 inhibitors and mineralocorticoid receptor antagonists should have been stable for at least 90 days prior to randomization
- Reduced serum C3 (defined as < 0.85 × lower limit of the central laboratory normal range, i.e., < 77 mg/dL) at Screening
- UPCR ≥ 1.0 g/g sampled from the first morning void urine sample at Day −75 and Day−15
- Estimated GFR (using the CKD-EPI formula, Levey et al 2009) or measured GFR ≥ 30 mL/min/1.73m^2 at Screening and Day −15
- Mandatory vaccination against *Neisseria meningitidis* and *Streptococcus pneumoniae* infection prior to the start of study treatment. If the participant had not been previously vaccinated, or if a booster was required, the vaccine should have been given according to local regulations at least 2 weeks prior to the first administration of study treatment. If study treatment had to start earlier than 2 weeks post vaccination, prophylactic antibiotic treatment should have been initiated
- If the participant had not been previously vaccinated, or if a booster was required, vaccination against *Haemophilus influenzae* infections should have been given, if available and according to local regulations, at least 2 weeks prior to the first study treatment administration. If study treatment had to start earlier than 2 weeks post vaccination, prophylactic antibiotic treatment should have been initiated.

Main exclusion criteria

Key exclusion criteria for the study population were as below:

- Participants who had received any cell or solid organ transplantation, including kidney transplantation
- Rapidly progressive crescentic glomerulonephritis (RPGN) defined as a 50% decline in the eGFR within 3 months with kidney biopsy findings of glomerular crescent formation seen in at least 50% of glomeruli
- Kidney biopsy showing interstitial fibrosis/tubular atrophy (IF/TA) of > 50%
- Monoclonal gammopathy of undetermined significance (MGUS) confirmed by the measurement of serum free light chains or other investigation as per local standard of care
- Acute post-infectious glomerulonephritis at Screening based upon the opinion of the investigator
- Participants with an active systemic bacterial, viral or fungal infection within 14 days prior to study treatment administration or the presence of fever≥ 38°C (100.4°F) within 7 days prior to study treatment administration
- A history of recurrent invasive infections caused by encapsulated organisms, e.g., meningococcus or pneumococcus
- The use of inhibitors of complement factors (e.g., Factor B, Factor D, C3 inhibitors, anti Complement 5 (C5) antibodies, C5a receptor antagonists) within 6 months prior to the Screening visit
- The use of immunosuppressants (except systemic prednisone at a dose ≤ 7.5 mg/day or equivalent dose for a similar corticosteroid medication and MPAs) or cyclophosphamide within 90 days of study drug administration

Treatments

Study drug:

Participants were randomized to one of two treatment arms in a 1:1 ratio (iptacopan:placebo).

- Iptacopan arm: Iptacopan orally at 200 mg (one 200 mg capsule) b.i.d. for 6 months (double-blind) followed by open-label iptacopan at 200 mg b.i.d. for an additional 6 months.
- Placebo arm: Placebo orally (1 matching capsule) b.i.d. for 6 months (double-blind) followed by open-label iptacopan at 200 mg b.i.d. for an additional 6 months.

Prior and concomitant therapies:

Prior therapy

Prior medications were defined as medications taken and *stopped* at least one day prior to the first dose of study treatment (i.e., prior to randomization).

C3G relevant concomitant therapy

All participants were required to be on a stable, maximum or maximally tolerated dose of an ACEI/ARB during Screening/run-in and throughout the study. MPAs, lower dose glucocorticoids and SGLT2 inhibitors were permitted at stable doses from screening to the end of study visit.

Objectives

The **primary objective** was to demonstrate the superiority of iptacopan compared to placebo in reducing proteinuria at 6 months of treatment.

For secondary objectives please refer to the table under Outcomes/endpoints in the chapter below.

Outcomes/endpoints

The primary endpoint was the Log-transformed ratio to baseline in UPCR (sampled from a 24-hour urine collection) at 6 months.

The secondary objectives and endpoints are presented in the following table:

Secondary objectives and endpoints

Secondary objectives	Endpoints
To demonstrate the superiority of iptacopan vs. placebo in improving eGFR	*Change from baseline in eGFR* at 6 months
To demonstrate the superiority of iptacopan vs. placebo in the proportion of participants who achieved a composite renal endpoint	A participant meets the requirements of the *composite renal endpoint* if he/she satisfies the following criteria at the 6-month time point: (1) a stable or improved eGFR compared to the baseline visit (≤ 15% reduction in eGFR), and (2) a ≥ 50% reduction in UPCR compared to the baseline visit. Initiation of treatment with any complement pathway modifying agent or initiation/intensification of corticosteroid or immunosuppressant or renal replacement therapy

	automatically designates the participant as not meeting the endpoint
To demonstrate the effect of iptacopan vs. placebo in reducing glomerular inflammation in the kidney	*Change from baseline in disease total activity score* in a renal biopsy at 6 months
To assess the effect of iptacopan compared to placebo in improvement of patient-reported fatigue	*Change from baseline to 6 months in the FACIT-Fatigue score*
To evaluate the safety and tolerability of iptacopan compared to placebo during the 6-month double-blind period	Occurrence of clinically significant vital signs (mean sitting DBP, mean sitting SBP, heart rate), ECGs, and safety laboratory measurements, as well as AEs, AEs of special interest, and study drug discontinuation due to an AE (or any safety issue) during the double-blind period of the study

Exploratory efficacy endpoints included change in annualized *eGFR slope from pre-iptacopan treatment slope to post-iptacopan treatment slope*, log-transformed ratio to baseline in *serum C3* at 6 months, change from baseline in *glomerular C3 deposit score*, and change from baseline in log-transformed *serum AP Wieslab assay, plasma Bb and plasma sC5b-9* at 6 months, change from baseline to 6 months in SF-36, EQ-5D summary scores and PGIS severity level for fatigue (*health-related QoL*).

Objectives and related endpoints for the 12-month treatment period: the objectives were to evaluate the long-term efficacy and safety of iptacopan. Key efficacy endpoints (UPCR, eGFR, composite renal endpoint, and FACIT-Fatigue score) and safety endpoints (AEs) were analysed up to 12 months for participants who continued in the open-label iptacopan treatment period with a cut-off date of 07-Nov-2023.

Sample size

For sample size estimation for the primary endpoint a reduction in UPCR of 60% in the iptacopan group vs. 20% in the placebo group (i.e., a relative reduction vs placebo in UPCR of 50%) and a standard deviation of 0.69 (on the log-scale) was assumed based on the interim analysis of study CLNP023X2202. A sample size of 34 adult participants per group (total 68 participants) provides at least 98% power at the one-sided 0.025 significance level. Assuming a reduction in UPCR of 50% in iptacopan group vs. 20% inplacebo group (i.e., a relative reduction vs placebo in UPCR of 37.5%), a sample size of 68 participants provides at least 80% power at the one-sided 0.025 significance level.

Randomisation

Participants were randomized to one of the two treatment arms below in a 1:1 ratio (iptacopan:placebo). To achieve a dose of 200 mg b.i.d. of iptacopan, participants took 1 iptacopan 200 mg capsule (size 0) or matching placebo twice a day (morning and evening).

• Iptacopan arm: Iptacopan orally at 200 mg (one 200 mg capsule) b.i.d. for 6 months (double-blind) followed by open-label iptacopan at 200 mg b.i.d. for an additional 6 months

• Placebo arm: Placebo orally (1 matching capsule) b.i.d. for 6 months (double-blind) followed by open-label iptacopan at 200 mg b.i.d. for an additional 6 months.

Blinding (masking)

This was a participant, investigator, and sponsor-blinded study. Participants, investigator staff, persons performing the assessments and the Clinical Trial Team remained blinded to the identity of treatment from the time of randomization until interim database lock after all participants had completed the double-blind treatment period. Unblinding could occur in the case of participant emergencies and at the conclusion of the double-blind treatment period.

Statistical methods

The primary endpoint was analyzed using a Mixed Model for Repeated Measures (MMRM) model for the log ratio to baseline measurements. For the primary endpoint, the model included treatment, time point, CS and/or MPA treatment at randomization (yes vs. no) as fixed effects, a treatment*time point interaction term and log (baseline UPCR) as a covariate. The correlations between visits within patients were modeled using an unstructured covariance matrix.

The handling of intercurrent events is described in the estimands section below. In alignment with the primary estimand initiation of any complement pathway modifying agent or renal replacement therapy (RRT), initiation or intensification of CS or immunosuppressant therapy were imputed assuming that a patient's mean profile follows that of placebo patients that remain in the study The "jump-reference" ("J2R") imputation approach (Carpenter et al., J Biopharm Stat 2013), and values for the placebo arm were imputed under the missing-at-random assumption. For discontinuations of study medication for any other reasons, UPCR measurements after discontinuation were collected and used in the analysis. Missing data linked to unavailability of 24-hour urine samples to evaluate the primary endpoint due to administrative reasons were implicitly handled using the MMRM model. Otherwise missing values were imputed under a model taking into account the participant's prior measurement history, important baseline covariates as well as participant status at the time of and the reasons for study discontinuation. E.g., in case of drop-out due to an adverse event or renal related death, data were imputed considering the AE as potentially indicative of a worsening in condition (using a "J2R" approach for the iptacopan group and MAR for the placebo group).

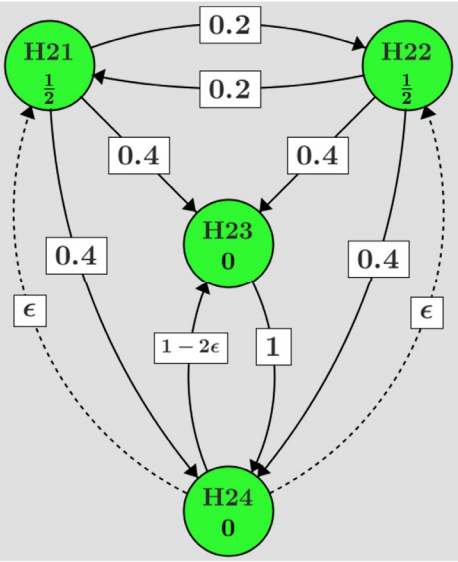
For all secondary estimands the same intercurrent events as for the primary estimand apply, apart from cases where the intercurrent events itself forms part of the endpoint attribute. The same strategies as for the primary estimand were used for handling intercurrent events applicable to the secondary estimands, except for the estimand for the renal composite endpoint for which the initiation or intensification of anti-proteinuric therapies or RRT was considered as treatment failures via the composite strategy. Multiple sensitivity analyses were planned as well as supplementary and supportive analysis, which are described in the results section.

Supplementary analysis included subgroup analyses based on sex, C3G disease subtype [C3GN vs. DDD], baseline UPCR [< 3 g/g vs. ≥ 3 g/g (< 339 mg/mmol vs. ≥ 339 mg/mmol)], and MPA and/or CS treatment at randomization [yes vs. no]). The mean difference between iptacopan versus placebo (and its 95% confidence interval) was calculated for the 6-month time point.

Four secondary endpoints were included in a multiple testing procedure that controlled the familywise error rate (FWER) one-sided 0.05. The hypotheses associated with the secondary endpoints were to be tested only if the null hypothesis associated with the primary endpoint was rejected. A graphical multiple test procedure was used for testing the hypotheses associated with four secondary endpoints. Given the ultra-rare nature of the disease, the multiple test procedures controlled the familywise error rate of the secondary endpoints at one-sided 0.05. In the graph (see below) the nodes denoted four secondary hypotheses (H21 Change from baseline to month 6 in eGFR, H22 Proportion of participants who achieved composite renal endpoint at month 6, H23 Change from baseline to month 6 in the histology total activity

score, H24 Change from baseline to month 6 in the FACIT-Fatigue total score) and the numbers on edges denoted the weights or proportions of alpha to be propagated to the next nodes according to the directed edges once the current hypothesis node was rejected.

Figure 22: Nodes denoted four secondary hypotheses



Change from baseline to month 6 in eGFR was analyzed using an MMRM model. This model included treatment, time point, MPA and/or CS treatment at randomization (yes vs. no) as fixed effects, a treatment*time point interaction term and baseline eGFR as a covariate. The correlations between visits within patients were modeled using an unstructured covariance matrix. The mean difference between iptacopan versus placebo (and its 95% confidence interval) was calculated for the 6-month time point.

The proportion of patients meeting the composite endpoint was analyzed using a logistic regression model that included treatment and CS or MPA treatment at randomization (yes vs. no) as factors. The differences were computed for comparisons of iptacopan versus placebo.

The change from baseline to month 6 in the histology total activity score was analyzed using an analysis of covariance (ANCOVA) model with treatment and CS or immunosuppressant treatment at randomization (yes vs. no) as fixed effects, and the baseline total activity score as a covariate. The mean difference between iptacopan versus placebo was calculated for the 6-month time point.

The change from baseline to 6 months in the FACIT-Fatigue total score was analyzed using a MMRM for the change from baseline to 6 months in the FACIT-Fatigue total score with missing data implicitly handled under the analysis model. This model included treatment, time point, CS and/or MPA at randomization (yes vs. no) as fixed effects, treatment*time point as interaction term and baseline FACIT-Fatigue total score as fixed covariate. The difference between the mean changes from baseline to 6 months for iptacopan vs. placebo was presented, together with its 2-sided 95% CI and associated 1-sided p-value.

As part of exploratory analyses, historical serum creatinine data were collected to derive eGFR values using the CKD-EPI formula for the two-year period prior to study Day 1 or since diagnosis where this was less than two years. The historical data were combined with all observed in-study eGFR data from scheduled visit Day 1 up to Day 360 with missing data handled implicitly through model. A longitudinal mixed effects model, with a common intercept, a pre-treatment slope and a change in the slope following iptacopan treatment was used to model the change in eGFR trajectory. Subject-level intercept and slope

were included in the model as random effects. The eGFR slope prior to iptacopan treatment and the change in slope after iptacopan treatment were estimated and presented graphically.

Primary estimands: The primary clinical question of interest: what was the treatment effect of iptacopan on proteinuria reduction as measured by UPCR (24-hour urine collection) in adult participants on stable background therapies with biopsy-confirmed C3G?

The primary estimand captures the effect of the study drug in the absence of potentially confounding effects of anti-proteinuric therapies or renal replacement therapy (RRT) that were not a part of the assigned treatment strategy.

The attributes of the primary estimand were:

- Population: participants with biopsy-confirmed C3G
- Endpoint: log-transformed ratio to baseline in UPCR at 6 months
- Treatment of interest: the randomized treatment (the investigational treatment iptacopan 200 mg b.i.d. or placebo) regardless of whether participant discontinues treatment for reasons other than the initiation of any complement anti-proteinuric pathway modifying agent, corticosteroid or other immunosuppressant therapies, or RRT
- Intercurrent events:

The initiation of treatment with any complement pathway modifying agent or the initiation or intensification of corticosteroid or immunosuppressant therapy was handled using the hypothetical strategy, which is as though these medications were not available.

The initiation of RRT (i.e., peritoneal dialysis, hemodialysis or transplantation) was handled using the hypothetical strategy, that is as though RRT was not initiated and disease continued to progress.

The discontinuation of study medication for any other reason (other than the initiation of treatment with any complement pathway modifying agent or the initiation or intensification of corticosteroids and/or any other immunosuppressant therapies) was handled with a treatment policy strategy, i.e., data collection was maintained, and available measurements post-treatment discontinuation were used.

- Summary measure: Ratio of geometric means between groups. The summary measure of the treatment effect was also presented on the percentage scale.

For the **secondary estimands** for the endpoints change from baseline to Month 6 in eGFR, the histology total activity score, and the scores of fatigue using the FACIT-Fatigue questionnaire, the same population, treatment of interest and intercurrent events were considered as for the primary estimand. The summary measures were the difference between means. The estimand for the composite renal endpoint is defined below:

- Population: participants with biopsy-confirmed C3G
- Endpoint: a participant is defined as having met the endpoint at 6 months if the following criteria are met:
- A stable or improved eGFR compared to the baseline visit (≤ 15% reduction in eGFR) and ≥ 50% reduction compared to the baseline visit in UPCR (based on 24-hour urine collection). Initiation of any complement pathway modifying agent or initiation/intensification of corticosteroid and/or other immunosuppressant therapy such as mycophenolic acid (MPA), or RRT automatically designates the participant as not having met the endpoint. Short-term (≤ 7 days) initiation or short-term (≤ 7 days) dose escalation of oral corticosteroids for any non-renal indication was permitted and did not result in designating the participant as not having met the endpoint.

- Treatment of interest: the randomized treatment (the investigational treatment iptacopan 200 mg b.i.d. or placebo) regardless of whether the participant discontinued the treatment
- Intercurrent events: treatment with any complement pathway modifying agent or initiation/intensification of corticosteroid or immunosuppressant therapy, or RRT was considered treatment failures and hence a part of the endpoint definition (composite strategy). However, short-term (≤ 7 days) initiation or short-term (≤ 7 days) dose escalation of oral corticosteroids for any non-renal indication was permitted and not considered an intercurrent event. The discontinuations of study medication for any other reason were handled with a treatment policy strategy.
- Summary measure: the proportion of participants who achieved the composite renal endpoint on each treatment in the studied patient population tested as the risk difference.

Results

Participant flow

A total of 132 participants were screened from 19 countries, of which 74 participants (56.1%) completed the screening and run-in period and were randomized. In the 58 participants (43.9%) who did not complete the screening or run-in period, the most common primary reasons were not meeting the required serum C3 level (32 participants, 24.2%), UPCR (20 participants, 15.2%) and eGFR (5 participants, 3.8%) inclusion criteria.

A total of 74 participants were randomized and treated with study drug: 38 participants in the iptacopan arm and 36 participants in the placebo arm. All 74 participants completed the 6-month double-blind treatment period. Of these, thirty-six participants in the iptacopan arm completed the double-blind period on treatment. There were two participants in the iptacopan arm who discontinued double-blind treatment due to participant decision and a technical issue (inadvertent unblinding at Day 90), respectively. Per protocol, both participants remained in the study, continued with double-blind study visits (without treatment), and at Day 180, transitioned to the open-label period where they attended study visits and received iptacopan. The 36 participants in the placebo arm completed the double-blind treatment period.

At the data cut-off date 07-Nov-2023, 43 participants had completed the study (6 months of double-blind period plus 6 months of open-label period), and 30 participants were ongoing in the open-label treatment period of the study. One participant originally randomized to the placebo arm initially discontinued treatment with the reason recorded as participant decision, was subsequently lost to follow up and discontinued from the study during the open-label period.

Table 7: Participant disposition (Full analysis set)

Disposition/Reason	Iptacopan 200 mg b.i.d. N=38 n (%)	Placebo N=36 n (%)	Total N=74 n (%)
Treated	38 (100)	36 (100)	74 (100)
Not treated	0	0	0
Treatment ongoing #	16 (42.1)	14 (38.9)	30 (40.5)
Completed double-blind treatment	36 (94.7)	36 (100)	72 (97.3)
Discontinued from double-blind treatment	2 (5.3)	0	2 (2.7)

Disposition/Reason	Iptacopan 200 mg b.i.d. N=38 n (%)	Placebo N=36 n (%)	Total N=74 n (%)
Reason for discontinuation			
Subject decision	1 (2.6)	0	1 (1.4)
Technical problems	1 (2.6)	0	1 (1.4)
Completed open-label treatment	22 (57.9)	21 (58.3)	43 (58.1)
Discontinued from open-label treatment	0	1 (2.8)	1 (1.4)
Reason for discontinuation			
Subject decision	0	1 (2.8)	1 (1.4)
Study ongoing #	16 (42.1)	14 (38.9)	30 (40.5)
Completed study	22 (57.9)	21 (58.3)	43 (58.1)
Discontinued study	0	1 (2.8)	1 (1.4)
Reason for discontinuation			
Lost to follow-up	0	1 (2.8)	1 (1.4)

Ongoing at the time of the data cut-off date 07-Nov-2023

Recruitment

Study initiation date: 28-Jul-2021 (first participant first visit)

Data cut-off date: 07-Nov-2023 (Primary endpoint completion date for the adult cohort)

Conduct of the study

Overall, 43/74 enrolled participants (58.1%) reported at least one protocol deviation during the double-blind period as of the data cut-off date. The most common protocol deviations were related to 'other GCP deviation' (41 participants, 55.4%). Examples of this included participants who had taken the wrong dose of investigational medicinal product (IMP, 10 participants, 13.5%). In several instances this related to IMP not being taken or being taken once daily rather than protocol mandated twice daily for 1-3 days, though there was 1 participant who took 0 or 1 capsule per day on 8 occasions for a total of 13 days (which was iptacopan), 1 instance of a participant not taking IMP during 2 periods for a total of 100 days (which was iptacopan), 1 participant who took 1 dose daily during 3 periods for a total of 32 days (which was iptacopan), 1 participant who took 1 dose daily for 30 days (which was placebo), 1 instance of taking 4 capsules daily for 49 days (which was placebo), and a participant who took 3 capsules per day on 2 occasions for a total of 5 days (which was iptacopan). None of the dosing errors were associated with adverse events (AEs). Other deviations included participants only collecting one instead of two 24h urine samples (10 participants, 13.5%), the blood sample collection being performed after the morning dose of iptacopan (9 participants, 12.2%), and 'FMV urine sample not collected when required' (7 participants, 9.5%). Upon notification of these protocol deviations, the sites were contacted and the importance of adherence with the study protocol was reemphasized to the investigator, who was instructed to re-discuss this with the participant in question as well as other participants from their site. All participants provided

at least one 24h urine sample for the measurement of UPCR at baseline and 6 months to allow assessment of the primary endpoint (1 sample in the iptacopan arm was delivered late by a courier and out of stability). Samples collected after IMP dosing (i.e., not at trough) were not included in the PK analysis.

Inclusion and exclusion criteria deviations occurred in 8 (10.8%) and 2 (2.7%) participants, respectively, with the most common reasons being those participants (7, 9.5%) who were not on a stable dose of ACEIs, ARBs or other antiproteinuric medications for a full 90 days prior to randomization.

In addition, 1 participant had a FMV UPCR< 1.0 g/g at Day −75, 1 participant had a missing FMV UPCR at Day −15 (sample not collected), and 3 participants had abnormal vital signs protocol deviations recorded during the Screening/run-in period.

A total of 4 participants had protocol deviations related to COVID-19 in the iptacopan arm. The COVID-19 pandemic related deviations were mostly due to a missed visit (5 missed visits in 4 participants in China)

No participant was removed from the FAS or the safety set due to a protocol deviation.

Baseline data

The following Table 8 summarizes baseline demographics and clinical characteristics.

Table 8: Baseline demographics and clinical characteristics

Characteristic Categories/Statistics	**LNP023 200 mg b.i.d. N=38 n (%)**	**Placebo N=36 n (%)**	**Total N=74 n (%)**
Age (years)			
Mean (SD)	26.1 (10.39)	29.8 (10.79)	27.9 (10.68)
Age at C3G diagnosis – n (%)			
< 18 years	15 (39.5)	6 (16.7)	21 (28.4)
≥ 18 years	23 (60.5)	30 (83.3)	53 (71.6)
Sex -n (%)			
Male	27 (71.1)	20 (55.6)	47 (63.5)
Female	11 (28.9)	16 (44.4)	27 (36.5)
Baseline 24-hour UPCR (g/g)			
n	38	36	74
Mean (SD)	3.85 (2.288)	2.93 (1.710)	3.40 (2.066)
CV%	59.4	58.4	60.7
Geo-mean	3.33	2.58	2.94
95% CI	2.793 - 3.968	2.178 - 3.051	2.600 - 3.323
Baseline UPCR (24h) – n (%)			
< 3 g/g (< 339 g/mol)	17 (44.7)	25 (69.4)	42 (56.8)

Characteristic Categories/Statistics	LNP023 200 mg b.i.d. N=38 n (%)	Placebo N=36 n (%)	Total N=74 n (%)
≥ 3 g/g (≥ 339 g/mol)	21 (55.3)	11 (30.6)	32 (43.2)
Baseline eGFR (mL/min/1.73m^2)			
Mean (SD)	89.3 (35.20)	99.2 (26.88)	94.1 (31.61)
Baseline eGFR – n (%)			
< 60 mL/min/1.73m^2	10 (26.3)	4 (11.1)	14 (18.9)
≥ 60 mL/min/1.73m^2	28 (73.7)	32 (88.9)	60 (81.1)
< 90 mL/min/1.73m^2	19 (50.0)	12 (33.3)	31 (41.9)
≥ 90 mL/min/1.73m^2	19 (50.0)	24 (66.7)	43 (58.1)
Corticosteroid and/or mycophenolic acid treatment at randomization – n (%)			
Yes	16 (42.1)	17 (47.2)	33 (44.6)
No	22(57.9)	19 (52.8)	41 (55.4)
Hypertension* – n (%)			
Yes	23 (60.5)	18 (50.0)	41 (55.4)
No	15 (39.5)	18 (50.0)	33 (44.6)
C3G subtype at diagnosis – n (%)			
C3GN	26 (68.4)	32 (88.9)	58 (78.4)
DDD	9 (23.7)	1 (2.8)	10 (13.5)
Mixed C3GN/DDD	2 (5.3)	2 (5.6)	4 (5.4)
Unknown	1 (2.6)	1 (2.8)	2 (2.7)

Baseline 24-hour UPCR refers to UPCR as measured by the geometric mean of two 24-hour urine collections at baseline.
Baseline total urinary protein 24-hour refers to total urinary protein as measured by the geometric mean of two 24-hour urine collections at baseline.
Baseline eGFR was defined as the arithmetic mean of two eGFR values at Day -15 visit and Day 1 visit.
* Hypertension is defined based on "hypertension at diagnosis" from C3G medical history and the reported hypertension terms from the medical history

Numbers analysed

All randomized participants were included in the FAS and the safety set.

Table 9: Analysis sets (Randomized set)

Analysis set	Iptacopan 200 mg b.i.d. n=38 n (%)	Placebo n=36 n (%)	Total n=74 n (%)
Screened #			132
Screened but not randomized #			58
Randomized set	38 (100)	36 (100)	74 (100)
Full analysis set	38 (100)	36 (100)	74 (100)
Safety set	38 (100)	36 (100)	74 (100)
Combined safety set	38 (100)	36 (100)	74 (100)
PK analysis set	36 (94.7)	NA	36 (48.6)

Not included in Randomized set but in Screening set.
The Randomized set includes all randomized participants.
The Full analysis set includes all participants to whom study treatment has been assigned by randomization: Participants to whom a randomization number has been assigned in error (mis-randomized participants) are excluded from the FAS.
The Safety set includes all participants who received at least 1 dose of study treatment.
The Combined safety set includes all participants who received at least 1 dose of iptacopan during the double-blind treatment period or the open-label treatment period.
PK analysis set includes all participants in the safety data set with at least 1 available valid (i.e., not flagged for exclusion) PK concentration measurement. NA=not applicable.

Outcomes and estimation

Primary endpoint

The study met its primary objective of demonstrating superiority of iptacopan over placebo in proteinuria reduction. The adjusted mean ratios to baseline of 24h UPCR at the Day 180 visit in the iptacopan arm and the placebo arm were 0.70 (95% CI: 0.572, 0.852) and 1.08 (95% CI: 0.881, 1.313), respectively (i.e., reduction of 24h UPCR from baseline with iptacopan was 30% compared to an increase of 8% with placebo). A 39.7% reduction in 24h UPCR was observed at Day 90 (the first on-treatment 24h UPCR) for iptacopan vs. placebo, which was maintained at Day 180.

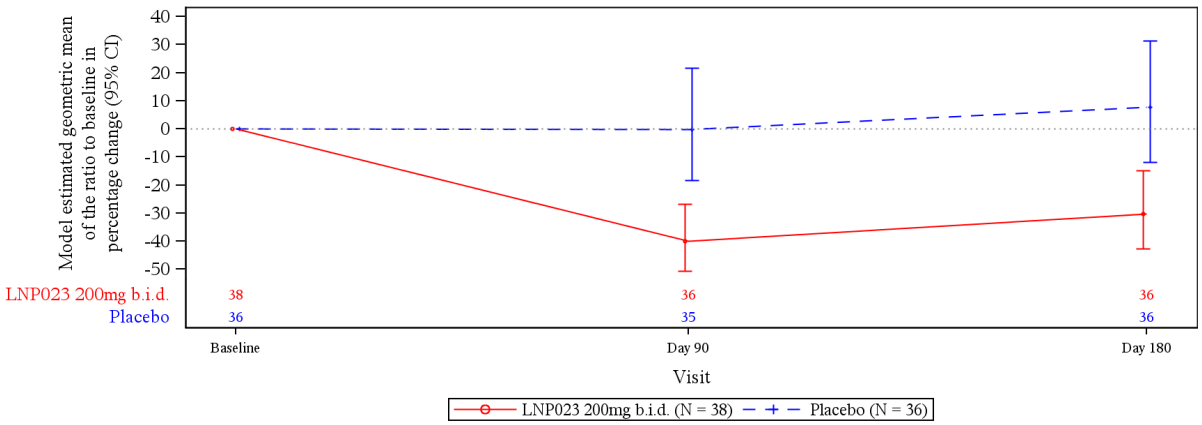
Table 10: Mixed model with repeated measures (MMRM) analysis of log-transformed ratio to baseline in 24h UPCR (g/g) (Full analysis set)

Visit	Treatment	N	n	Geometric adjusted mean (95% CI)	Iptacopan 200 mg b.i.d. vs Placebo Geometric mean ratio (95% CI)	% Reduction (95% CI)	1-sided p-value
Day 90	Iptacopan	38	36	0.601 (0.493, 0.731)	0.603 (0.454, 0.800)	39.7 (20.0, 54.6)	
	Placebo	36	35	0.996 (0.816, 1.217)			
Day 180	Iptacopan	38	36	0.698 (0.572, 0.852)	**0.649 (0.489, 0.862)**	**35.1 (13.8, 51.1)**	**0.0014**

Visit	Treatment	N	n	Geometric adjusted mean (95% CI)	Iptacopan 200 mg b.i.d. vs Placebo Geometric mean ratio (95% CI)	% Reduction (95% CI)	1-sided p-value
	Placebo	36	36	1.076 (0.881, 1.313)			

N: number of all participants included in the analysis (with non-missing baseline and covariates).
n: number of participants with values non-missing and not imputed as per intercurrent event (I/C) handling strategy at designate visit.
I/Cs handled with hypothetical strategy: values after the initiation or intensification of anti-proteinuric therapies and RRT were multiply imputed under J2R and MAR for the iptacopan and placebo groups, respectively.
Mixed Model of Repeated Measures (MMRM) was used and included treatment, visit, corticosteroid or mycophenolic acid treatment at randomization (yes vs. no) as fixed effects, treatment*visits as interaction term and log (baseline UPCR) as covariate.
Correlations between visits within participants were modelled using an unstructured covariance matrix.
Log transformation used natural log (base of e). Results were back-transformed and expressed as geometric means.

Figure 23: Model estimated geometric mean of the ratio to baseline in percentage change (95% CI) plot of 24h UPCR (g/g) up to month 6 by treatment group (Full analysis set)



Vertical bars represent 95% confidence intervals.
N=number of participants in full analysis set at each time point shown along the x-axis.
Log transformed ratio to baseline was analyzed using a MMRM which included treatment, visit, stratification variable as fixed effects, treatment*visit as interaction term and log (baseline UPCR) as covariate.

Sensitivity analyses for primary endpoint

Pre-specified sensitivity analyses

Sensitivity analyses were pre-specified for the primary endpoint to consider alternative imputation approaches following the intercurrent events. Intercurrent events were reported in 3 participants (7.9%) in the iptacopan arm.

Table 11: Frequency and proportion (%) of intercurrent events during the double-blind period (Full analysis set)

Intercurrent event	Iptacopan 200 mg b.i.d. N=38 n (%)	Placebo N=36 n (%)
Participants with any intercurrent event	3 (7.9)	0 (0.0)
Total number of events	3	0
The initiation or intensification of anti-proteinuric therapies	1 (2.6)	0 (0.0)
Initiate or intensify corticosteroid or immunosuppressant for a renal indication after randomization	1 (2.6)	0 (0.0)
Discontinued from double-blind treatment	2 (5.3)	0 (0.0)
Subject Decision	1 (2.6)	0 (0.0)
Technical Problems	1 (2.6)	0 (0.0)

n: Total number of participants in the category; N: Total number of participants in each group.
Events that occurred in the double-blind period were considered.

One participant in the iptacopan group had an intercurrent event of increasing corticosteroid dose from 7 mg QD to 30 mg QD on study Day 106 of the double-blind period. Multiple imputation was used to impute the UPCR measurement after this intercurrent event occurred per the pre-specified hypothetical strategy. Two other participants in the iptacopan arm discontinued the double-blind treatment on study Day 91 (technical reason) and Day 111 (participant decision). UPCR measurements after discontinuation of study treatment were collected and used in the primary analysis per the treatment policy strategy.

Table 12: Summary of sensitivity analyses for primary estimand

Endpoint	Analysis description	Iptacopan 200 mg b.i.d. vs placebo % Reduction (95% CI)	1-sided p-value
Log-transformed ratio to baseline in UPCR (sampled from 24h urine collection) at 6 months	**Primary analysis:** "Jump-reference" imputation approach following the intercurrent event*	35.1 (13.8, 51.1)	0.0014
	Sensitivity analysis 1: Imputation under the missing at random assumption following the intercurrent event*	35.7 (14.7, 51.6)	0.0011
	Sensitivity analysis 2: "Copy-reference" imputation approach following the intercurrent event*	35.4 (14.3, 51.3)	0.0012

*Hypothetical strategy was applied to handle intercurrent event of increasing corticosteroid dose (note only one event occurred at study Day 106 in the iptacopan group). Treatment policy strategy was applied to handle two intercurrent events of treatment discontinuation for all analyses.

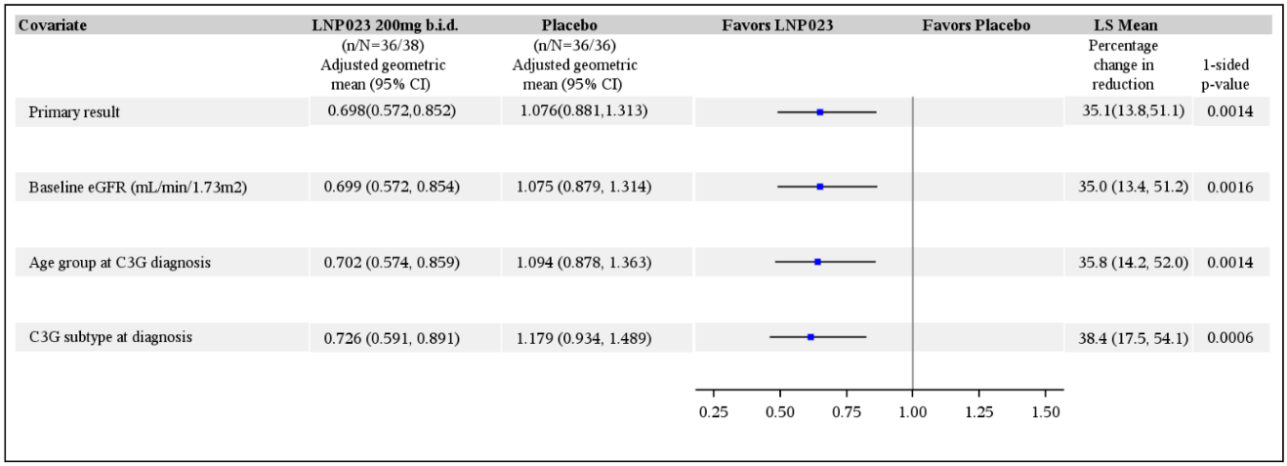
A pre-specified supplementary analysis was performed where intercurrent events of initiation with any

anti-proteinuric therapies were handled with the treatment policy strategy. This analysis showed a statistically significant (1-sided p=0.0017) reduction in 24h UPCR of 35.3% (95% CI: 13.9%, 51.4%) following 6 months of treatment with iptacopan compared to placebo which is consistent with the primary analysis.

Post-hoc sensitivity analyses

The primary analysis included the stratification factor (corticosteroid and/or MPA treatment at randomization) and baseline UPCR as covariate. Given the observed imbalances at baseline for several baseline characteristics, additional post-hoc sensitivity analyses were carried out to assess the impact of adjustment for other baseline covariates. Results are depicted in the following Figure 24:

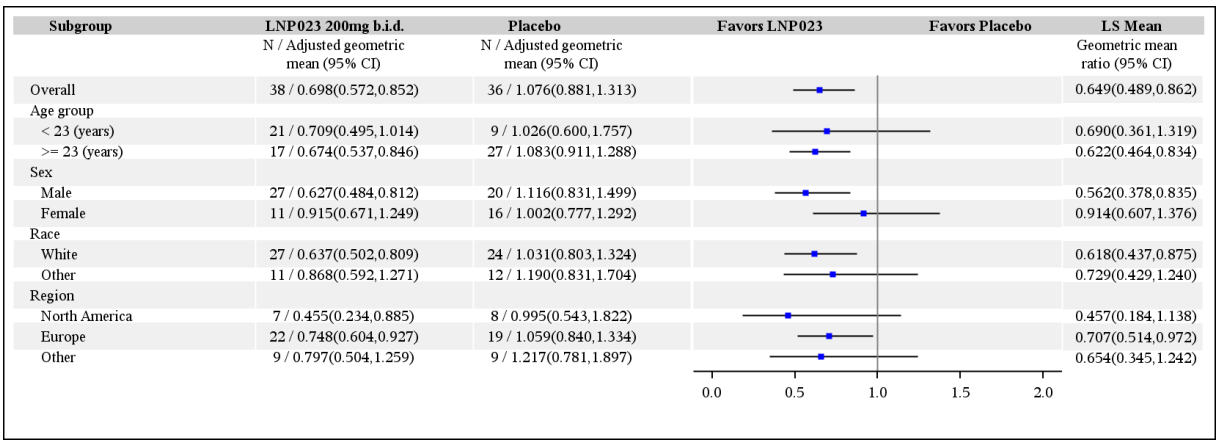
Figure 24: Additional post-hoc sensitivity analyses

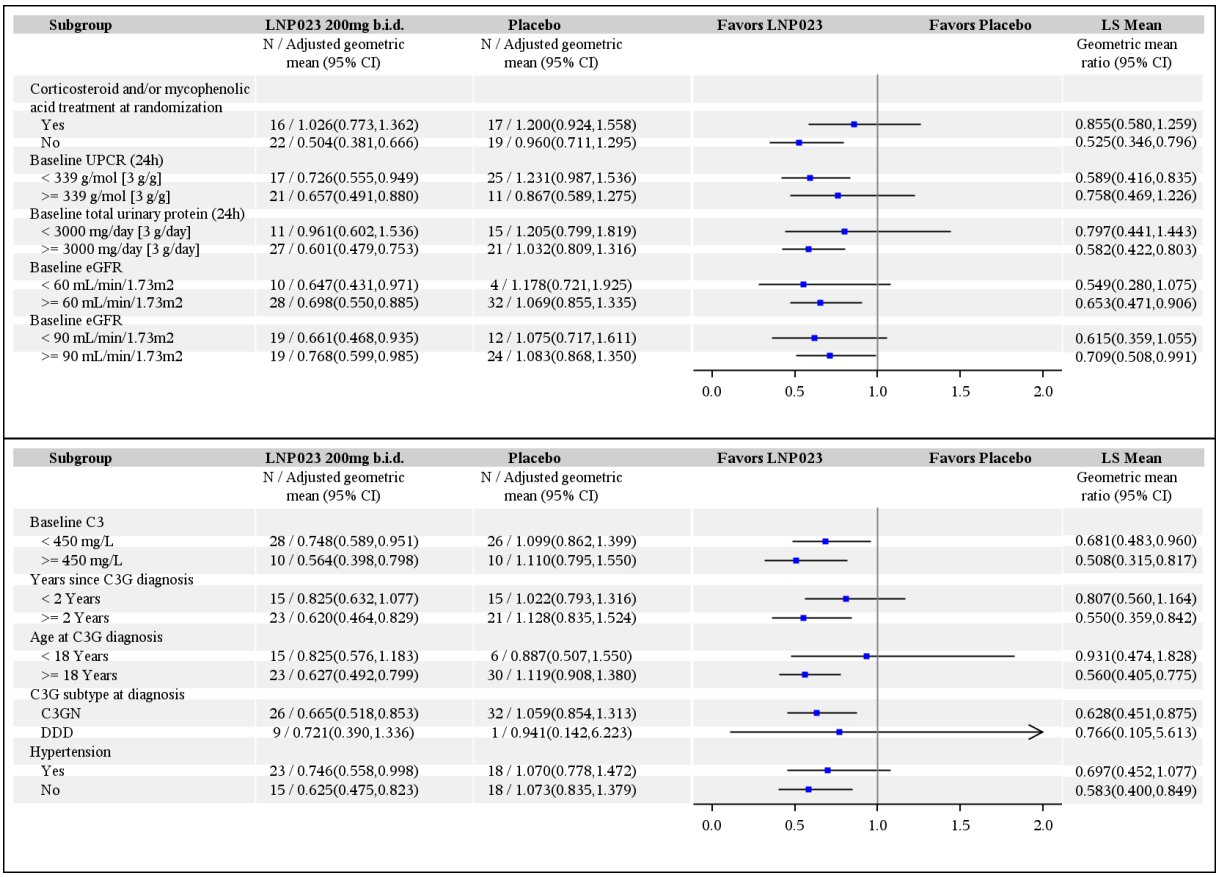


Subgroup analyses for the primary endpoint and for the secondary endpoint change from BL in eGFR

Results of the primary efficacy endpoint in subgroups by demographic factors (age, sex, race) and baseline disease variables (UPCR, eGFR, C3G subtype) are shown in the following Figure 25:

Figure 25: Subgroup analysis of log-transformed ratio to baseline in 24h UPCR (g/g) to 6 months (Full analysis set)





N: number of all participants included in the analysis (with non-missing baseline and covariates).

Log transformed ratio to baseline was analyzed using a MMRM which included treatment, visit, stratification variable as fixed effects, treatment*visit as interaction term and log (baseline UPCR) as covariate, unless the stratification variable was removed per SAP specified strategy.

Table 13: Subgroup analysis of change from baseline to month 6 in eGFR (mL/min/1.73m²) (Full analysis set)

Subgroup	Iptacopan 200 mg b.i.d. N/ adjusted mean (95% CI)	Placebo N/ adjusted mean (95% CI)	LS mean Adjusted mean difference (95% CI)
Baseline 24h UPCR			
< 339 g/mol (3 g/g)	17/ 2.071 (−3.475, 7.617)	25/ 1.061 (−3.511, 5.634)	1.009 (−6.180, 8.198)
≥ 339 g/mol (3 g/g)	21/ 1.091 (−3.010, 5.192)	11/ −5.758 (−11.311, −0.205)	6.849 (−0.059, 13.758)
Baseline eGFR			
< 90 mL/min/1.73m²	19/ −1.346 (−7.096, 4.404)	12/ 0.017 (−7.059, 7.093)	−1.363 (−10.464, 7.738)
≥ 90 mL/min/1.73m²	19/ 2.643 (−1.525, 6.810)	24/ −1.526 (−5.228, 2.176)	4.168 (−1.419, 9.756)
CS and/or MPA at randomization			
Yes	16/ 0.357 (−4.108, 4.822)	17/ 1.489 (−2.734, 5.713)	−1.132 (−7.280, 5.016)
No	22/ 1.916 (−3.119, 6.951)	19/ −2.752 (−8.184, 2.680)	4.668 (−2.769, 12.104)

N: number of all participants included in the analysis (with non-missing baseline and covariates).
CS=corticosteroids, MPA=mycophenolic acids.
Change from baseline in eGFR was analyzed using a MMRM which included treatment, visit, stratification variable as fixed effects, treatment*visit as interaction term and baseline eGFR as covariate, unless the stratification variable was removed per SAP specified strategy.

Supplementary analyses for primary endpoint

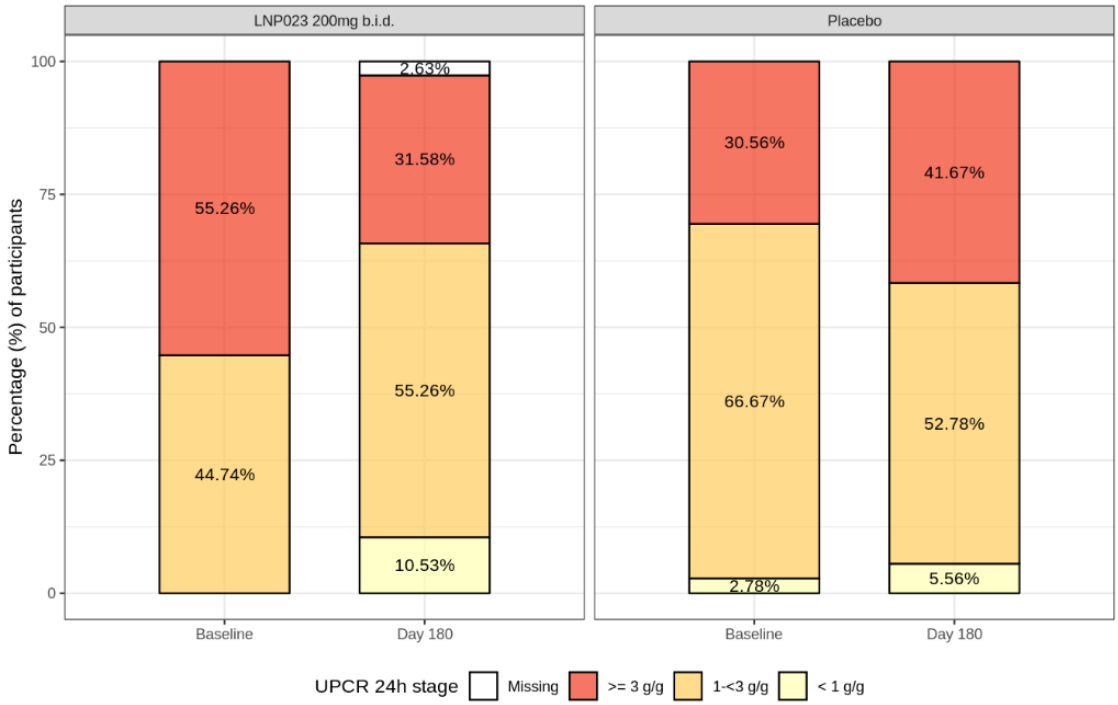
Effects in participants with high level proteinuria

Post-hoc analyses:

The proportion of participants that transitioned from nephrotic range proteinuria (>3 g/g 24h UPCR) to sub-nephrotic range proteinuria (< 3 g/g 24h UPCR) or achieved a 24h UPCR <1 g/g or in the iptacopan arm compared to placebo is as follows:

- In the iptacopan arm, the proportion of participants with nephrotic range proteinuria decreased from 55.3% at baseline to 31.6% at Day 180 compared to an increase of 30.6% at baseline to 41.7% at Day 180 in the placebo group.
- In addition, the proportion of participants that achieved a 24h UPCR < 1 g/g increased from 0 at baseline to 10.5% at day 180 with iptacopan treatment and from 2.8% to 5.6% with placebo.

Figure 26: Proportion of participants with different levels of proteinuria (24h UPCR) up to Day 180 (Full analysis set)



24-hour UPCR from baseline to up to Month 12 (durability of effect)

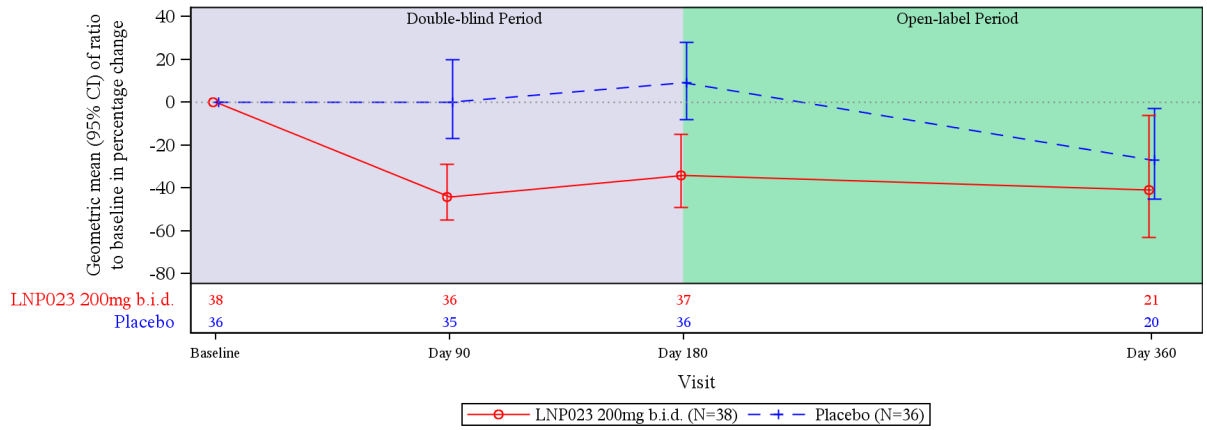
Baseline characteristics, including 24h UPCR and eGFR, for those participants that completed Day 360 of the study (21 iptacopan, 20 placebo) were similar to those of the overall study population.

At Day 180, 24h UPCR (g/g) geometric mean ratios to baseline were 0.66 (95% CI: 0.51, 0.85) in the iptacopan arm and 1.09 (95% CI: 0.92, 1.28) in the placebo arm. At Day 360, 24h UPCR (g/g) geometric mean ratios to baseline were 0.59 (95% CI: 0.37, 0.94) in the iptacopan arm and 0.73 (95% CI: 0.55, 0.97) in the placebo arm.

In the iptacopan arm, the reduction in 24h UPCR at Day 360 was 41% compared to baseline for the 21 out of 38 participants who completed the Day 360 visit at the time of data cut-off.

The reduction of 24h UPCR in participants originally randomized to placebo and who were transitioned to open-label iptacopan at Day 180 (20 out of 36) was 27% at Day 360 compared to the Day 1 baseline.

Figure 27: Plot of geometric mean (95% CI) of ratio to baseline in percentage change of 24h UPCR (g/g) over time by treatment group (Full analysis set)



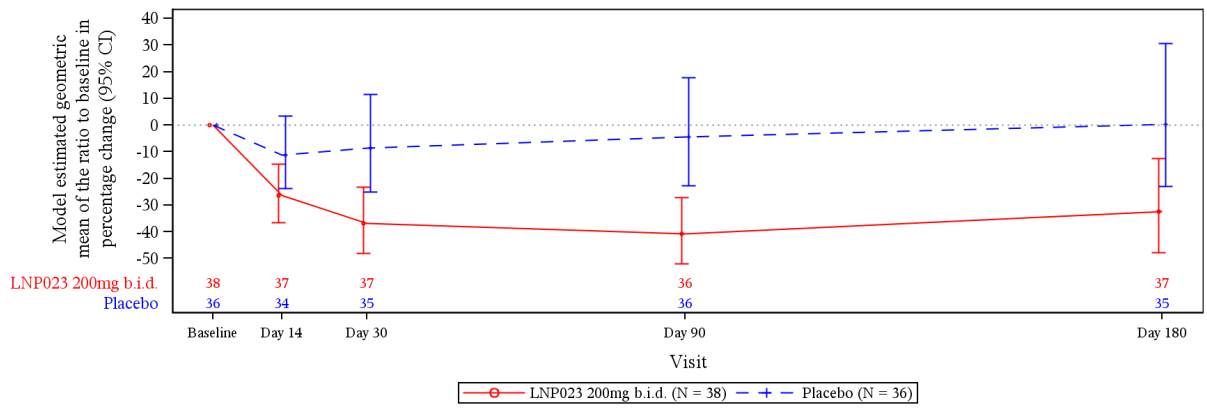
Vertical bars represent 95% confidence intervals.

N=number of participants in full analysis set at each time point shown along the x-axis.

FMV UPCR at 6 months

Results from this supplementary analysis were consistent with analysis of the primary analysis based on 24h UPCR. There was a rapid onset of proteinuria (FMV) reduction from baseline (26.3%) in the iptacopan arm as early as the first visit on Day 14. Proteinuria continued to decrease up to Day 90 and was stable up to Day 180. The percent reduction in FMV UPCR at Day 180 was 32.6% (95% CI: 2.6%, 53.4%, 1-sided p=0.0179) vs. placebo. At Day 180, the geometric means of the ratios to baseline were 0.68 (95% CI: 0.523, 0.874) for the iptacopan arm and 1.00 (95% CI: 0.770, 1.305) for the placebo arm (i.e., adjusted reduction of FMV UPCR from baseline with iptacopan was 32% compared to no change with placebo).

Figure 28: Model estimated geometric mean of the ratio to baseline in percentage change (95% CI) plot of FMV UPCR (g/g) up to month 6 by treatment group (Full analysis set)



Vertical bars represent 95% confidence intervals.

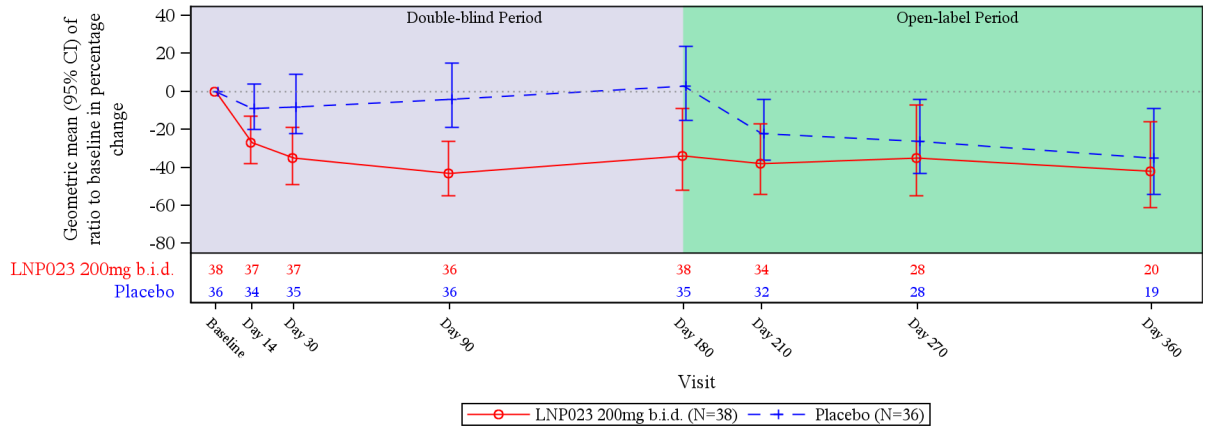
N=number of participants in full analysis set at each time point shown along the x-axis.

Log transformed ratio to baseline was analyzed using a MMRM which included treatment, visit, stratification variable as fixed effects, treatment*visit as interaction term and log (baseline UPCR) as covariate.

FMV urine UPCR from baseline to up to Month 12 (durability of effect)

FMV UPCR results up to 12 months were consistent with results from 24h UPCR. In the iptacopan arm, the reduction in FMV UPCR observed at Day 180 was sustained up to Day 360 (34% and 42% reduction in FMV UPCR compared to baseline at Day 180 (n=38) and Day 360 (n=20), respectively). The reduction of FMV UPCR in participants originally randomized to placebo and who were transitioned to open-label iptacopan at Day 180 (19 out of 36) was 35% at Day 360 compared to the Day 1 baseline. This treatment effect of iptacopan was comparable to the treatment effect of 34% observed after 6 months of double-blind iptacopan treatment.

Figure 29: Plot of geometric mean (95% CI) of ratio to baseline in percentage change of FMV UPCR (g/g) over time by treatment group (Full analysis set)



Vertical bars represent 95% confidence intervals.

N=number of participants in full analysis set at each time point shown along the x-axis.

Secondary endpoints

eGFR

Baseline mean eGFR in the iptacopan and placebo arms was 89.3 and 99.2 mL/min/1.73m^2, respectively. The mean eGFR was 87.1 mL/min/1.73m^2 at baseline and 86.4 mL/min/1.73m^2 at Day 360 in 22 participants in the iptacopan arm who completed the Day 360 visit by the time of data cut-off.

Iptacopan showed a *numerical improvement in eGFR after 6 months of treatment* compared with a decline in eGFR observed in the placebo group. The iptacopan-treated patients had an early increase from baseline in eGFR at Day 14 (+3.5 mL/min/1.73m^2), which stabilized at Day 30 to +1.3 mL/min/1.73m^2, and subsequently remained completely stable at 6 months (+1.3 mL/min/1.73m^2). In comparison, the placebo group showed a stable eGFR for the first 30 days and subsequently declined to a change from baseline of −0.9 mL/min/1.73m^2 at 6 months. The adjusted mean difference between the iptacopan and placebo arms was +2.16 mL/min/1.73m^2 (95% CI: −2.749, 7.061; nominal 1-sided p=0.1945, multiplicity adjusted 1-sided p=0.3241) (numerically in favor of iptacopan).

Table 14: MMRM for change from baseline in eGFR (mL/min/1.73m²) at 6 months in APPEAR-C3G (FAS)

Treatment	N	n	Adjusted mean (95% CI)	Adjusted mean difference (95% CI)	Nominal 1-sided p-value
Iptacopan	38	37	1.295 (−2.136, 4.726)	2.156 (−2.749, 7.061)	0.1945
Placebo	36	36	−0.861 (−4.357, 2.635)		

N: number of all patients included in the analysis (with non-missing baseline and covariates).

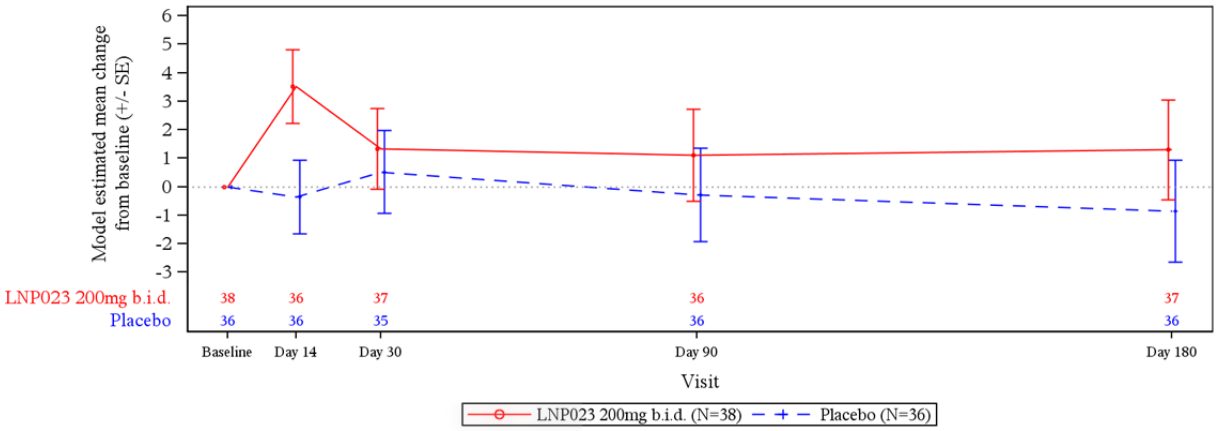
n: number of patients with values non-missing and not imputed as per intercurrent event (I/C) handling strategy at designate visit.

I/Cs handled with the following strategy: values after initiation or intensification of anti-proteinuric therapies were multiply imputed under J2R and MAR for LNP023 and placebo arms, respectively. Treatment discontinuation for any reason was handled with treatment policy strategy.

Change from baseline in eGFR was analyzed using a Mixed Model of Repeated Measures (MMRM) which included treatment, visit, corticosteroid or MPA treatment at randomization (yes vs. no) as fixed effects, treatment*visits as interaction term and baseline eGFR as covariate.

Correlations between visits within patients were modelled using an unstructured covariance matrix.

Figure 30: Model estimated mean change from baseline (± SE) of eGFR (mL/min/1.73m²) by treatment up to month 6 in APPEAR-C3G (FAS)



Vertical bars represent standard error.

N=number of patients in full analysis set at each time point shown along the x-axis.

Change from baseline in eGFR was analyzed using a MMRM which included treatment, visit, stratification variable as fixed effects, treatment*visit as interaction term and baseline eGFR as covariate.

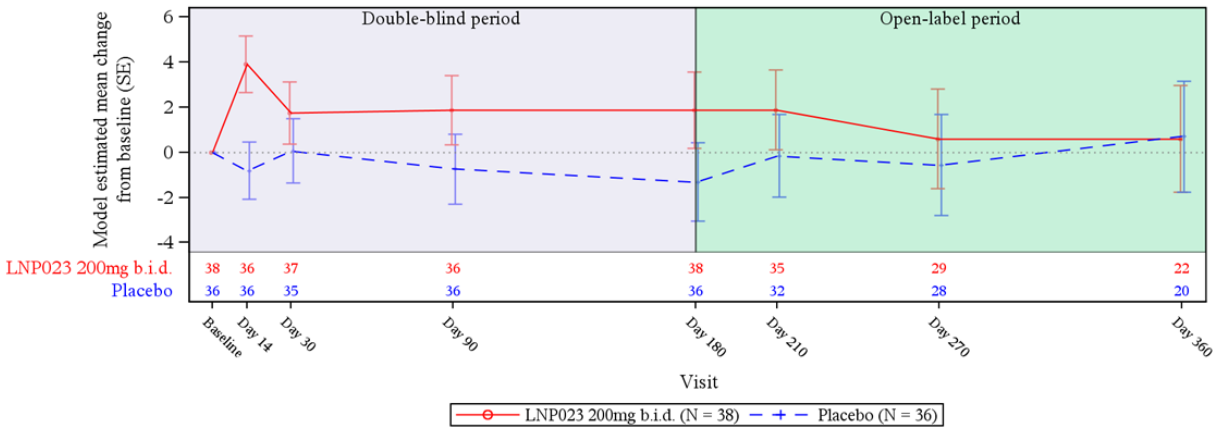
Correlations between visits within patients were modelled using an unstructured covariance matrix.

Post-hoc analysis: analysis of the impact of baseline proteinuria by *including the additional covariate of baseline UPCR* showed consistently *greater separation* of the treatment arms at all timepoints, mainly driven by faster decline of eGFR in the placebo arm compared with the original model, while the iptacopan arm showed stabilization of eGFR at similar magnitude. After adjusting for baseline UPCR, the treatment difference between iptacopan and placebo arms at 6 months increased from +2.16 mL/min/1.73m² (95% CI: −2.749, 7.061) to +3.20 mL/min/1.73m² (95% CI: −1.614, 8.012; nominal 1-sided p=0.0963).

Post-hoc analysis: preliminary eGFR data at 12 months (n=42) *adjusted for baseline UPCR imbalances* indicated that patients who were initially randomized to receive iptacopan showed stable eGFR throughout

the 12 months (change from baseline of +0.59 mL/min/1.73m^2 (95% CI: −4.151, 5.335 at 12 months). For patients switching from placebo to iptacopan during the open-label period, eGFR improved after initiation of iptacopan treatment, reaching a similar level as that in patients randomized to iptacopan (change from baseline of +0.69 mL/min/1.73m^2 (95% CI: −4.221, 5.609) at 12 months).

Figure 31: MMRM mean change from baseline (± SE) of eGFR (mL/min/1.73m2) adjusted for log-transformed baseline 24h UPCR (g/g) by treatment up to month 12 (Full analysis set)



Vertical bars represent standard error.

N=number of participants in full analysis set.

Change from baseline in eGFR was analyzed using a MMRM which included treatment, visit, stratification variable as fixed effects, treatment*visit as interaction term and baseline eGFR as well as log-transformed baseline UPCR as covariate.

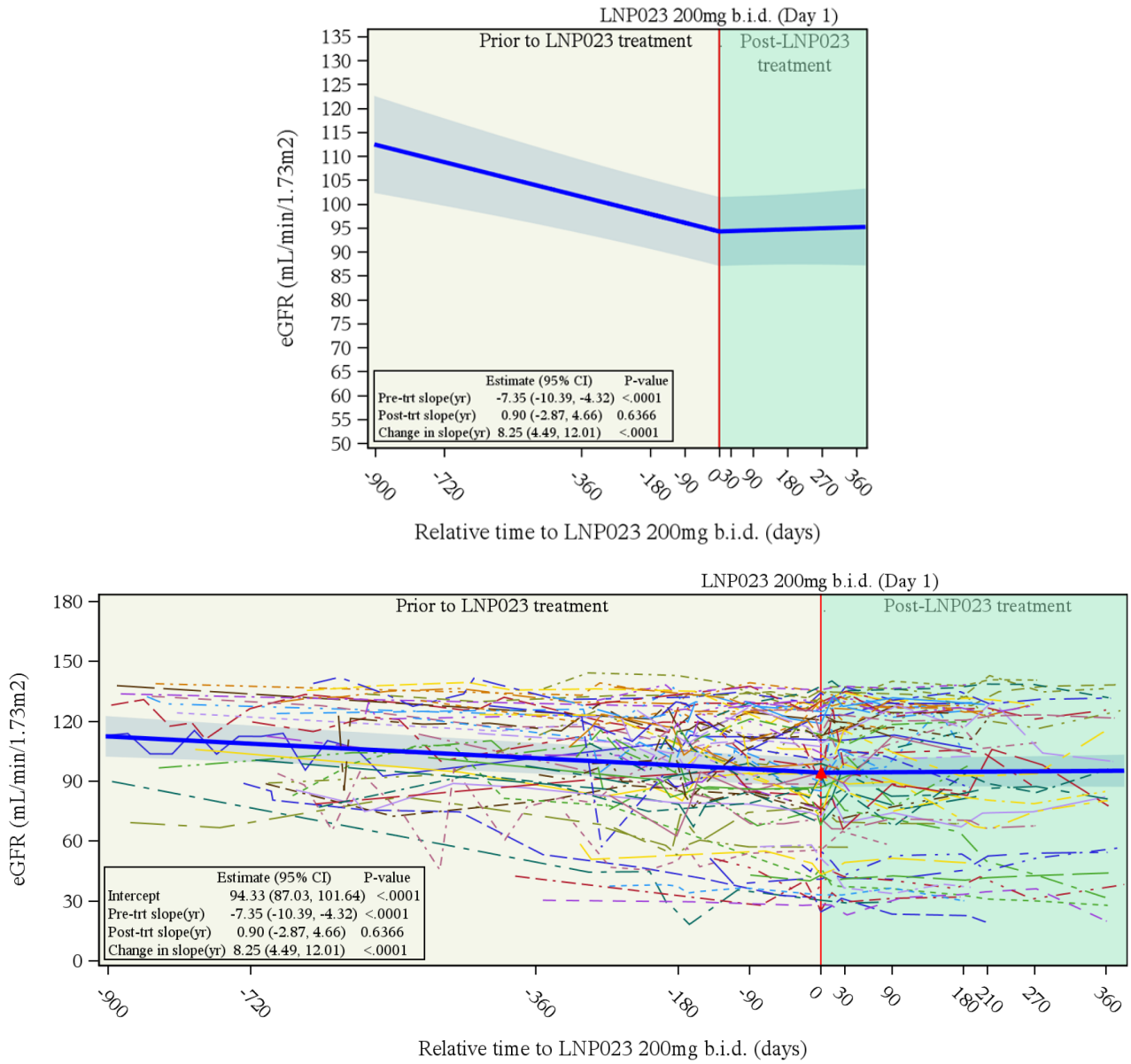
Correlations between visits within participants were modelled using an unstructured covariance matrix.

Additional eGFR data analyses conducted using historical data

Collection of pre-treatment serum creatinine values for up to two years allowed estimation of eGFR slope pre and post iptacopan treatment. The pre-specified slope analyses that included all randomized patients (iptacopan and placebo arms, where time on placebo was incorporated into the pre-treatment period) indicated that the overall APPEAR-C3G population was at risk of fast progression to kidney failure (mean pre-treatment eGFR slope of −7.35 mL/min/1.73m^2/year).

Post-iptacopan treatment up to 12 months, the slope was +0.90 mL/min/1.73m2/year, which equated to a predicted preservation of eGFR of 8.25 mL/min/1.73m2 (2-sided p<0.0001) over one year compared with the scenario where iptacopan had not been initiated and eGFR continued to deteriorate at the pre-treatment rate.

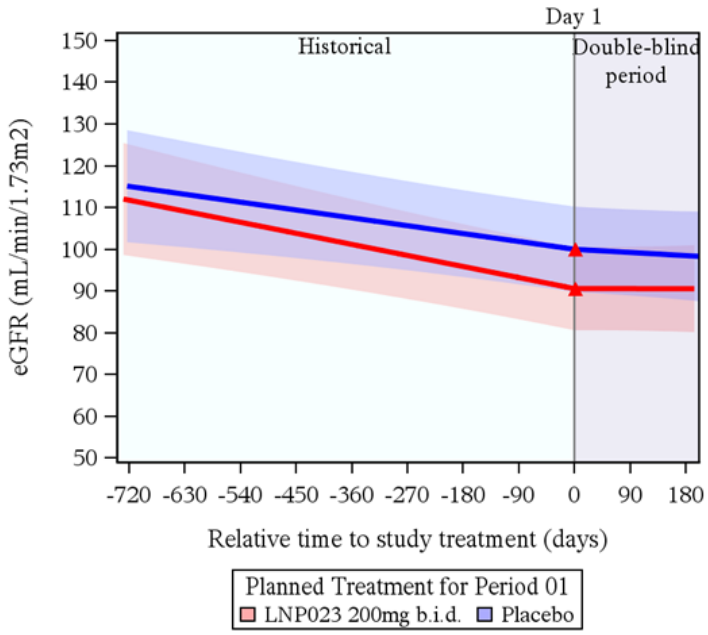
Figure 32: Average predicted eGFR over time pre- and post-iptacopan treatment: all randomized patients from APPEAR-C3G (FAS)



43 of the 74 randomized patients completed the study by the data cut-off date. The remaining 30 patients were ongoing and 1 patient discontinued in the open-label period at the time of data cut-off.
The x-axis represents the relative study day to iptacopan treatment. Thick blue line shows the predicted eGFR over time. The placebo data during the first 6-month treatment period were considered as part of the historical data in the analysis. The grey shaded area represents the 95% CIs.
A generalized linear mixed model, with a common intercept, a pre-treatment slope and a change in the slope following iptacopan treatment was used to predict the pre-post iptacopan change in eGFR over time.
The Spaghetti diagram visualises time courses for all patients and available data points

In post-hoc analysis of eGFR slope by treatment arm, the pre-treatment eGFR decline was steeper in the iptacopan arm than in the placebo arm (−10.75 vs. −7.64 mL/min/1.73m^2/year). During the double-blind treatment period, iptacopan halted the decline of eGFR, resulting in a post-treatment slope of −0.03 mL/min/1.73m2/year and a *slope change of 10.73 mL/min/1.73m2/year* (p=0.0057). In the *placebo* arm, the eGFR continued to decline post-treatment, but at a slower rate than that observed in the historical data (post-treatment slope of −3.08 mL/min/1.73m2/year and *slope change of 4.56 mL/min/1.73m2/year*, p=0.2267).

Figure 33: Predicted eGFR over time by randomized treatment: all patients from APPEAR-C3G (FAS)



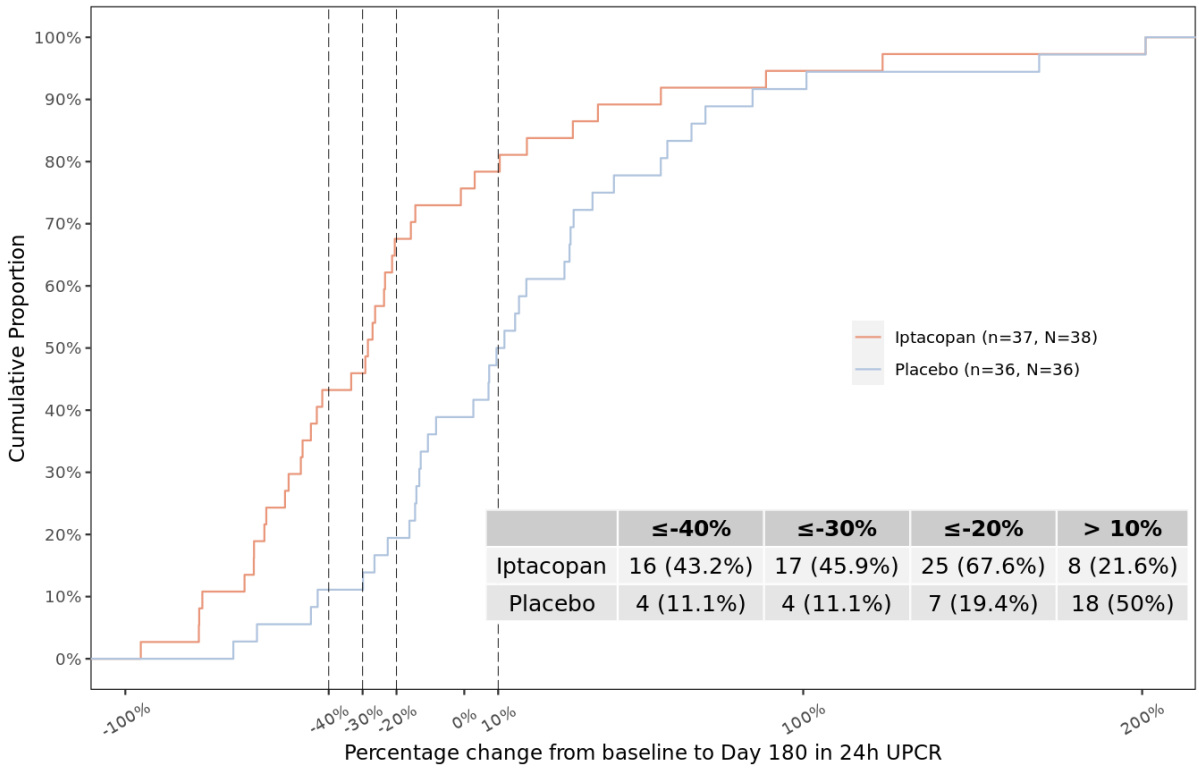
Number of patients in the iptacopan group: 38; Number of patients in the placebo group: 36.
x-axis represents the study analysis day. Thick red and blue lines show the predicted eGFR over time.
A generalized linear mixed model, with an intercept, treatment group effect, a pre-treatment slope, interaction between treatment group and pre-treatment slope, a change in the slope on Day 1 and interaction between treatment group and slope change on Day 1 was used to predict the change in eGFR over time.

Composite renal endpoint (=proportion of patients achieving a ≥50% reduction in proteinuria combined with ≤15% reduction in eGFR)

Treatment with iptacopan for 6 months significantly increased the odds of patients meeting the composite renal endpoint by 7-fold (29.7% of patients in the iptacopan arm vs. 5.6% of patients on placebo; odds ratio=7.15 (95% CI: 1.43, 35.72), adjusted 1-sided p=0.0166).

Additional post-hoc analyses to assess categorical changes in 24-hour UPCR showed that the proportions of patients who met different thresholds of reduction in 24-hour UPCR at 6 months were consistently greater in the iptacopan arm compared with the placebo arm. In the iptacopan arm, 67.6%, 45.9%, 43.2% and 29.7% of patients had UPCR decreases ≥20%, ≥30%, ≥40% and ≥50%, respectively, whereas these thresholds were achieved by only 19.4%, 11.1%, 11.1% and 5.6%, respectively, in the placebo arm. In contrast, the proportion of participants with an increase in 24h UPCR of >10% was 50% in the placebo arm and 21.6% in the iptacopan arm.

Figure 34: Cumulative distribution function plot of 24h UPCR (g/g) change to Day 180 – APPEAR-C3G (Full analysis set)



	≤-40%	≤-30%	≤-20%	> 10%
Iptacopan	16 (43.2%)	17 (45.9%)	25 (67.6%)	8 (21.6%)
Placebo	4 (11.1%)	4 (11.1%)	7 (19.4%)	18 (50%)

The effect of iptacopan on the composite renal endpoint was sustained for up to 12 months, increasing from 29.7% at 6 months to 45.5% of patients in the iptacopan arm with data at 12 months.

For patients switching from placebo to iptacopan in the open-label period, the percentage of patients achieving the composite renal endpoint increased from 5.6% at 6 months to 25% at 12 months, consistent with the results observed in patients randomized to iptacopan during the 6-months double blind period.

The treatment effect of iptacopan on the composite renal endpoint was similar when an additional pre-specified supplementary analysis refining the definition of the composite renal endpoint to incorporate a ≤ *10% rather than 15% reduction* in eGFR was performed. In this analysis, 26.4% of patients met the endpoint criteria at 6 months (OR:6.183; 1-sided p=0.0134).

C3G histologic total activity score

Kidney biopsy was conducted at the beginning and the end of the 6 month double blind period. These biopsies were evaluated by 3 expert nephropathologists who scored them independently.

Kidney biopsy tissue was analyzed from a total of 67 participants of which 33 were in the iptacopan arm and 34 in the placebo arm at Day 180.

The baseline mean (SD) histologic total activity scores were 10.0 (2.55) and 9.0 (2.59) on a scale of 0 (no inflammation) to 21 (high inflammation) in the iptacopan arm and placebo arm, respectively. Iptacopan decreased the C3G total activity score by a mean of −1.95 (95% CI: −2.691, −1.201); however, a mean decrease of −1.11 (95% CI: −1.831, −0.394) was also observed in the placebo arm. The comparison of iptacopan vs. placebo provided a mean difference of −0.83 (95% CI: −1.872, 0.205) at Day 180, which was not statistically significant (nominal 1-sided p=0.0579) (multiplicity adjusted 1-sided p=0.2895).

Table 15: Change from baseline in the histology total activity score (Full analysis set)

Visit	Treatment	N	n	Adjusted mean (95% CI)	Iptacopan 200 mg b.i.d. vs Placebo Adjusted mean difference (95% CI)	1-sided p-value
Day 180	Iptacopan	37	32	−1.946 (−2.691, −1.201)	−0.833 (−1.872, 0.205)	0.0579
	Placebo	36	34	−1.113 (−1.831, −0.394)		

N: Number of all participants included in the analysis (with non-missing baseline and covariates).

n: Number of participants with values non-missing and not imputed as per the intercurrent event (I/C) handling strategy at designate visit.

I/Cs handled with hypothetical strategy: values after the initiation or intensification of anti-proteinuric therapies were multiply imputed using control-based pattern imputation for the iptacopan and placebo groups. Treatment discontinuation for any reason was handled with a treatment policy strategy.

Change from baseline in the histology total activity score was analyzed using an ANCOVA model which included treatment, stratification variable as fixed effects and the baseline total activity score as covariate.

Post-hoc analyses:

The decrease in total activity score was driven by reductions in endocapillary proliferation (adjusted mean difference in iptacopan vs. placebo, −0.44, 95% CI: −0.883, −0.004; 1-sided p=0.0240) and leukocyte infiltration (adjusted mean difference in iptacopan vs. placebo, −0.46, 95% CI: −0.899, −0.022; 1-sided p=0.0199) in the capillaries and mesangium in favor of iptacopan, with little to no difference in change from baseline in iptacopan vs. placebo in the other 5 domains. (membranoproliferative glomerulonephritis morphology, mesangial hypercellularity, crescent formation, fibrinoid necrosis, and interstitial inflammation) of the activity score.

Table 16: Change from baseline to month 6 for individual components of the histologic total activity score (Full analysis set)

Parameter[#]	LNP023 200mg b.i.d. vs Placebo Treatment	N/n	Adjusted mean difference	1-sided p-value
Endocapillary proliferation	Iptacopan	37/33	−0.443	0.0240
	Placebo	36/34		
Leukocyte infiltration	Iptacopan	37/33	−0.461	0.0199
	Placebo	36/34		
Interstitial inflammation	Iptacopan	37/33	0.013	0.7030;
	Placebo	36/34		
Mesangial hypercellularity	Iptacopan	37/33	0.073	0.7942
	Placebo	36/34		
Membranoproliferative morphology	Iptacopan	37/33	0.027	0.6270
	Placebo	36/34		
Crescent formation	Iptacopan	37/33	−0.029	0.1681
	Placebo	36/34		

Parameter[#]	LNP023 200mg b.i.d. vs Placebo Treatment	N/n	Adjusted mean difference	1-sided p-value

N: number of all participants included in the analysis (with non-missing baseline and covariates).

n: number of participants with values non-missing and non-missing baseline at designate visit.

I/Cs handled with a treatment policy strategy: values after the initiation or intensification of anti-proteinuric therapies and initiation of RRT were handled with a treatment policy strategy. Treatment discontinuation for any reason was also handled with a treatment policy strategy.

Change from baseline in the histology total activity score was analyzed using an ANCOVA model which included treatment, stratification variable as fixed effects and the baseline score as covariate.

[#]There was no fibrinoid necrosis identified in the biopsy images from participants in either the iptacopan or placebo arm.

C3 deposit score

Kidney biopsy tissue was analyzed from a total of 67 participants of which 32 were in the iptacopan arm and 35 in the placebo arm at Day 180. Baseline C3 IF intensity was elevated in both the iptacopan (mean (SD) of 9.2 (2.9) on a scale of 0-12) and placebo (mean (SD) 9.6 (2.9)) treatment groups. Iptacopan reduced glomerular C3 deposition, as demonstrated by an adjusted mean difference for iptacopan vs. placebo of −1.88 (95% CI: −3.298, −0.452) in the C3 deposit score at Day 180 (1-sided p=0.0053)

Table 17: Change from baseline in glomerular C3 deposit scores to 6 months (Full analysis set)

Visit	Treatment	N	n	Adjusted mean (95% CI)	Iptacopan 200 mg b.i.d. vs Placebo Adjusted mean difference (95% CI)	1-sided p-value
Day 180	Iptacopan	35	32	−0.781 (−1.811, 0.250)	−1.875 (−3.298, −0.452)	0.0053
	Placebo	36	35	1.094 (0.111, 2.078)		

N: Number of all participants included in the analysis (with non-missing baseline and covariates).

n: Number of participants with values non-missing at designate visit.

I/Cs handled with a treatment policy strategy: values after the initiation or intensification of anti-proteinuric therapies and initiation of RRT were handled with a treatment policy strategy.

Treatment discontinuation for any reason was also handled with a treatment policy strategy.

Change from baseline in C3 deposit score was analyzed using an analysis of covariance (ANCOVA) model which included treatment, corticosteroid or mycophenolic acid treatment at randomization (yes vs. no) as fixed effects and baseline C3 deposit score as covariate.

Biomarker

Information on biomarkers investigated in APPEAR C3G is given in the PD Part of this AR.

Change from baseline in FACIT-Fatigue

Mean (SD) FACIT-Fatigue scores at baseline were in the normal range in the iptacopan arm 42.4 (10.08) and in the placebo arm 41.9 (8.91). Participants taking iptacopan did not show an improvement in fatigue. The adjusted mean difference of change from baseline in the FACIT-Fatigue total score in the iptacopan and placebo arms was −2.60 (1-sided p=0.9310) and remained stable through Day 180.

FACIT-Fatigue total score ranges from 0 (lowest score, worst fatigue) to 52 (maximum score, best possible score indicating no fatigue), the general population norm value has been reported to be 43.5 (Montan et al 2018). Mean (SD) FACIT-Fatigue scores at baseline were near the general population norm (43.5) for both treatment arms: 42.4 (10.08) in the iptacopan arm and 41.9 (8.91) in the placebo arm.

Participants taking iptacopan did not show an improvement in the reduction of fatigue. The adjusted mean difference of change from baseline in the FACIT-Fatigue total score in the iptacopan and placebo arms was −2.60 (95% CI: −6.032, 0.835; nominal 1-sided p=0.9310) (multiplicity adjusted 1-sided p=0.9310) at six months.

Table 18: MMRM analysis of change from baseline in the FACIT-Fatigue total score (Full analysis set)

					Iptacopan 200 mg b.i.d. vs. Placebo	
Visit	Treatment	N	n	Adjusted mean (95% CI)	Adjusted mean diff. (95% CI)	1-sided p-value
Day 14	Iptacopan	36	34	−0.218 (−1.904, 1.468)	−1.788 (−4.247, 0.671)	
	Placebo	31	30	1.570 (−0.239, 3.379)		
Day 30	Iptacopan	36	34	−0.609 (−2.513, 1.295)	−1.865 (−4.646, 0.917)	
	Placebo	31	30	1.255 (−0.789, 3.300)		
Day 90	Iptacopan	36	34	−0.890 (−3.353, 1.573)	−2.820 (−6.414, 0.774)	
	Placebo	31	31	1.930 (−0.701, 4.561)		
Day 180	Iptacopan	36	35	−0.410 (−2.755, 1.935)	−2.598 (−6.032, 0.835)	0.9310
	Placebo	31	31	2.188 (−0.334, 4.711)		

N: Number of all participants included in the analysis (with non-missing baseline and covariates).

n: Number of participants with values non-missing and not imputed as per intercurrent event (I/C) handling strategy at designate visit.
I/Cs handled with the following strategy: values after initiation or intensification of anti-proteinuric therapies were multiply imputed under J2R and MAR for iptacopan and placebo groups, respectively. Treatment discontinuation for any reason was handled with treatment policy strategy.

Change from baseline in the FACIT-Fatigue total score was analyzed using MMRM which included treatment, visit, corticosteroid or mycophenolic acid treatment at randomization (yes vs. no) as fixed effects, treatment*visit as interaction term and the baseline FACIT-Fatigue total score as covariate.

Correlations between visits within participants were modelled using an unstructured covariance matrix.

A responder analysis of the proportion of participants achieving ≥ 5-point improvement in the FACIT-Fatigue total score was performed. A participant was considered a responder if they had at least a 5-point improvement in the FACIT-Fatigue total score from baseline at 6 months. Consistent with the results of change from baseline in FACIT-Fatigue scores, there was no difference in the proportion of participants who achieved ≥ 5-point improvement in the FACIT-Fatigue total score between iptacopan and placebo arms at Day 180 (−0.08, 95% CI: −0.246, 0.084) (p=0.3359).

Other PRO outcome measures

Additional PRO questionnaires applied were the Patient Global Impression of Severity of fatigue (PGIS) score, and the SF-36 v2, and EQ-5D-5L scores.

- SF-36 v2: The SF-36 assessed the Health-Related Quality of Life (HRQoL) of participants. Given the acute nature of this disease, version 2, with a one-week recall period, was used in this study.

- EQ-5D-5L: The EQ-5D-5L is a widely used questionnaire designed to assess health status in adults.

- PGIS: PGIS was pre-specified as an anchor, to calibrate the performance of FACIT-Fatigue in the context of treatment with iptacopan. PGIS is a self-reported instrument asking "How would you rate your overall symptoms of fatigue in the past 7 days?". It was used to understand the overall severity of fatigue experienced by the participants and the clinical meaningfulness of treatment effects experienced during this study.

Similar to what was found with the FACIT-Fatigue analysis, participants in both the iptacopan and placebo arms reported having no symptoms of fatigue or mild fatigue on the *PGIS* at baseline. Throughout the study, the majority of participant's PGIS scores remained stable, supporting that there were no meaningful changes in fatigue during the study. Participant's *SF-36 and EQ-5D score*s at baseline reflected general population normal values and did not show any significant changes throughout the course of the study.

Ancillary analyses

An update of the CSR for the APPEAR-C3G study had been submitted with the responses to the first request for supplementary information. The update contained the final 12-month results; data cut-off 06-May-2024 (last participant last visit for the adult cohort). The update of the CSR is titled

"A multicenter, randomized, double-blind, parallel group, placebo-controlled study to evaluate the efficacy and safety of iptacopan (LNP023) in complement 3 glomerulopathy"; release date: 03-Oct-2024."

Patients

A total of 74 adult C3G patients were randomized to either iptacopan 200 mg b.i.d. (N=38) or placebo (N=36) and all 74 randomized patients completed the 6-month double-blind treatment period at the time of the 6-month primary analysis. **Of the 74 randomized participants, *73 (98.6%) completed the open-label treatment period*.** One participant, who was originally randomized to the placebo arm, discontinued treatment during the open-label period (due to participant decision) and was subsequently lost to follow-up.

Table 19: Participant disposition (Full analysis set)

Disposition/Reason	Iptacopan 200 mg b.i.d. N=38 n (%)	Placebo N=36 n (%)	Total N=74 n (%)
Treated	38 (100)	36 (100)	74 (100)
Not treated	0	0	0
Completed double-blind treatment	36 (94.7)	36 (100)	72 (97.3)
Completed double-blind period	38 (100)	36 (100)	74 (100)
Discontinued from double-blind treatment	2 (5.3)	0	2 (2.7)
Reason for discontinuation			
Subject decision	1 (2.6)	0	1 (1.4)
Technical problems	1 (2.6)	0	1 (1.4)
Completed open-label treatment	38 (100)	35 (97.2)	73 (98.6)
Discontinued from open-label treatment	0	1 (2.8)	1 (1.4)
Reason for discontinuation			
Subject decision	0	1 (2.8)	1 (1.4)
Completed study	38 (100)	35 (97.2)	73 (98.6)
Discontinued study	0	1 (2.8)	1 (1.4)
Reason for discontinuation			
Lost to follow-up	0	1 (2.8)	1 (1.4)

Overview of changes of 12-month results between the originally submitted CSR and the updated CSR

Table 20: Comparison of efficacy results at 12 months between the 6-month and 12-month CSRs (Full Analysis Set)

Endpoint	Criteria	6-month CSR Result	12-month CSR Result
24 h UPCR log transformed ratio to baseline at 12 months			
24h UPCR (g/g) at Day 360	Iptacopan geometric mean ratio (95% CI) (n)	0.59 (0.37, 0.94) (n=21)	0.**60** (0.**45**, 0.**80**) (n=**37**)
	Placebo geometric mean ratio (95% CI) (N)	0.73 (0.55, 0.97) (n=20)	0.73 (0.5**8**, 0.9**2**) (n=**34**)
	Source	[Study B12301 6-month-Table 14.2-1.3a]	[Study B12301 12-month-Table 14.2-1.3a]
Proportion of patients with nephrotic range proteinuria ≥3 g/g			
Proportion of patients with 24h UPCR ≥3 g/g at Day 180 and Day 360	Iptacopan – %		
	Baseline	55.3	No change
	Day 180	31.6	No change
	Day 360	Not available	36.8
	Placebo - %		
	Baseline	30.6	No change
	Day 180	41.7	No change
	Day 360	Not available	27.8
	Source	[Study B12301 6-month-Figure 11-6]	[Study B12301-Figure 11-7]

Endpoint	Criteria	6-month CSR Result	12-month CSR Result
Composite renal endpoint at 12 months			
Composite renal endpoint at Day 360	Iptacopan – n/m (%)	10/22 (45.5)	**17/38 (44.7)**
	Placebo – n/m (%)	5/20 (25.0)	**8/34 (23.5)**
	Source	[Study B12301 6-month-Figure 11-19]	[Study B12301 12-month-Figure 11-19]
eGFR change from baseline at 12 months			
eGFR change from baseline (mL/min/1.73m^2) at Day 360	Iptacopan adjusted mean (95% CI) (n)	0.122 (−4.544, 4.787) (n=22)	0.**439** (−**3.762**, 4.**641**) (n=**38**)
	Placebo adjusted mean (95% CI) (n)	1.209 (−3.620, 6.038) (n=20)	1.**152** (−3.**222**, **5.526**) (n=**34**)
	Source	[Study B12301 6-month-Table 14.2-3.6.1]	[Study B12301 12-month-Table 11-7]
Pre-specified eGFR slope analysis for overall population at 12 months			
Overall population - eGFR slope (mL/min/1.73m^2/ year) up to Day 360[1]	n	43	**74**
	Pre-iptacopan eGFR slope (95% CI)	−7.35 (−10.39, −4.32)	−7.**57** (−10.**57**, −4.**56**)
	Post-iptacopan eGFR slope (95% CI)	+0.90 (−2.87, 4.66)	+**1.44** (−2.**18**, **5.06**)
	Change in eGFR slope (95% CI)	+8.25	+**9.01**
	2-sided p-value	<0.0001	<0.0001
	Source	[Study B12301 6-month-Figure 11-14]	[Study B12301 12-month-Table 14.2-16.6.1]
Post-hoc eGFR slope analysis for the iptacopan arm at 12 months			
Iptacopan arm - eGFR slope (mL/min/1.73m^2/ year) up to Day 360[2]	n	Not available	38
	Pre-iptacopan eGFR slope (95% CI)		−10.68 (−15.85, −5.51)
	Post-iptacopan eGFR slope (95% CI)		−1.26 (−6.40, 3.89)
	Change in eGFR slope (95% CI)		+9.42 (4.87, 13.98)
	2-sided p-value		0.0002
	Source		[Study B12301 12-month-Table 14.2-16.5.1]
Exploratory endpoint: serum complement C3			
Serum C3 (mg/L) ratio to baseline at Day 360	Iptacopan geometric mean ratio (95% CI) (n)	3.02 (2.22, 4.12) (n=22)	3.**23** (2.**59**, 4.**04**) (n=**38**)
	Placebo geometric mean ratio (95% CI) (n)	3.01 (2.35, 3.85) (n=20)	**2.96** (2.**46**, 3.**57**) (n=**34**)
	Source	[Study B12301 6-month-Table 14.2-7.2]	[Study B12301 12-month-Table 14.2-7.2]
Exploratory endpoint: serum Wieslab assay			
Serum Wieslab assay (%) ratio to baseline at Day 360	Iptacopan geometric mean ratio (95% CI) (n)	0.59 (0.41, 0.84) (n=18)	0.5**8** (0.4**5**, 0.**76**) (n=**31**)
	Placebo geometric mean ratio (95% CI) (n)	0.67 (0.49, 0.92) (n=17)	0.6**0** (0.4**7**, 0.**77**) (n=**33**)
	Source	[Study B12301 6-month-Table 14.2-7.2]	[Study B12301 12-month-Table 14.2-7.2]
Exploratory endpoint: plasma Bb			
Plasma Bb (ng/mL) ratio to baseline at Day 360	Iptacopan geometric mean ratio (95% CI) (n)	0.95 (0.79, 1.15) (n=18)	**1.02** (0.**88**, 1.1**8**) (n=**31**)
	Placebo geometric mean ratio (95% CI) (n)	1.16 (1.02, 1.33) (n=17)	1.16 (1.0**3**, 1.3**0**) (n=**33**)

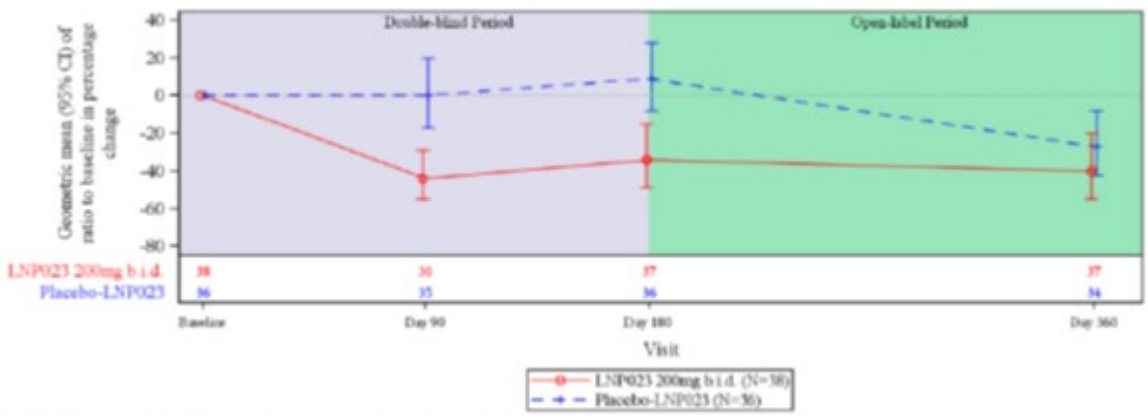
Endpoint	Criteria	6-month CSR Result	12-month CSR Result
	Source	[Study B12301 6-month-Table 14.2-7.2]	[Study B12301 12-month-Table 14.2-7.2]
Exploratory endpoint: plasma sC5b-9			
Plasma sC5b-9 (ng/mL) ratio to baseline at Day 360	Iptacopan geometric mean ratio (95% CI) (n)	0.33 (0.24, 0.46) (n=16)	0.33 (0.2**6**, 0.4**2**) (n=**31**)
	Placebo geometric mean ratio (95% CI) (n)	0.39 (0.29, 0.51) (n=15)	0.3**3** (0.2**8**, 0.**39**) (n=**33**)
	Source	[Study B12301 6-month-Table 14.2-7.2]	[Study B12301 12-month-Table 14.2-7.2]
Exploratory endpoint: urinary sC5b-9/creatinine			
Urinary sC5b-9/ creatinine (pg/nmol) ratio to baseline at Day 360	Iptacopan geometric mean ratio (95% CI) (n)	0.19 (0.08, 0.45) (n=17)	0.1**6** (0.0**9**, 0.**29**) (n=**30**)
	Placebo geometric mean ratio (95% CI) (n)	0.18 (0.08, 0.39) (n=15)	0.1**5** (0.08, 0.**27**) (n=**30**)
	Source	[Study B12301 6-month-Table 14.2-7.2]	[Study B12301 12-month-Table 14.2-7.2]

[1] All 74 randomized participants included in eGFR slope analysis. For participants randomized to placebo, eGFR data collected during the double-blind period were added to the Screening/run-in and historical data, generating a total of 2.5 years of eGFR data prior to commencing iptacopan. The eGFR data post-iptacopan treatment in the overall population included data from double-blind and open-label periods for participants in the iptacopan arm and data from open-label study period for participants in the placebo arm.

[2] Analysis included only 38 study participants randomized to iptacopan (to evaluate participants with 12 months exposure to iptacopan).

-The iptacopan arm showed a sustained reduction of **40%** in 24h UPCR at Day 360, which is consistent with the 41% reduction reported previously. The placebo arm showed the same reduction of 27% between baseline and Day 360 as reported in the 6-month CSR, and a reduction of 31% between the initiation of iptacopan at Day 180 and Day 360.

Figure 35: Plot of geometric mean of the ratio to baseline in percentage change (95% CI) of 24h UPCR (g/g) up to Month 12 by treatment group (Full analysis set)

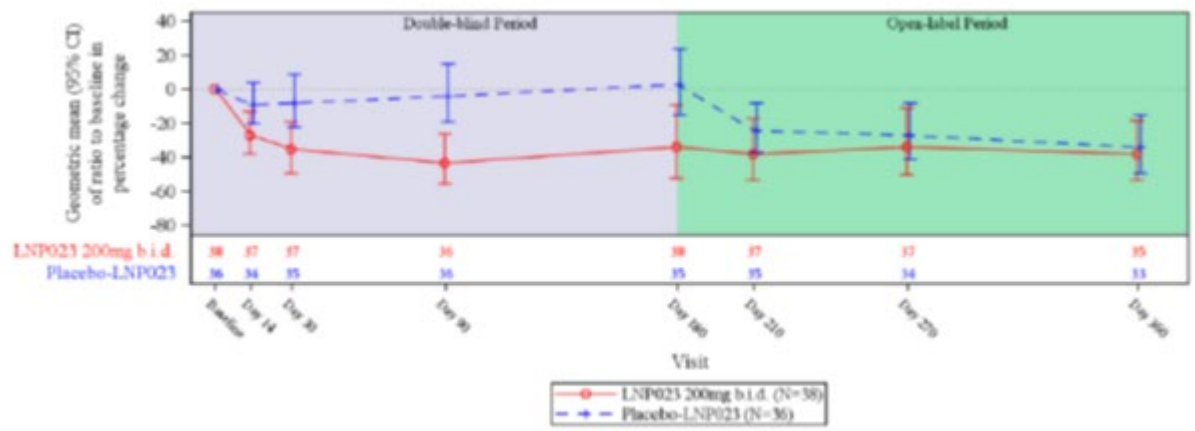


Vertical bars represent 95% confidence intervals.
N: number of all participants included in the analysis.

- The reduction in geometric mean of FMV UPCR in participants randomized to the iptacopan arm was 34% at Day 180 (n=38) and this was sustained up to Day 360 (n=35) with a 38% reduction compared to baseline. The reduction in geometric mean of FMV UPCR in participants originally randomized to placebo and who were transitioned to open-label iptacopan at Day 180, was 34% at Day 360 (n=33) compared to the Day 1 baseline. A rapid reduction of FMV UPCR was observed in the iptacopan arm (Day 1 to Day 14)

and was replicated in the placebo arm (Day 180 to Day 210) after initiation of iptacopan at Day 180.

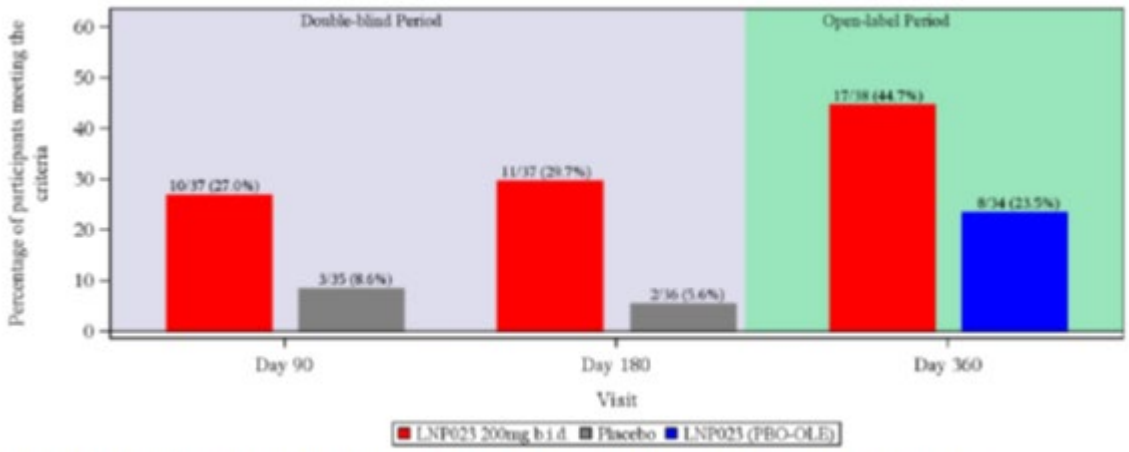
Figure 36: Plot of geometric mean of the ratio to baseline in percentage change of FMV UPCR (g/g) up to Month 12 by treatment group (Full analysis set)



Vertical bars represent 95% confidence intervals.
N=number of participants in full analysis set.

-The proportion of patients in the iptacopan arm (**44.7%**) who achieved the composite renal endpoint at 12 months was similar to that reported in the 6-month CSR (45.5%). After initiation of iptacopan, **23.5%** (previously reported 12 month results 25.0%) of participants in the placebo arm achieved the composite renal endpoint, similar to the effect seen for iptacopan in the double-blind period.

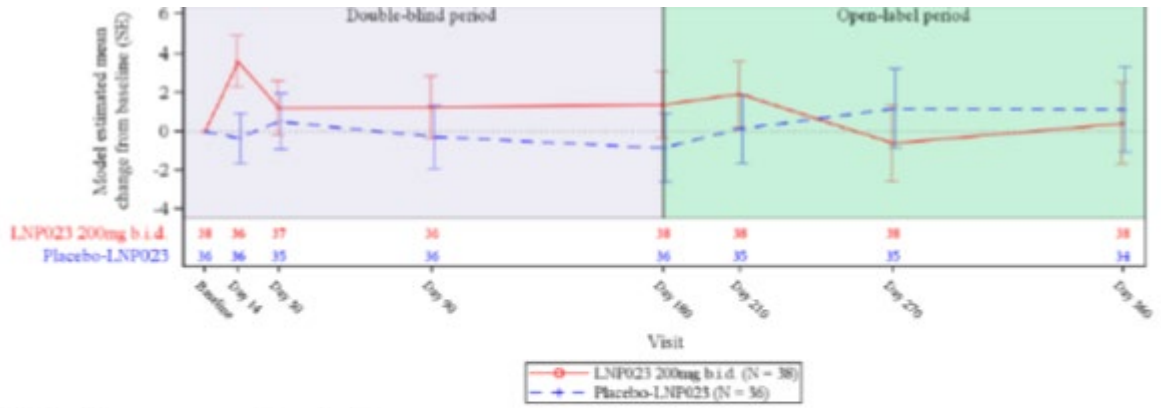
Figure 37: Bar chart of the proportion of participants who achieved composite renal endpoint up to Month 12 by treatment group (Full analysis set)



Note that participants in placebo arm were all receiving iptacopan at the time at Day 360.

-Results from the 12-month data for *eGFR change from baseline* showed less iptacopan induced amelioration of eGFR decline compared to the data in the originally submitted CSR in the Iptacopan arm and a largely unchanged effect in the placebo arm: Iptacopan adjusted mean (95% CI):*originally submitted CSR* 0.122 (−4.544, 4.787) (n=22); *updated CSR* **0.439** (−3.762, 4.641) (n=38).
Placebo adjusted mean (95% CI): *originally submitted CSR* 1.209 (−3.620, 6.038) (n=20); *updated CSR* **1.152** (−3.222, 5.526) (n=34).

Figure 38: Plot of model estimated mean change from baseline (± SE) of eGFR (mL/min/1.73m^2) up to Month 12 by treatment group (Full analysis set)



Vertical bars represent standard error.

N=number of participants in full analysis set.

Change from baseline in eGFR was analyzed using a MMRM which included treatment, visit, stratification variable as fixed effects, treatment*visit as an interaction term and baseline eGFR as a covariate.

Correlations between visits within participants were modelled using an unstructured covariance matrix.

Table 21: Mixed model with repeated measures (MMRM) analysis of change from baseline in eGFR (mL/min/1.73m^2) up to Month 12 (Full analysis set)

				Iptacopan 200 mg b.i.d. vs Placebo	
Visit	Treatment	N	n	Adjusted mean [SE] (95% CI)	Adjusted mean difference (95% CI)
Day 14	Iptacopan	38	36	3.598 [1.299] (1.008, 6.188)	3.944 (0.267, 7.621)
	Placebo	36	36	−0.346 [1.300] (−2.939, 2.247)	
Day 30	Iptacopan	38	37	1.209 [1.416] (−1.615, 4.033)	0.676 (−3.376, 4.728)
	Placebo	36	35	0.532 [1.450] (−2.361, 3.425)	
Day 90	Iptacopan	38	36	1.254 [1.610] (−1.956, 4.463)	1.528 (−3.048, 6.104)
	Placebo	36	36	−0.274 [1.630] (−3.525, 2.977)	
Day 180	Iptacopan	38	38	1.382 [1.723] (−2.052, 4.817)	2.230 (−2.700, 7.160)
	Placebo	36	36	−0.848 [1.770] (−4.375, 2.680)	
Day 210	Iptacopan	38	38	1.928 [1.706] (−1.473, 5.330)	
	Placebo	36	35	0.136 [1.764] (−3.380, 3.652)	
Day 270	Iptacopan	38	38	−0.605 [1.981] (−4.556, 3.346)	
	Placebo	36	35	1.184 [2.046] (−2.897, 5.264)	
Day 360	Iptacopan	38	38	0.439 [2.106] (−3.762, 4.641)	
	Placebo	36	34	1.152 [2.194] (−3.222, 5.526)	

N: number of all participants included in the analysis (with non-missing baseline and covariates).

n: number of participants with values non-missing and non-missing baseline at the designated visit.

I/Cs handled with the following strategy: values after the initiation or intensification of anti-proteinuric therapies, initiation of RRT, and treatment discontinuation for any reason were handled with a treatment policy strategy.

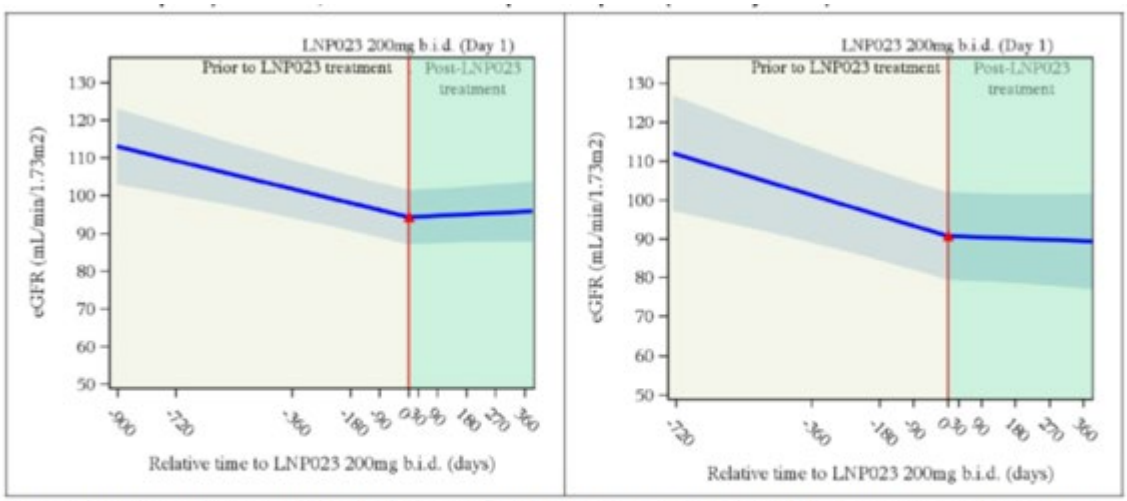
Change from baseline in eGFR was analyzed using all observed data via an MMRM which included treatment, visit, and stratification variable as fixed effects, treatment*visit as an interaction term, and baseline eGFR as a covariate.

Correlations between visits within participants were modelled using an unstructured covariance matrix.

The pre-specified eGFR slope analysis appeared to show stabilization of eGFR over 12 months in the overall population. The additional eGFR data collected between the 6-month and 12-month analyses (based on 43 and 74 patients, respectively) resulted in an update to the eGFR slope change from +8.25 to **+9.01** mL/min/1.73m^2/year (updated figures: pre-treatment slope -7.57, post-treatment slope 1.44 mL/min/1.73m^2).

An additional post-hoc eGFR slope analysis was conducted in the 12-month CSR evaluating only patients randomized to iptacopan to have a pool of patient with 12 months of treatment (no such analysis was performed in the previous CSR). The change in eGFR slope was **+9.42** mL/min/1.73m^2 over one year compared to the pre-iptacopan treatment period (pre-treatment slope -10.68, post-treatment slope -1.26 ml/min/1.73m^2).

Figure 39: eGFR slope change overall (left panel*) and eGFR slope change of participants randomized to iptacopan (right panel): historical, double-blind and open-label period (full analysis set)



Number of participants of iptacopan 200 mg b.i.d. (Overall): 74 (left panel). Number of participants in the iptacopan group: 38 (right panel).
x-axis represents the relative study day to iptacopan treatment. Thick blue line shows the predicted eGFR over time; the shaded band is a pointwise 95% confidence interval.
*The placebo data during the first 6-month treatment period were considered as part of the historical data in the analysis.
eGFR slopes per year were analyzed using a linear mixed effects model including time (analysis day before or after change point (Day 1 of iptacopan treatment)) as a continuous covariate, participant-level intercept and slope (time) as random effects.

There were minor changes to complement biomarkers (serum C3, serum Wieslab, plasma Bb, plasma sC5b-9, urinary SC5b-9/creatinine) at 12 months due to the additional data collected from the open-label period. The final complement biomarker results showed inhibition of AP over the entire study period.

Summary of main study

The following Table 22 summarises the efficacy results from APPEAR-C3G supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22: Summary of Efficacy for trial CLNP023B12301 (APPEAR-C3G)

Title: A multicenter, randomized, double-blind, parallel group, placebo-controlled study to evaluate the efficacy and safety of iptacopan (LNP023) in Complement 3 Glomerulopathy	
Study identifier	Protocol number: CLNP023B12301 EudraCT number: 2020-004589-21

Design	This study was a multicenter, randomized, double-blind, parallel group, placebo-controlled study to evaluate the efficacy and safety of iptacopan in adult patients with C3G. The study comprised a screening/run-in period, a treatment period (including a 6-month double-blind treatment part and a 6-month open-label treatment part), and a 30-day Safety follow-up period (or optionally, transition to an open-label extension study). 74 adult participants were randomized in the study. Half of the participants (n=38) received iptacopan 200 mg b.i.d. as blinded treatment for 6 months followed by 6 months of open-label iptacopan 200 mg b.i.d. The other half of the participants (n=36) received placebo b.i.d. as blinded treatment for 6 months followed by 6 months of open-label iptacopan 200 mg b.i.d. All patients received supportive care with a maximally tolerated dose of ACEIs/ARBs. Randomization was stratified by corticosteroids (CS) and/or mycophenolic acid (MPA) treatment at randomization (yes vs. no). An independent cohort for adolescent participants (aged 12-17 years) with C3G is still ongoing in this study and is not reported in these results.		
	Duration of Screening/run-in period: Duration of double-blind treatment period: Duration of the open-label treatment period: Duration of safety period:		90 days 180 days 180 days 30 days (or optionally, transition to an open-label extension study).
Hypothesis	Superiority		
Treatment groups	Iptacopan:		200 mg b.i.d. oral use for 360 days. 38 participants randomized.
	Placebo/iptacopan:		Placebo oral use for 180 days followed by iptacopan 200 mg b.i.d. oral use for 180 days. 36 participants randomized.
Endpoints and definitions	Primary Endpoint	Log-transformed ratio to baseline in UPCR (sampled from a 24-hour urine collection) at 6 months, reported as difference in percentage change from baseline.	The primary objective was to demonstrate the superiority of iptacopan compared to placebo in reducing proteinuria at 6 months of treatment.
	Key secondary Endpoint	Change from baseline in eGFR at 6 months.	To demonstrate the superiority of iptacopan vs. placebo in improving eGFR.

	Key secondary Endpoint	Proportion of participants achieving the composite renal endpoint at 6 months defined as: (1) a stable or improved eGFR compared to the baseline visit (≤15% reduction in eGFR), and (2) a ≥50% reduction in UPCR compared to the baseline at the 6-month time point. Initiation of treatment with any complement pathway modifying agent or initiation/intensification of corticosteroid or immunosuppressant or renal replacement therapy automatically designated the participant as not meeting the endpoint.	To demonstrate the superiority of iptacopan vs. placebo in the proportion of participants who achieved the composite renal endpoint.
	Key secondary Endpoint	Change from baseline in disease total activity score on kidney biopsy at 6 months.	To demonstrate the effect of iptacopan vs placebo in reducing glomerular inflammation in the kidney.
	Key other Endpoint	Change from baseline in Glomerular C3 deposition on kidney biopsy at 6 months.	To evaluate the effect of iptacopan compared to placebo on glomerular C3 deposition.
	Key other Endpoint	Change in annualized eGFR slope from pre-iptacopan treatment to post-iptacopan treatment initiation after 12 months.	To evaluate the change in eGFR slope prior to iptacopan initiation vs post iptacopan initiation.
Database lock	30-May-2024		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set (FAS): all randomised patients. Time point: Between Day 1 to Day 180 for all endpoints except eGFR slope pre-iptacopan (up to 2.5 years prior to iptacopan initiation) and post-iptacopan initiation (up to 12 months).		
Descriptive statistics and estimate variability	Treatment group:	**Iptacopan**	**Placebo**
	Number of subjects:	38	36

	Percent change from baseline in 24-hour UPCR (sampled from a 24-hour urine collection) at 6 months. Percentage change converted from geometric mean ratio:	-30.2%	+7.6%
	95% CI:	(-42.8%, -14.8%)	(-11.9%, 31.2%)
	Change from baseline in eGFR (ml/min/1.73m^2) at 6 months. Least square mean:	1.295	-0.861
	95% CI:	(-2.136, 4.726)	(-4.357, 2.635)
	Composite renal endpoint. Proportion of participants meeting composite renal endpoint at month 6. Marginal proportion:	29.0%	5.7%
	95% CI:	(14.9%, 43.1%)	(-1.9%, 13.4%)[#]
	Change from baseline in disease total activity score in a renal biopsy at 6 months. Least square mean:	-1.946	-1.113
	95% CI:	(-2.691, -1.201)	(-1.831, -0.394)
	Change from baseline to month 6 in histology C3 deposit score. Least square mean:	-0.781	1.094
	95% CI:	(-1.811, 0.250)	(0.111, 2.078)
	eGFR slope (ml/min/1.73m^2/year) pre- vs. post-iptacopan initiation. Annualized eGFR slope:	Historical slope pre-iptacopan -7.57	Post-iptacopan 1.44
	95% CI:	(−10.57, −4.56)	(−2.18, 5.06)

		Comparison groups	**Iptacopan vs. placebo**
Effect estimate per comparison	Percent change from baseline in UPCR (sampled from a 24-hour urine collection) at 6 months.	Relative % reduction; Mixed Model for Repeated Measures (MMRM):	35.1%
		95% CI:	(13.8%, 51.1%)
		One-sided p-value:	0.0014*

	Change from baseline in eGFR (ml/min/1.73m^2) at 6 months.	Difference in least square means; Mixed Model for Repeated Measures (MMRM):	+2.156
		95% CI:	(-2.749, 7.061)
		One-sided p-value:	0.3241
	Proportion of participants meeting composite renal endpoint at month 6	Odds ratio; logistic regression:	7.145
		95% CI:	(1.429, 35.723)
		One-sided p-value:	0.0166*
	Change from baseline in histology disease total activity score in a renal biopsy at 6 months.	Difference in least square means; analysis of covariance (ANCOVA):	-0.833
		95% CI:	(-1.872, 0.205)
		One-sided p-value:	0.2895
	Change from baseline to month 6 in histology C3 deposit score	Difference in least square mean; analysis of covariance (ANCOVA):	-1.875
		95% CI:	(-3.298, -0.452)
		Nominal one-sided p-value:	0.0053
	eGFR slope (ml/min/1.73m^2/year) pre- vs. post-iptacopan initiation	Comparison groups:	pre- iptacopan vs. post-iptacopan initiation
		Change in eGFR slope; Linear mixed effects model (LMM):	+9.01
		95% CI:	(5.43, 12.60)
		Nominal 2-sided p-value:	<0.0001
Notes	* Significant p-values were determined per the following multiplicity adjustment scheme. The hypotheses associated with the secondary endpoints would only be tested if the null hypothesis for the primary endpoint was rejected. All secondary endpoints were tested following the pre-defined scheme for multiplicity adjustment in order to control Type I error rate. # The lower bound of the confidence interval was negative due to use of the normal approximation for calculating the confidence interval when the proportion of placebo participants achieving the composite renal endpoint was close to zero.		

Supportive studies

Two open-label non-randomized single-arm studies provide supportive evidence:

- The completed phase 2 Study CLNP023X2202 (Study X2202) in patients with C3G or recurrent C3G (*submitted and assessed during the initial MAA and described in the **PD part of this report**)*

- The ongoing roll-over Phase 3b extension Study (Study B12001B). Patients who completed Studies X2202 and the APPEAR-C3G study were eligible to enter the roll-over extension protocol (REP) study B12001B. The *interim analysis report submitted with this application* did include results up to 30 months from patients who transitioned from study X2202. At time of submission, no results were available for the 35 (out of 74 patients) patients who transitioned from the APPEAR-C3G study into the open-label extension.

Extension study (CLNP023B12001B, *ongoing*)

Study title: An open-label, non-randomized extension study to evaluate the long-term efficacy, safety and tolerability of iptacopan in subjects with C3 glomerulopathy, *30-month interim analysis*.

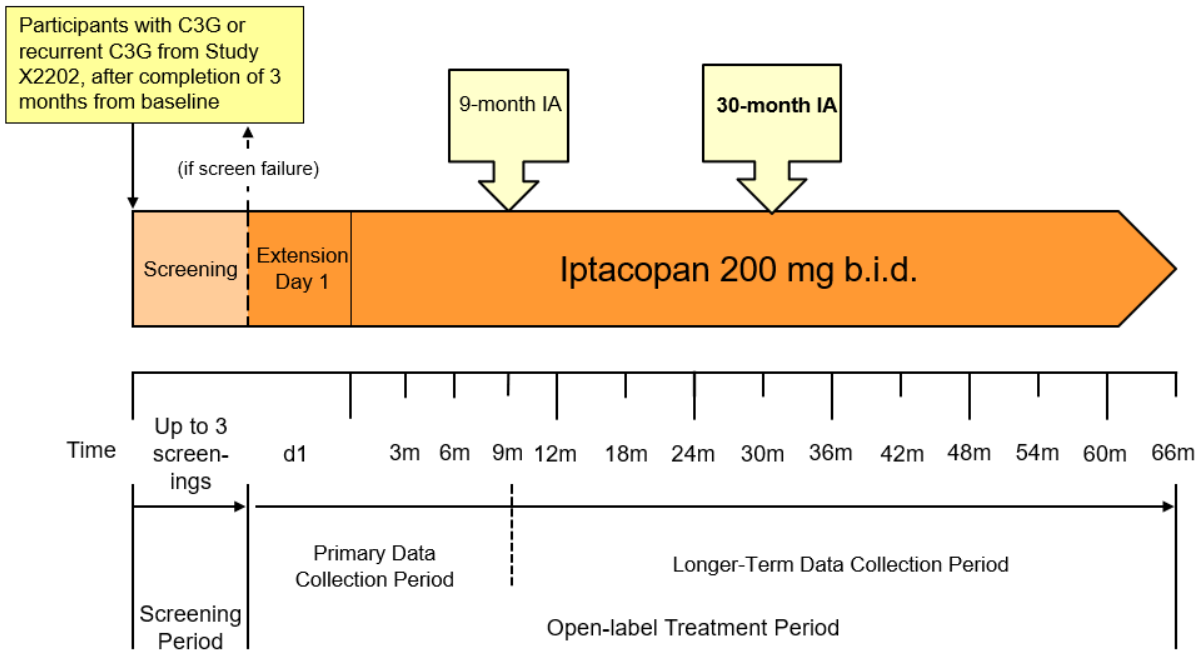
Test drug/investigational product: Iptacopan

Indication studied: C3 glomerulopathy

Study initiation date: 03-Oct-2019 (first subject first visit)

Data cut-off date: 01-Oct-2023

Study design for participants entering Study B12001B from study X2202



Primary endpoints

1. **Cohort A:** The number and percentage of participants meeting the requirements of the *3-component composite renal endpoint* at the 9-month visit in this extension study.
2. **Cohort B:** Change from baseline in the *C3 Deposit Score* (based on immunofluorescence microscopy) compared to baseline at the 6- to 9-month visit in this extension study.

3-component composite renal endpoint definition (primary endpoint for Cohort A):

A participant was considered to have met the criteria for composite renal endpoint if they fulfilled the criteria for all three of its individual components, i.e.,

1. A stable or improved eGFR, defined as ≤10% reduction in eGFR compared to the baseline in Study X2202, and
2. Either a ≥ 50% reduction in UPCR compared to the baseline in Study X2202 or a reduction to <300 mg/g in UPCR (sampled from a 24-hour or FMV urine collection), and
3. Either a ≥ 50% increase in serum C3 compared to baseline in Study X2202 or an increase to ≥ 90 mg/dL in serum C3 (i.e., ≥ the LLN).

Initiation of treatment with eculizumab or any other complement pathway modifying agent automatically designated the participant as not having met the criteria.

C3 deposit score (primary endpoint for Cohort B)

The C3 deposit score quantifies C3 protein deposition (specific antibodies against C3 or its fragments, such as C3c or C3d with staining technique) in kidney tissue The C3 deposit score varies from 0 to 3 graded intensity values for C3 deposition for the mesangial and capillary location (both scored separately). The score for each location (mesangial and capillary) was multiplied with a factor of 1 for segmental and a factor of 2 for global extent. The total score ranged from 0 to 12.

Patient disposition

A total of 26 participants, 16 participants with C3G (Cohort A) and 10 participants with recurrent C3G (Cohort B) entered into this extension study. One participant in Cohort B completed the follow-up period in Study X2202 and did not rollover into the B12001B study.

Table 23: Participant Disposition (Screened analysis set)

	Cohort A N=16 n (%)	Cohort B N=10 n (%)	Overall N=26 n (%)
Participants			
Enrolled (Entered the extension study and not screen failed)	16 (100.0)	10 (100.0)	26 (100.0)
Completed 12-month/Day 354 visit (9 month in extension)	16 (100.0)	9 (90.0)	25 (96.2)
Completed 21-month/Day 624 visit (18 month in extension)	14 (87.5)	9 (90.0)	23 (88.5)
Completed 33-month/Day 984 visit (30 month in extension)	14 (87.5)	8 (80.0)	22 (84.6)
Ongoing (continue to receive study treatment)	12 (75.0)	7 (70.0)	19 (73.1)
Discontinued treatment	4 (25.0)	3 (30.0)	7 (26.9)
Discontinued study	4 (25.0)	2 (20.0)	6 (23.1)
Main cause of treatment discontinuation			
Adverse Event	0 (0.0)	2 (20.0)	2 (7.7)
Progressive Disease	1 (6.3)	0 (0.0)	1 (3.8)
Death	1 (6.3)	0 (0.0)	1 (3.8)
Physician Decision	0 (0.0)	1 (10.0)	1 (3.8)
Subject Decision	2 (12.5)	0 (0.0)	2 (7.7)
Main cause of study discontinuation			

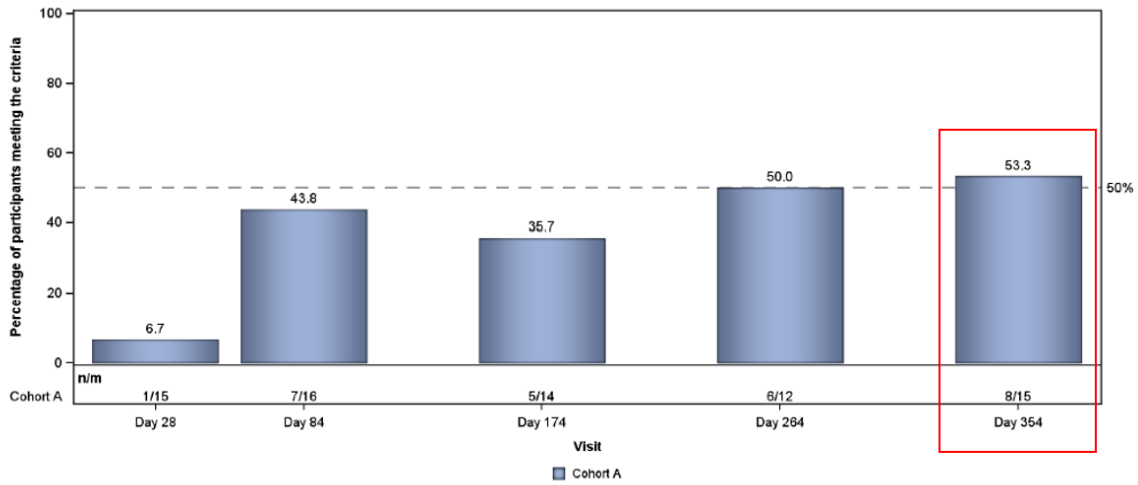
	Cohort A N=16 n (%)	Cohort B N=10 n (%)	Overall N=26 n (%)
Adverse Event	0 (0.0)	2 (20.0)	2 (7.7)
Progressive Disease	1 (6.3)	0 (0.0)	1 (3.8)
Death	1 (6.3)	0 (0.0)	1 (3.8)
Subject Decision	2 (12.5)	0 (0.0)	2 (7.7)

N=Number of participants in the screened analysis set
n=Number of participants under each disposition category

Results

The number of participants in Cohort A who met the criteria for the 3-component composite renal endpoint increased with time until Day 354, when they were met by 8 out of 15 participants (53.3%; 95% CI: 30.1, 75.2). None of the Cohort A participants received treatment with eculizumab or any other complement pathway modifying agent during the study.

Figure 40: Proportion of participants who achieved 3-component composite renal endpoint over time in Cohort A (Safety analysis set)



The 9-month visit in Study B12001B (Day 354 of treatment) is the primary endpoint time point. 24h UPCR was used for Day 28, 84 visits; 24h or FMV UPCR was used for Day 354 visit; FMV UPCR was used for the remaining visits. m=number of participants at each time point. n=number of participants meeting the criteria at each time point. Visits on days 174, 264, 354 correspond to 3, 6, 9 months in the extension study.

Table 24: Summary of proportion of participants who achieved 3-component composite renal endpoint by visit in Cohort A (Safety analysis set)

Visit	Cohort A N=16 n/m (%) [95% Wilson CI]
Day 7	1/15 (6.7) [1.2, 29.8]
Day 14	1/16 (6.3) [1.1, 28.3]
Day 21	2/16 (12.5) [3.5, 36.0]

Visit	Cohort A N=16 n/m (%) [95% Wilson CI]
Day 28	1/15 (6.7) [1.2, 29.8]
Day 36	4/15 (26.7) [10.9, 52.0]
Day 64	5/14 (35.7) [16.3, 61.2]
Day 84	7/16 (43.8) [23.1, 66.8]
Day 174	5/14 (35.7) [16.3, 61.2]
Day 264	6/12 (50.0) [25.4, 74.6]
Day 354	**8/15 (53.3) [30.1, 75.2]**

A summary of the Results for each individual component of the 3-component composite renal endpoint is given in the following:

Individual component 1 (eGFR): for approximately 90% of participants, eGFR was stable or improved (defined as ≤10% reduction in eGFR compared to the baseline) from Day 7 to Day 354. At Day 354, 15 out of 16 (93.8%; 95% CI: 71.7, 98.9) participants met the criteria for stable or improved eGFR in Cohort A.

Individual component 2 (UPCR): the effect of iptacopan on the composite renal endpoint was mainly driven by individual component 2 (UPCR; defined as either a ≥ 50% reduction in UPCR compared to the baseline or a reduction to <300 mg/g in UPCR). The number of participants in Cohort A who met the individual component 2 (UPCR) increased with time. At Day 354, 8 out of 15 (53.3%; 95% CI: 30.1, 75.2) participants met individual component 2.

Individual component 3 (serum C3): all participants from Day 21 met the individual component 3 (serum C3), defined as either a ≥ 50% increase in serum C3 compared to baseline or an increase to ≥ 90 mg/dL (i.e., ≥ LLN).

Primary endpoint for Cohort B - Effect on C3 deposit score from 6–9-month visit

To evaluate the effect of iptacopan treatment on glomerular C3 deposition in participants with recurrent C3G, the C3 deposit score (determined through C3c immunofluorescence microscopy) was assessed at Day 84 visit in Study X2202 and 6-9-month visit (264-354 days of treatment) and compared to the baseline in Study X2202.

The C3 deposit score ranged from 0 to 12, with a higher score indicating a greater degree of glomerular C3 deposition. At the 6–9-month visit, *only 4 participants* in Cohort B had a renal biopsy performed, from which tissue was suitable for the assessment of C3 deposit score. For these 4 participants, the median baseline C3 deposit score was 7.50.

In participants with recurrent C3G (Cohort B), iptacopan treatment was associated with a reduction in the median C3 deposit score of 2.00 (n=7; 95% CI: -5.00, 2.50; p=0.3438) from baseline to Day 84 in Study X2202. Additional reduction was observed with a longer duration of iptacopan treatment. By 6-9 months (264-354 days of treatment), the reduction in the median C3 deposit score from baseline was 5.50 (80% CI: −10.0, 4.00; p=0.3750; based on 4 patients with available renal biopsy).

Important secondary endpoints

In **Cohort A**, the mean baseline 24h UPCR was 4.02 g/g. *A 57% reduction in the adjusted geometric mean ratio of 24h UPCR from baseline was observed at Day 354.* Ongoing treatment with iptacopan was associated with an additional proteinuria reduction compared to that previously observed at Day 84.

Table 25: MMRM model analysis of log-transformed ratio to baseline in 24h UPCR (g/g) in Cohort A (N=16, Safety analysis set)

Visit	n	Adjusted geometric mean ratio to baseline (95% CI)	p-value*
Day 28	15	0.78 (0.57, 1.06)	
Day 84	16	0.55 (0.40, 0.75)	
Day 354	**15**	**0.43 (0.31, 0.59)**	**<0.0001**

The 9-month visit in Study B12001B (Day 354 of treatment) is the primary endpoint timepoint visit and marked in bold.
Log-transformed ratio to baseline was analyzed using a MMRM model.

The model included timepoint (as study day relative to the date of first administration of study treatment) as a fixed effect, and the Study X2202 log-transformed baseline measurement as fixed covariate. Timepoint was included as a repeated factor with an autoregressive covariance matrix to allow adjustment for correlations between timepoints within participants.
Three participants had missing 24h UPCR values at Day 354: These 24h UPCR values were imputed by their FMV values at Day 354 and the corresponding baseline FMV UPCR values were used in the calculation of the change from baseline.

Baseline was defined as the 24h urine collection on Day -1 to Day 1 in Study X2202

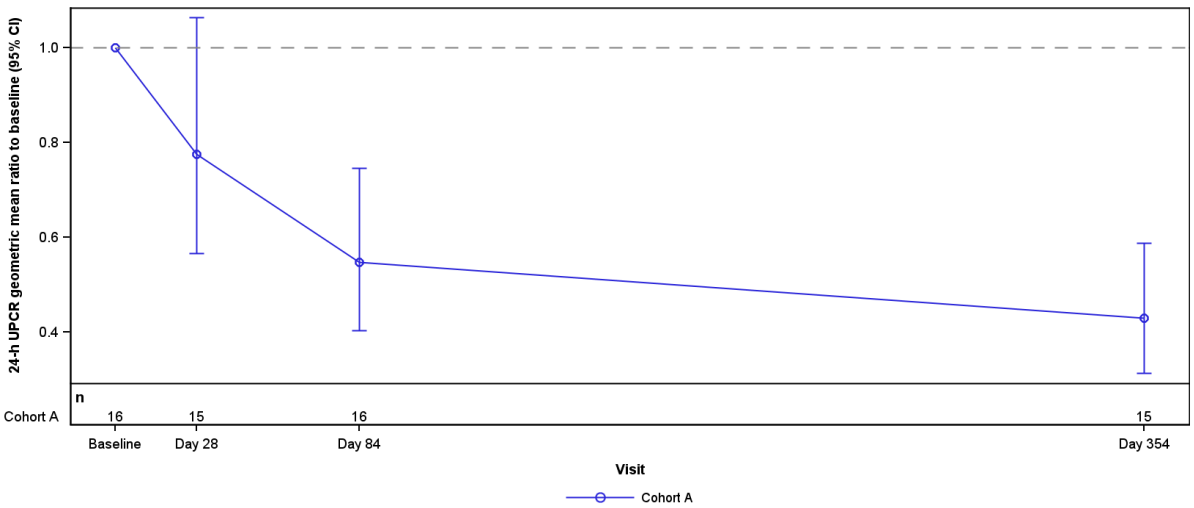
Visits on days 174, 264, 354 correspond to 3, 6, 9 months in the extension study.

*Calculated from two-sided hypothesis test.

N=number of participants included in the analysis.

n=number of participants with non-missing values in the visit

Figure 41: Model estimated geometric mean ratio to baseline (95% CI) plot of 24h UPCR (g/g) by cohort over time in Cohort A (Safety analysis set)



n=number of participants with non-missing measurements.

Baseline was defined as the 24h urine collection on Day -1 to Day 1 in Study X2202

The 9-month visit in Study B12001B (Day 354 of treatment) is the primary interest visit.

Visits on days 174, 264, 354 correspond to 3, 6, 9 months in the extension study.

Change from baseline in eGFR

Change from baseline in eGFR - Cohort A

Adjusted arithmetic mean eGFR change from baseline remained stable at all visits up to and including Day 804. At Day 984 (Month 30), the change in adjusted arithmetic mean from baseline was −3.18 mL/min/1.73m^2.

Out of 16 participants in Cohort A, 2 participants discontinued the study early due to death (Day 501; and subject decision (Day 631), respectively. Of the 14 participants remaining in the study at Day 984, 10/14 participants (71.4%; 95% CI: 45.4, 88.3) had a stable or improved eGFR (defined as ≤10% reduction in eGFR compared to baseline), and 4 participants had eGFR >10% of decline.

The slight overall decrease in eGFR at Day 984 was driven by 4 participants, who experienced a >10% reduction compared to baseline (individual changes in eGFR of −40.35 mL/min/1.73m^2 , −29.98 mL/min/1.73m^2, −19.86 mL/min/1.73m^2, and −4.29 mL/min/1.73m^2. One of these four participants experienced a decline in renal function starting after a urinary tract infection. No specific reasons were reported for the decline in renal function for the other 3 participants.

Table 26: MMRM model analysis of change from baseline in eGFR (mL/min/1.73m^2) in Cohort A (N=16, Safety analysis set)

Visit	n	Adjusted arithmetic mean change from baseline (95% CI)
Day 7	16	0.78 (-5.60, 7.16)
Day 14	16	3.90 (-2.48, 10.28)
Day 21	16	3.61 (-2.77, 9.99)
Day 28	14	5.72 (-0.81, 12.26)
Day 36	15	4.14 (-2.32, 10.60)
Day 64	15	3.64 (-2.80, 10.09)
Day 84	16	2.47 (-3.91, 8.85)
Day 174	15	5.75 (-0.69, 12.20)
Day 264	14	4.26 (-2.25, 10.78)
Day 354	**16**	**6.54 (0.16, 12.92)**
Day 444	15	4.74 (-1.72, 11.20)
Day 624	13	2.44 (-4.25, 9.12)
Day 804	14	0.73 (-5.98, 7.43)
Day 984	14	-3.18 (-9.94, 3.58)

Visits on days 174, 264, 354, 444, 624, 804, 984 correspond to 3, 6, 9, 12, 18, 24, 30 months in the extension study.

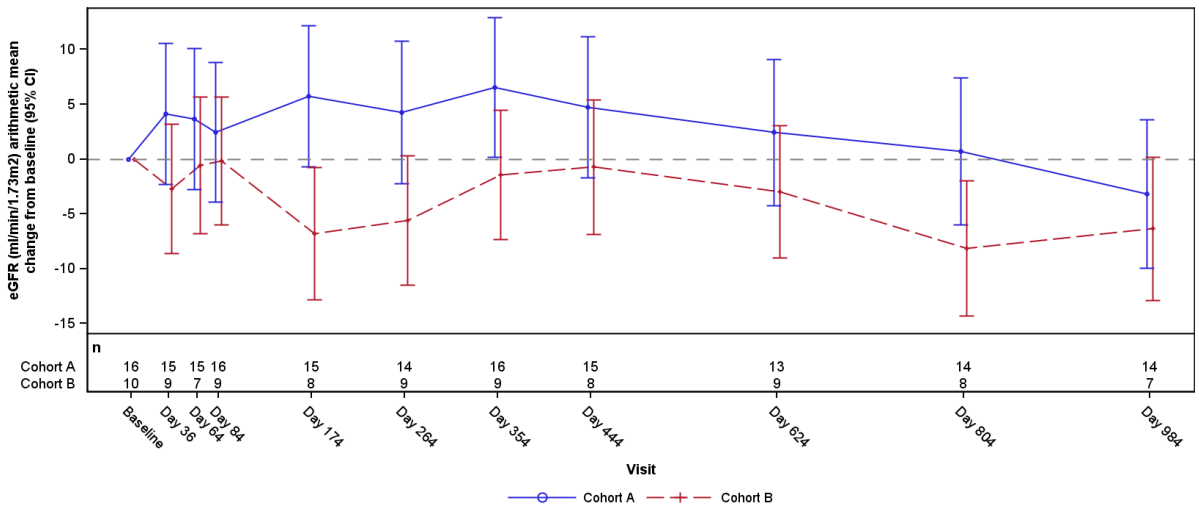
The change from baseline was analyzed using a MMRM model.

The model included timepoint (as study day relative to the date of first administration of study treatment) as a fixed effect, and the Study X2202 baseline measurement as fixed covariate. Timepoint is included as a repeated factor with an autoregressive covariance matrix to allow adjustment for correlations between timepoints within participants.

Baseline was defined as the last available assessment prior to the first dose of study drug in Study X2202

N=number of participants included in the analysis. n=number of participants with non-missing values in the visit.

Figure 42: Model estimated arithmetic mean change from baseline (95% CI) plot of eGFR by cohort over time (Safety analysis set)

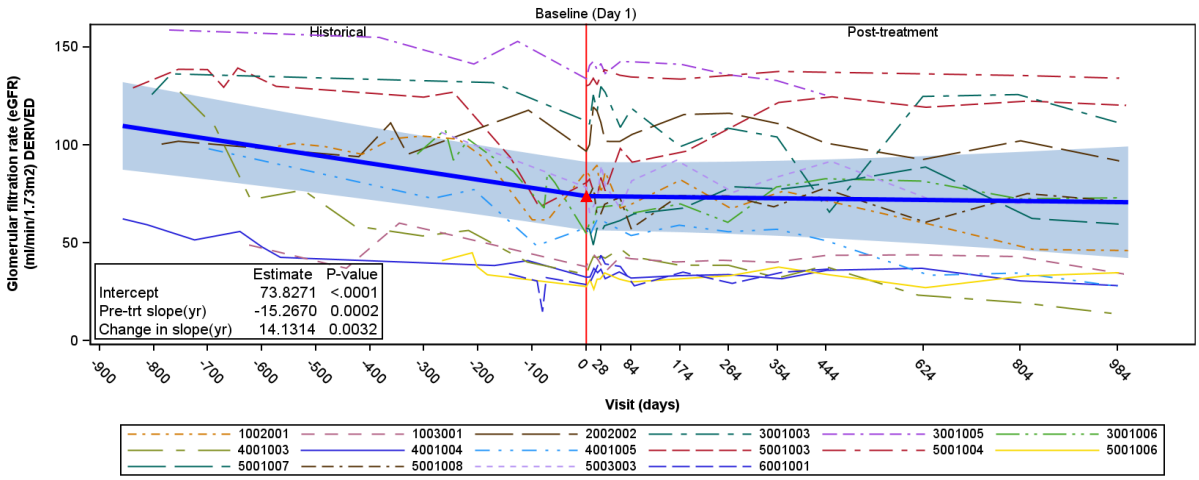


n=number of participants with non-missing measurements. Baseline was defined as the last available assessment prior to the first dose of study drug in Study X2202. Visits on days 174, 264, 354, 444, 624, 804, 984 correspond to 3, 6, 9, 12, 18, 24, 30 months in the extension study.

Results of eGFR slope comparison pre-treatment versus post-treatment, Cohort A

Compared with the APPEAR study, the C3G patients from Study X2202 had a significantly lower eGFR (mean: 70.1 mL/min/1.73m2) and steeper historical eGFR slope (annualized eGFR -15.27 mL/min/1.73m^2) at baseline. Based on the historical eGFR data slope analysis, the pre-treatment annualized eGFR slope was −15.27 mL/min/1.73m2/year, whereas the post-treatment annualized eGFR slope was −1.14 mL/min/1.73m2/year.

Figure 43: Change in annualized eGFR slope based on the historical data in patients with C3G from Study X2202 in Study B12001B (Safety analysis set)



Visits on Days 174, 264, 354, 444, 624, 804, 984 correspond to 3, 6, 9, 12, 18, 24, 30 months in extension study.
Blue line shows mean value with 95% CI in shared area

Results of important secondary endpoints, Cohort B

Baseline *UPCR* was within the normal range (0.21g/g). Still, UPCR was reduced after 12 months treatment with iptacopan by 29% (95% CI 10%; 54%); it remained in the normal range. The pre-study

annualized eGFR slope for patients with recurrent C3G was −3.75 mL/min/1.73m2/year. The post-treatment annualized eGFR slope (N=10) was –4.49 mL/min/1.73m2/year, representing a change in the annualized eGFR slope of –0.74 mL/min/1.73m2/year.

2.4.3. Discussion on clinical efficacy

Claimed indication:

"Fabhalta is indicated for the treatment of adult patients with complement 3 glomerulopathy (C3G) in combination with a renin-angiotensin system (RAS) inhibitor, or in patients who are RAS-inhibitor intolerant, or for whom a RAS inhibitor is contraindicated (see section 5.1)."

This application is mainly supported by:

- 74 adult C3G patients who completed the *6-month randomized, double-blind, placebo-controlled part* of the **pivotal phase 3 study APPEAR-C3G**

Supportive evidence came from:

- 12-month data of APPEAR-C3G: 73 patients completed 12-months (6 months double-blind placebo-controlled period + 6 months open-label period).
- completed **phase 2 study X2202**: 27 adult patients with C3G (n=16) or recurrent C3G (n=11) who completed 3 months of treatment;
- ongoing **long-term extension study CLNP023B12001B (66 months)**. Patients who completed APPEAR-C3G and Study X2202 and rolled over into Study B12001B; n=7 recurrent patients with 39 month data.

Design and conduct of clinical studies

*Phase 3 study **APPEAR-C3G**:*

This study included a 6-month double- blind, placebo-controlled period, followed by a 6-month period in which all subjects received open-label iptacopan. Limiting the study duration to 6-months (placebo-controlled double-blind treatment phase) is understandable in this ultra-rare condition.

Study objectives and endpoints

The primary objective of this study was to demonstrate the superiority of iptacopan 200 mg twice daily against placebo in reducing proteinuria as measured by UPCR from a 24-hour urine collection. The *primary endpoint* of *UPCR reduction* from baseline to six month is accepted. As outlined in the given CHMP SA, a reduction should be accompanied by an improvement in eGFR (in line with the outcome of the 2018 NKF, EMA, FDA workshop, published by Holtkamp et al., 2020 which found a stronger correlation for eGFR-based endpoints with renal outcome as compared to proteinuria reduction). Foreseeably, the six-month double-blind period could only deliver limited data on *eGFR changes from baseline* (secondary endpoint). Hence, as recommended in the SA, eGFR was evaluated by annualised *eGFR slope* comparisons pre-treatment versus on-treatment. To this end, historical eGFR data over the two years prior to study enrolment were collected and combined with in-study data for all participants to establish the progression of eGFR prior to the initiation of iptacopan treatment.

Proteinuria was additionally captured by determination in first morning void urine samples.

A *composite response endpoint* was defined as secondary endpoint, including a) decline in eGFR from baseline to six months by no more than 15% and b) ≥50% reduction in proteinuria from baseline to six

months. The first component (up to 15% decline in eGFR) cannot be counted unequivocally as treatment success within the response endpoint. The second component (≥50% reduction in proteinuria) is considered more important, as published data (Caravanca-Fontan F et al., 2022, GLOSEN study group; Masoud S et al., 2024, RaDaR Registry) reported that this degree of proteinuria reduction was associated with a lower risk of kidney failure in patients with C3G (registry data not considered eligible to qualify proteinuria as a sole surrogate in C3G).

Renal histopathology was evaluated within renal biopsies obtained at day 45 and day 180 (6-months); as secondary endpoints the *disease total activity score* =total activity plus total chronicity score was determined. These endpoints are of value as the *disease total activity score* has the potential to predict disease progression in C3G (Bomback et al., 2018). In addition, the *C3 deposit score* was determined in renal biopsy samples. The total score ranged from 0 to 12. No studies have investigated a link between changes in immunofluorescence staining and long-term renal outcomes. However, given that C3 deposition is the defining element in the pathophysiology of C3G and considered causal to kidney impairment, it appears plausible that any reduction in C3 staining in response to therapy indicates improvement.

Patient reported outcomes (PROs) were evaluated using FACIT-Fatigue, a 13-item questionnaire that assesses self-reported fatigue and its impact on daily activities and function. Fatigue is one of the most debilitating and commonly reported symptoms mainly in chronic dialysis patients (Chao et al 2016) but also mentioned in patients with C3G (Feldman et al 2018). Changes in FACIT-Fatigue scores from baseline to 6 months was a secondary endpoint for APPEAR-C3G. A participant was considered as a responder if they had at least a 5-point improvement in the FACIT-Fatigue total score from baseline at 6 months. Change from baseline to 6 months in SF-36 summary scores (QoL), EQ-5D and PGIS severity level for fatigue supplemented the PRO assessment.

Blood and urinary biomarkers (Serum C3, Plasma sC5b-9, Urinary sC5b-9/creatinine, Serum Wieslab, Urinary lipocalin-2 (NGAL)/creatinine) were exploratory endpoints. They were measured to quantitate the degree and persistence of complement alternative pathway inhibition produced by iptacopan as well as assessing the effects of iptacopan on markers of kidney injury (methodology and results are given in the PD part of this AR).

Dose

The approved dose for PNH (iptacopan 200mg bid) was likewise used in APPEAR-C3G (and in the label); this is acceptable as both entities share a common pathophysiology. Both diseases are expected to benefit from inhibition of complement biomarkers (Wieslab, plasma Bb, plasma sC5b-9) which were used as PD markers in the dose-finding for PHN patients. PK data showed a similar exposure in PNH and C3G (with some increase in recurrent C3G; see PK part of this report). Ascending doses were used in study X2202 in patients with C3G which showed maximum changes in complement biomarkers with 200 mg bid compared to lower doses between 10 and 100 mg iptacopan.

Concomitant medication

Overall, 37 (97.4%) patients in the iptacopan arm and 35 (97.2%) patients in the placebo arm received at least one concomitant medication affecting proteinuria. Nearly all patients received background RASi therapy, which per protocol was required to be taken on a stable, maximally tolerated dose throughout the study. Approximately, one-third of patients were taking glucocorticoids or MPAs as immunosuppressives. Use of RASi therapy as background therapy is reflected in the proposed indication wording. Of note, RASi therapy is not approved for the treatment of C3G, but is considered standard of care; current *KDIGO 2021 practice points for the management of C3G* recommend blockade of RAS with either ACEIs or ARBs for patients with sub-nephrotic or even nephrotic range proteinuria and relatively preserved kidney function (KDIGO 2021). As all patients in APPEAR-C3G were treated with background

ACEi/ARBs in line with KDIGO recommendations, it is agreed with the Applicant to reflect use of ACEi/ARBs in the indication wording.

Studied population

Adult patients with a histologically confirmed diagnosis of C3G and on ACEI or ARB treatment for at least 90 days were included in APPEAR-C3G. Only patients with high proteinuria (UPCR ≥ 1.0 g/g) were included; priorly, this was agreed at scientific advice.

Only patients with reduced serum C3 (defined as less than 0.85 x lower limit of the central laboratory normal range) were included. However, a relevant proportion of C3G patients appears to exhibit normal C3 levels (about 30-50%; Bomback AS et al., 2018; Servais A et al., 2012; Iatropoulos P et al., 2018). Of note, the most common reason for exclusion after screening/run-in was not meeting the required serum C3 level (32 participants, 24.2%). Hence, the Applicant was asked to justify the extrapolation of APPEAR-C3G results to patients with normal serum C3. As no trend towards decreased proteinuria lowering in patients with relatively higher baseline serum C3 became discernible in the requested subgroup analyses of the APPEAR-C3G population and the impact of serum C3 on renal outcome parameters appears to be limited according to recently published literature (Ndife, 2023; Masoud et al., 2024), no restriction of the target population to patients with low serum C3 was considered justified.

Patients with baseline eGFR<30ml/min/1.73m^2 were excluded. Patients with severe renal impairment might benefit from complement targeted therapy (and discontinuation of iptacopan when eGFR falls below 30ml/min/1.73m^2 may not be warranted). The current SmPC statement indicating that "no data are available" adequately reflects the issue.

Statistical methods

The statistical methods are considered adequate.

Primary and secondary estimands are acceptable and address relevant clinical questions. Imputation of values for the hypothetical strategy using the "jump to reference" ("J2R") method is an appropriate approach. Handling of missing data is acceptable and the impact of missing data was very limited as the amount was low in the study. Statistical models (MMRM, logistic regression, ANCOVA) for the different endpoints are appropriate. The approach to control for multiple analyses across the primary and secondary endpoints is acceptable. The alpha level of 0.05 one sided and reporting of one-sided p-values for secondary endpoints can be accepted considering the very rare nature of the disease. The statistical methods for the exploratory slope analysis using historical serum creatinine data estimate eGFR values employing the CKD-EPI formula for up to two years prior to study combined with all observed in-study eGFR data is considered appropriate, using all available data from all subjects. Robustness of the analysis is considered acceptable considering the contribution of data in terms of completeness of subjects contributing and the number of observations per subject included. Additional sensitivity analysis confirm the consistency of the slope change analysis results with regard to impact of number of observations per subject and observation period included.

Conduct

The study was well conducted with very few discontinuations or intercurrent events. GCP compliance was confirmed by the MAH. During assessment no issue of GCP non-compliance arose.

Design supportive studies (study X2202, completed; long-term extension study B12001B ongoing).

These studies were conducted non-controlled and open-label. Study X2202 included 27 adult patients with C3G of whom *11 had recurrent disease (*Cohort B*) in the transplanted kidney,* a population not investigated in APPEAR-C3G. All patients completed the 12-week study duration (for details on study

design, in- and exclusion criteria please see PD part of this report). As primary endpoints, 24 h UPCR ratio to baseline in Cohort A and change from baseline in C3 Deposit Score in Cohort B were defined.

Thirty-nine-month interim data have been submitted for the ongoing long-term extension study B12001B (total duration 66 months). Patients from the APPEAR-C3G study and from study X2202 could transit into this extension study. As primary endpoints, FMV UPCR change from baseline in patients from Cohort A and C3 deposit score in patients from Cohort B were used. The Applicant committed to provide updates to this category 3 study as described in the RMP.

Efficacy data and additional analyses

Baseline characteristics

Except for the following, baseline characteristics were balanced across treatment groups: patients with a more severe phenotype of C3G were included in the iptacopan group. Patients randomised to iptacopan had heavier proteinuria (iptacopan 3.33 g/g, 95% CI 2.793 - 3.968); placebo 2.58 g/g, 95% CI 2.178 - 3.051); 55% of participants presented with nephrotic range proteinuria in the iptacopan arm compared to 30% in the placebo arm; eGFR at baseline was approximately 10 mL/min/1.73m2 lower in the iptacopan arm compared to the placebo arm. The impact of this chance imbalance is difficult to estimate. Theoretically, it is conceivable that the iptacopan effect on UPCR is stronger in patients with more severe disease (high baseline proteinuria may facilitate demonstrating a certain change from baseline). However, also the opposite could be true, i.e. a weaker iptacopan effect in more severe disease could indicate advanced, non-reversible morphological changes in the kidneys. The Applicant evaluated the impact of this baseline imbalance by post-hoc sensitivity analyses (see Results part of this report below). This is considered to sufficiently address this issue.

A larger proportion of patients had dense deposit disease (DDD) in the iptacopan arm (n=9, 23.7% in the iptacopan arm; n=1, 2.8% in the placebo arm). Implications regarding differences in prognosis are not clear due to ambiguous findings in clinical studies; while better rates of remission or lower rates of progression have been observed in C3GN (Servais A et al., 2010, Sethi S et al., 2011), a more recent cohort analysis showed similar outcomes (worsening of proteinuria, progression to ESKD) in the DDD and C3GN subgroups (Bomback et al., 2018).

Results

Primary endpoint- proteinuria reduction

APPEAR-C3G met its primary objective of demonstrating superiority of iptacopan over placebo in proteinuria reduction. There was a statistically significant (1-sided p=0.0014) ***relative reduction in 24h UPCR of 35.1%*** (95% CI: 13.8%, 51.1%) following 6 months of treatment with iptacopan compared to placebo. The adjusted geometric mean ratios to baseline of 24h UPCR at Day 180 in the iptacopan and placebo arms were 0.70 (95% CI: 0.572, 0.852) and 1.08 (95% CI: 0.881, 1.313), respectively (i.e., reduction of 24h UPCR from baseline with iptacopan was 30% compared to an increase of 8% with placebo). The effect size of proteinuria reduction can be regarded as moderate. However, the effect size on proteinuria reduction (30% with iptacopan) is indicating clinical meaningfulness as it has been described to be associated with renal outcome benefit (Caravaca-Fontán et al 2022a, Masoud et al 2024). Nevertheless, these databases were small, therefore, support by eGFR data in the current dossier is considered of importance.

The robustness of the primary endpoint results was evidenced by consistency across several sensitivity analyses. Baseline imbalances in UPCR and eGFR across the two treatment arms did not affect the primary efficacy results.

In the iptacopan arm, the proportion of participants with nephrotic range proteinuria decreased from 55.3% at baseline to 31.6% at Day 180 compared to an increase of 30.6% at baseline to 41.7% at Day 180 in the placebo group. More participants in the iptacopan arm (10.5%) achieved < 1g/g of proteinuria at Day 180 than in the placebo arm (5.6%) despite the higher baseline UPCR in the iptacopan arm.

The reduction in 24h UPCR with iptacopan treatment was sustained to Day 360 in the subset of participants initially randomized to iptacopan (−40%, n=37). Additionally, the reduction of 24h UPCR in a subset of participants originally randomized to placebo and who were transitioned to open-label iptacopan at Day 180 was 27% (n=34) at Day 360 compared to the Day 1 baseline.

FMV UPCR analyses were consistent with the primary endpoint analysis; the reduction in FMV UPCR at Day 180 was 32.6% vs. placebo and sustained throughout Day 360.

Overall, results on proteinuria reduction show a moderate, but clinically relevant effect size. Consistency of results in sensitivity analyses adjusting for baseline imbalances as well as proteinuria reduction in FMV urine samples strengthen the robustness of the primary endpoint results. Further, reduction in the percentage of patients with nephrotic range proteinuria by 23.7% is considered clinically meaningful; nephrotic range proteinuria is associated in the short-term with potentially severe complications and co-morbidities including infection, thrombosis and thromboembolism, and dyslipidemia (Ravindran et al. 2018, Lomax-Brown et al. 2022). Sustained reduction in proteinuria lowering was shown (up to Day 360).

Primary and secondary endpoint results in subgroups

Iptacopan showed a consistent effect on 24 h UPCR at 6 months in subgroups by demographic factors (age, sex, and race) and baseline disease variables (UPCR, eGFR, C3G subtype).

There was a slightly larger effect on proteinuria reduction in the subgroup of patients with non-nephrotic range proteinuria (nephrotic range proteinuria; 0.76, 95% CI: 0.469, 1.226; i.e., 24% reduction; subgroup without nephrotic range proteinuria 0.59, 95% CI: 0.416, 0.835; i.e., 41% reduction). The larger effect size for proteinuria reduction in the subgroup of patients with non-nephrotic range proteinuria was explained by differences in the placebo arm; placebo patients with sub-nephrotic proteinuria <3 g/g showed a worsening of proteinuria at 6 months compared to the modest decrease in placebo patients with nephrotic proteinuria ≥ 3 g/g (geo-mean: 1.23 vs. 0.87). The iptacopan-treated patients showed similar proteinuria reduction in both subgroups (geo-mean: 0.73 and 0.66).

To further substantiate efficacy in patients with low proteinuria the Applicant had been asked to submit an additional subgroup analysis separating at 1.8g/g baseline proteinuria. The subset with baseline proteinuria below 1.8 g/g was small (n=5 in the iptacopan group; n=8 in the placebo group), representing 18% of the overall APPEAR-C3G population. The geometric mean (CI) was 0.84 (0.27-2.60) in this subgroup. Albeit the precision of this estimation is low (wide CI), this result hints at maintained proteinuria lowering efficacy in patients with lower degrees of proteinuria. It was further pointed out in the MAHs response, that according to natural history data (Caravanca-Fontan, 2022) only 10% of C3G patients present with proteinuria below 1g/g; hence, the APPEAR-C3G population is considered largely representative for the overall C3G population.

Contrarily, subgroup analysis of *eGFR change* according to baseline proteinuria demonstrated a lower efficacy in those with lower baseline proteinuria. The Applicant was asked to explain the discrepancy between the results of the subgroup analyses per baseline proteinuria (which showed a larger effect size of proteinuria reduction in the subgroup with non-nephrotic range proteinuria) and the results of the subgroup analysis of eGFR change according to baseline proteinuria (which showed a smaller effect size on change from baseline in eGFR in the group with non-nephrotic range proteinuria at baseline).

The smaller between-treatment difference with regard to eGFR decline in patients with lower-grades of proteinuria was explained by a fast eGFR decline in the placebo group nephrotic range patients. In

contrast, placebo patients with sub-nephrotic proteinuria had a rather stable eGFR over the 6 months duration of the double-blind period (−5.76 vs. 1.06 mL/min/1.73m^2). The iptacopan arm showed stable eGFR in both nephrotic and sub-nephrotic proteinuria subgroups (1.09 and 2.07 mL/min/1.73m^2, respectively), suggesting that iptacopan was effective regardless of baseline nephrotic status and that the numerical difference in eGFR effect sizes between the subgroups is mainly due to the differences in the placebo arm. The requested post-hoc subgroup analysis for eGFR separating at 1.8g/g (subgroup with baseline proteinuria<1.8 g/g: 5 patients in the iptacopan group, 8 patients in the placebo group) did not add conclusive information. Overall, proteinuria reduction appeared largely maintained at lower baseline proteinuria levels. Albeit a clear hold in eGFR decline was not shown by the data in patients with baseline proteinuria below 1.8g/g, a restriction of the target population is not adequate. Iptacopan should be started once the diagnosis of C3G is made in order to prevent irreversible renal function loss.

About 36% of patients received concomitant immunosuppressives (IS) in both treatment groups. The effect size of proteinuria reduction was about 3-fold larger in patients without concomitant use of IS (geometric mean ratio in 24-hour UPCR for iptacopan vs. placebo 0.86, 95% CI: 0.580, 1.259, i.e., 14.5% reduction for the subgroup with background immunosuppressant use, and 0.53, 95% CI: 0.346, 0.796, i.e., 47.5% reduction for the subgroup without background use of IS).

In general, IS treated patients may suffer from a more treatment resistant form of C3G, which is supported by high levels of proteinuria in APPEAR-C3G at baseline (mean UPCR 24h 3.26 g/g) despite prolonged prior treatment with IS agents. The relatively small effect size on proteinuria reduction of 14.5% has to be seen in the light of prior unresponsiveness to prolonged background therapy. IS-treated placebo patients showed a 20% increase in 24-hour UPCR while IS-untreated placebo patients showed a 4% decrease over the six month double-blind period in APPEAR-C3G; a switch from placebo to iptacopan at Day 180 led to a reversal of the aforementioned 20% increase in UPCR from Day 180 to Day 360 (adjusted geometric mean ratio to baseline decreased from 1.20 (95% CI: 0.92, 1.57) at Day 180 to 0.97 (95% CI: 0.72, 1.30) at Day 360). This decrease upon iptacopan initiation is considered a benefit, especially when contrasting it to the prior increase in proteinuria despite treatment with optimized SoC (immunosuppressive agents and RASi agents).

PK interactions between IS drugs and iptacopan have been investigated by DDI studies in the PNH study program; there was no indication that iptacopan impacts the PK of immunosuppressive agents.

Subgroup analyses by background use of IS therapy were performed to explore the impact of concomitantly applied IS therapy on iptacopan PD (serum C3 and plasma sC5b-9). This subgroup analysis showed comparable normalization of serum C3 and reduction of plasma sC5b-9 between the subgroups of patients who used or did not use IS at the time of randomization. Therefore, the three-fold difference in proteinuria reduction between the subgroups is unlikely to be explained by PD or PK interactions.

Overall, albeit the effect size of proteinuria reduction in the IS-treated subset was low, the benefit/risk in these subset is considered positive. From an efficacy point of view this is due to a maintained MoA, the demonstrated 20% increase in proteinuria shown in the placebo IS treated patients during the six months double-blind period (= patients on currently available best SoC), and its reversibility upon iptacopan initiation during the open-label period. The most likely reason for the low efficacy in the IS treated patients (14.5% proteinuria reduction) is a more aggressive and treatment resistant nature of the disease (which had initially led to the physician's decision to start IS therapy). Treatment of AP overactivation in these patients ameliorated deterioration in UPCR, which otherwise could not be treated. The lower effect size is accounted for by insertion of a warning to section 4.4 of the SmPC.

Main secondary and exploratory endpoints

A clinically meaningful change in *eGFR change from baseline* could not be expected within a 6-month placebo-controlled period. A *numerical (not statistically significant) trend in eGFR change favoring*

iptacopan became discernible (adjusted mean difference between iptacopan and placebo arm 2.16 ml/min/1.73m^2, p=0.3241; adjusted mean changes from baseline in the iptacopan arm and the placebo arm 1.30 mL/min/1.73m^2, 95% CI: −2.136, 4.726 and –0.86 mL/min/1.73m^2, 95% CI: −4.357, 2.635, respectively). This trend became slightly larger after adjusting for the baseline difference in proteinuria (3.20 ml/min/1.73m^2).

The impact of the acute positive effect was explored by a sensitivity analysis excluding eGFR data captured during the first 30 days. The treatment difference during the 6-month double-blind period for total slope was 3.61 (−6.34, 13.56) and for chronic slope was 3.11 (−9.02, 15.23) ml/min/1.73m^2, although extrapolation from 6 months to 12 months has been applied. Hence, the increase in eGFR observed upon iptacopan initiation has little impact on the treatment effect over the longer-term. The mechanism causing the acute positive effect on eGFR remained unclear.

The mean ***pre-treatment annualized eGFR slope*** showed rapid decline with −7.57 mL/min/1.73m^2/year. Following initiation of iptacopan, there was stabilization of annualized eGFR slope at +1.44 mL/min/1.73m^2/year, which equated to a predicted preservation of eGFR of 9.01 mL/min/1.73m^2/year (p <0.0001), compared with the scenario where iptacopan had not been commenced and eGFR continued to deteriorate at the pre-treatment rate.

In the patients randomized to iptacopan, the eGFR slope after 12 months of treatment was −1.26 mL/min/1.73m2/year representing an improvement of +9.42 mL/min/1.73m^2/year compared to their historical rate of decline, indicative of stable eGFR over time.

In light of the baseline imbalances between iptacopan and placebo arms (higher proteinuria and lower eGFR in the iptacopan arm), additional post-hoc analyses were conducted to investigate eGFR slope separately by treatment arm. In this analysis the pre-treatment eGFR decline was steeper in the (future) iptacopan arm than in the placebo arm (−10.75 vs. −7.64 mL/min/1.73m^2/year). During the double-blind treatment period, iptacopan halted the decline of eGFR, resulting in a post-treatment slope of −0.03 mL/min/1.73m^2/year and a slope change of 10.73 mL/min/1.73m^2/year (p=0.0057). In the placebo arm, the eGFR continued to decline post-treatment, but at a slower rate than that observed in the historical data (post-treatment slope of −3.08 mL/min/1.73m^2/year and slope change of 4.56 mL/min/1.73m^2/year, p=0.2267).

The apparent improvement of eGFR slope in the placebo group during the double-blind study period vs. pre-treatment is not entirely unexpected as mere inclusion in the study might have led to (behavioral) changes which might partly explain the raise in eGFR in the placebo arm. The Applicant found no clear explanation for the eGFR improvement in the placebo arm, as there were no changes in concomitant therapies. As some uncertainty as regards the eGFR slope increase in the placebo arm of 4.56 mL/min/1.73m2/year could not be removed and this (ill-defined) interventional effect likely added to iptacopan action, the pre- and on-treatment eGFR slope comparison lacks robustness; as a consequence, the respective paragraph was removed from section 5.1 of the SmPC.

Treatment with iptacopan for 6 months significantly increased the odds of patients meeting the composite renal endpoint by 7-fold (29.7% of patients in the iptacopan arm vs. 5.6% of patients on placebo; odds ratio=7.15 (95% CI: 1.43, 35.72), adjusted 1-sided p=0.0166).

The composite renal endpoint is considered of subordinate importance for the benefit evaluation as the second component "eGFR decline by not more than 15%" cannot be unequivocally counted as treatment success. Given that the proportion of patients with a ≤15% reduction in eGFR from baseline to 6 months was similar across the arms (89.5% in the iptacopan arm vs. 88.9% in the placebo arm) the effect of iptacopan on the composite renal endpoint was driven predominantly by proteinuria reduction (29.7% of patients in the iptacopan group had a reduction in proteinuria of ≥50% while this applied to 5.6% in the placebo group).

A small numerical difference in the histological total activity score in favor of iptacopan was observed at Day 180. Iptacopan decreased the C3G total activity score by a mean of −1.95 (95% CI: −2.691, −1.201); however, a mean decrease of −1.11 (95% CI: −1.831, −0.394) was also observed in the placebo arm. The clinical relevance of this small difference between treatment groups observed over a 6 month period is questionable. Some components of the activity score (membranoproliferative glomerulonephritis morphology, mesangial hypercellularity) are not expected to change over a six month period. Longer-term data were sparse, as biopsies at Month 12 were only performed in six patients. Histological scores in these limited datasets were stable up to Month 12.

Iptacopan reduced glomerular C3 deposition, as demonstrated by an adjusted mean difference for iptacopan vs. placebo of −1.88 (95% CI: −3.298, −0.452) in the C3 deposit score at Day 180 (1-sided p=0.0053). The diagnosis of C3G is confirmed by histologic assessment of C3 staining intensity in the glomerulus. Therefore, a reduction in C3 staining intensity following complement inhibition may be well interpreted as an inhibition of the underlying process that causes C3G.

Baseline scores for FACIT-fatigue were very close to the general patient norm value in both the iptacopan and the placebo arm (mean FACIT-Fatigue scores at baseline: iptacopan arm 42.4, placebo arm 41.9; the adjusted mean difference of change from baseline in the FACIT-Fatigue total score in the iptacopan and placebo arms was −2.60, 1-sided p=0.9310). There was no improvement in patient reported fatigue with iptacopan. Likewise, no meaningful changes were found in the PIGIS score (fatigue) and in the patient's perceived general well-being and QoL (normal values in SF-36 and EQ-5D scores at baseline and no change thereafter).

Main results from supportive studies

Study X2202: treatment with iptacopan in participants with C3G in Cohort A led to significant reductions in UPCR (45% reduction from baseline to Week 12, two-sided p=0.0003), and to a stabilization of kidney function (eGFR, SCR, CrCL), as such supporting the primary outcome in APPEAR-C3G (similar effect size).

In Cohort B of this study, patients with recurrent C3G based on their histopathology were included. These patients had normal proteinuria (24-hour UPCR 2.21 g/g) and normal post-transplant eGFR at baseline indicative of low baseline disease activity. During treatment, proteinuria and eGFR remained largely unchanged, a finding difficult to evaluate in the absence of a control arm.

The MAH pointed out that the faster course of disease progression in recurrent C3G supports starting iptacopan treatment as soon as the C3G recurrence in the transplanted kidney is confirmed by renal biopsy. Therefore, it is recommended in the SmPC that routine post-transplant biopsy should be screened for C3 deposition so that treatment can start before clinical signs such as proteinuria occur; vice versa, if clinical signs suggest recurrence of C3G, this should be confirmed with a biopsy (section 4.2 of the SmPC).

Mechanistically, iptacopan appeared to work also in recurrent disease, as it led to a reduction of C3 deposit score through Months 6-9. Decreasing of glomerular C3 deposition in the transplanted kidney appears favourable in respect to allograft survival, independent from the disease that necessitated transplantation (Panzer et al. 2019, Kidney Int Rep 4: 582–593).

In addition, iptacopan durably inhibited the complement alternative pathway up to 39 months of treatment, as indicated by increases and normalization of serum C3. As regards proteinuria, 24-hour UPCR was reduced by 29% on average (95% CI: −10%, 54%) at 12 months, despite the majority of patients having normal baseline proteinuria. FMV UPCR was within normal range (<0.2 g/g) for most participants at baseline and remained <0.4 g/g up to 39 months (at Month 39 four out of 7 patients had values within the normal range, one patient had a value just above the normal range, and two patients were above the normal range). Of note, in Cohort B only two patients had relevantly elevated UPCR so

that the usual endpoint, reduction in UPCR, could not be applied in a meaningful way. In addition, eGFR was in the normal range for transplanted patients. Diagnosis of C3G was based on histology.

The MAH's analysis of individual patient data revealed that eGFR and UPCR remained largely unchanged during the long-term extension study. However, the values of the individual patients were subjected to marked fluctuation over time, which hampers the identification of clear trends; two subjects showed disease progression despite iptacopan therapy. These two subjects had marked (nephrotic-range) proteinuria at treatment start, which could only be transiently controlled by iptacopan. This may indicate that an early start of treatment is important. These two subjects had several accompanying events, e.g. viral infections, and one displayed cocaine abuse. The MAH assumed that these conditions probably contributed to the deterioration of renal function. This view is agreed.

Overall, the finding that with iptacopan UPCR and eGFR essentially remained stable for up to 48 months in patients with recurrent disease is reassuring since literature reporting on the spontaneous course of C3G in SoC treated recurrent C3G patients points to a fast progression to kidney failure. The two drop-outs with renal deterioration had several additional conditions that could have contributed to renal damage. It is also plausible from a mechanistic point of view that iptacopan is similar effective in native and recurrent C3G. In general, due to a common pathophysiology Iptacopan is expected to likewise work in recurrent disease. These patients are at risk of allograft loss and have a high medical need for eGFR decline decelerating therapy.

The observed effects of iptacopan in recurrent C3G are described in Section 5.1 of the SmPC.

Study B12001B: preliminary data in Cohort A patients who transitioned from study X2202 showed a sustained reduction of proteinuria (57%; 95% CI 41%, 69%) from baseline to 12 months which was maintained up to 33 months of follow up with a 41% reduction in proteinuria FMV UPCR from baseline (95% CI 0.40-0.88). Results on eGFR were less clear and need to be further explored upon availability of more complete data which are recommended to the applicant to be submitted post-authorisation. No conclusion can be drawn as regards durability of action in recurrent C3G (Cohort B); only four patients contributed to the primary endpoint assessment (histopathology in renal biopsy), which may have been prone to selection bias. In addition, efficacy cannot be reliably extrapolated from histological changes in four renal biopsy samples, as any renal tissue obtained by biopsy is randomly sampled and may not be representative of wider changes in the kidney.

2.4.4. Conclusions on the clinical efficacy

Data from the completed 6-month double-blind period of the pivotal APPEAR-C3G study showed that iptacopan 200 mg twice daily resulted in a modest but clinically meaningful and statistically significant reduction in proteinuria in native C3G patients on a background therapy with SoC RASi.

Reduction in proteinuria was supported by a larger stabilisation of eGFR with iptacopan compared to placebo during the double-blind period. Longer-term data showed sustained proteinuria reduction and a stable eGFR trajectory. Stable eGFR is considered a benefit given the progressive decline in eGFR shown in the systematically collected pre-treatment data as well as in natural history data (which also link a halt of the eGFR decline to renal outcome benefit). The clinical efficacy is mechanistically supported by reduction of biomarkers reflective of alternative pathway activation and further substantiated by a clear reduction of C3 deposition. Results were less clear for a change in the disease activity score. In addition, improvement in functional markers did not translate into changes in the patient`s perceived well-being and QoL.

As the pathophysiology of C3G in the allograft is considered similar to C3G in the native kidney, iptacopan is expected to work also in recurrent C3G. The benefit in recurrent C3G is based on mechanistic

considerations as well as on the demonstration of relatively stable proteinuria and eGFR with iptacopan in the majority of Cohort B patients in study X2202.

The observed lower efficacy in patients with immunosuppressive therapy is reflected in the SmPC.

Overall, therapy with iptacopan could be started once the diagnosis of C3G is made to prevent further decline in renal function.

The efficacy of iptacopan in the claimed indication is considered demonstrated.

2.5. Clinical safety

Introduction

For safety analysis, the MAH defined pooled data sets from more than one study to increase the number of events, allowing conclusions that are more robust. Placebo-controlled data came from the double-blind period (6 months) of phase 3 study APPEAR-C3G. Uncontrolled data came from the uncontrolled, unblinded period of APPEAR-C3G, from the phase 2 study X2202 and from the roll-over study B12001B. The latter will provide a treatment duration for up to 66 months. Data cut-off was October 2023. Until cut-off, treatment duration was up to around 44 months.

The analysis sets for safety evaluation are defined below.

Controlled 200 mg b.i.d. safety set: hereafter referred to in text as the Controlled safety set. This safety set was defined for data, during the controlled double-blind period of APPEAR-C3G, from all patients with at least one dose of iptacopan 200 mg b.i.d. or placebo.

Broad 200 mg b.i.d. safety set: hereafter referred to in text as the Broad safety set. This safety set was defined for the C3G Broad safety pool and included iptacopan 200 mg b.i.d. data from all patients who received at least one dose of iptacopan 200 mg b.i.d. in the treatment periods of the studies (APPEAR-C3G, Study X2202, Study B12001B as applicable).

Patient exposure

The size of the data sets and the exposure expressed as patient-years are tabulated below.

Table 27: Sample sizes and duration of exposure to iptacopan 200mg b.i.d. in C3G studies (adult patients)

			Controlled 200 mg safety set		Broad 200 mg b.i.d. safety set[1]	
Parent study	**No. of patients in the parent study safety set**	**No. of patients continued in roll-over extension Study B12001B**	**No. of patients**	**Exposure duration in PY**	**No. of patients**	**Exposure duration in PY**
APPEAR C3G Pivotal Phase 3	74	35	Iptacopan 38 Placebo: 36	Iptacopan: 18.0 Placebo: 17.7	74	60.1
X2202 Phase 2 (C3G)	16	16	NA	NA	16	52.6

Parent study	No. of patients in the parent study safety set	No. of patients continued in roll-over extension Study B12001B	Controlled 200 mg safety set		Broad 200 mg b.i.d. safety set[1]	
			No. of patients	Exposure duration in PY	No. of patients	Exposure duration in PY
X2202 Phase 2 (recurrent C3G)	11	10	NA	NA	11	28.5
Total	101	61	Iptacopan: 38 Placebo 36	Iptacopan: 18.0 Placebo: 17.7	101	141.2

[1] Includes all iptacopan 200 mg b.i.d. treatment periods from parent study and, if available, the roll-over extension study.

Adverse events

An overview of the frequency of the different classes of adverse events (AEs) is provided in the Table 28 below. The percentage of patients suffering at least one AE or one serious AE (SAE) was numerically higher with iptacopan (marked LNP023 in the Table 28) than with placebo, 76.3% vs. 66.7% for all AEs, 7.9% vs. 2.8% for SAEs).

Table 28: (CO) Overview of TEAEs for C3G studies (Controlled 200 mg b.i.d. Safety Set and Broad 200 mg b.i.d. Safety Set)

	Controlled 200 mg b.i.d. Safety Set				Broad 200 mg b.i.d. Safety Set	
	LNP023 200 mg b.i.d.		Placebo		LNP023 200 mg b.i.d.	
Adverse events	N=38 n (%)	Total exp=18.3 PY m (OccR)	N=36 n (%)	Total exp=17.8 PY m (OccR)	N=101 n (%)	Total exp=142.0 PY m (OccR)
Any AE	29 (76.3)	78 (426.3)	24 (66.7)	59 (331.3)	78 (77.2)	385 (271.0)
SAEs	3 (7.9)	3 (16.4)	1 (2.8)	2 (11.2)	17 (16.8)	31 (21.8)
SAEs suspected to be related to study treatment	1 (2.6)	1 (5.5)	0	0 (0.0)	3 (3.0)	8 (5.6)
Deaths	0		0		1 (1.0)	
Severe AEs	2 (5.3)	2 (10.9)	1 (2.8)	1 (5.6)	9 (8.9)	14 (9.9)
AEs leading to study drug discontinuation	0	0 (0.0)	0	0 (0.0)	2 (2.0)	2 (1.4)
AEs leading to study drug interruption	4 (10.5)	6 (32.8)	4 (11.1)	4 (22.5)	9 (8.9)	22 (15.5)
AEs suspected to be related to study treatment	6 (15.8)	10 (54.7)	5 (13.9)	5 (28.1)	21 (20.8)	44 (31.0)

n: number of patients with at least one event; m: number of AE episodes. Total exposure in patient-years is computed as (sum of the duration of on-treatment periods over patients, in days)/365.25.
OccR = occurrence rate (number of episodes per 100 patient-years) is calculated as 100*(m divided by the total exposure in patient-years).
MedDRA version 26.1

Update with D90 Response:

With the D90 Response to the first RSI, the MAH has submitted an update of the safety analysis, covering a longer period of the open-label extension study phases. In the original submission, 142.0 patient-years (PY) of treatment with 200 mg bid iptacopan were covered. With the update, 189.9 PY are covered.

Reassuringly, no relevant changes in the number of episodes per 100 PY (occurrence rate, OccR, right column of the Table 29 below) were observed compared to the previous evaluation. In all AE categories, the occurrence rate was numerically slightly lower than previously.

There was also a minor update of the data from the placebo-controlled study phase, with one more patient with an AE suspected related now listed in the iptacopan group. This does not alter the overall conclusion on safety.

Table 29: Treatment emergent adverse events, by categories - C3G studies; Controlled 200mg b.i.d. Safety Set and Broad 200mg b.i.d. Safety Set

	Controlled 200 mg b.i.d. Safety Set				Broad 200mg b.i.d. Safety Set	
	LNP023 200mg b.i.d.		Placebo		LNP023 200mg b.i.d.	
	N=38 n (%)	**Total exp=18.3 PY m (OccR)**	**N=36 n (%)**	**Total exp=17.8 PY m (OccR)**	**N=101 n (%)**	**Total exp=189.8 PY m (OccR)**
Any AE	30 (78.9)	79 (431.8)	24 (66.7)	59 (331.3)	86 (85.1)	506 (266.5)
SAEs	3 (7.9)	3 (16.4)	1 (2.8)	2 (11.2)	20 (19.8)	36 (19.0)
SAEs suspected to be related to study treatment	1 (2.6)	1 (5.5)	0	0 (0.0)	4 (4.0)	9 (4.7)
Deaths	0		0		1 (1.0)	
Severe AEs	2 (5.3)	2 (10.9)	1 (2.8)	1 (5.6)	12 (11.9)	17 (9.0)
AEs leading to study drug discontinuation	0	0 (0.0)	0	0 (0.0)	3 (3.0)	3 (1.6)
AEs leading to study drug interruption	4 (10.5)	6 (32.8)	4 (11.1)	4 (22.5)	11 (10.9)	25 (13.2)
AEs suspected to be related to study treatment	7 (18.4)	11 (60.1)	4 (11.1)	4 (22.5)	23 (22.8)	51 (26.9)

Regarding the types of AEs, the following Table 30 reveals a numerical increase with iptacopan compared to placebo for infections and investigations. The difference in investigations was due to an imbalance in findings of increased serum CK and creatinine; anaemia was also reported in two cases in the iptacopan vs. no case in the placebo group. The imbalance in infections was mainly due to an imbalance in nasopharyngitis. However, the number of patients suffering the mentioned types of AEs was low so that firm conclusions are not possible. After the first round of the procedure, the applicant has submitted a summary of the 12-month results of the APPEAR-C3G study, i.e. after completion of the 6-month uncontrolled treatment period that followed the initial 6-month placebo-controlled period. This analysis did not reveal any unexpected safety findings.

Table 30: (SCS) TEAEs by SOC (with absolute between group rate differences greater than or equal to 5%) for C3G studies (Controlled 200mg b.i.d. Safety Set and Broad 200mg b.i.d. Safety Set)

	Controlled 200mg b.i.d. Safety Set					**Broad 200mg b.i.d. Safety Set**	
	LNP023 200mg b.i.d.		**Placebo**		**LNP023 200mg b.i.d. vs. Placebo**	**LNP023 200mg b.i.d.**	
System organ class	**N=38 n (%)**	**Total exp=18.3 PY m (OccR)**	**N=36 n (%)**	**Total exp=17.8 PY m (OccR)**	**Difference in % (95% CI)**	**N=101 n (%)**	**Total exp=142.0 PY m (OccR)**
Number of patients with at least one event	29 (76.3)	78 (426.3)	24 (66.7)	59 (331.3)	9.65 (-10.98, 29.40)	78 (77.2)	385 (271.0)
Infections and infestations	18 (47.4)	27 (147.6)	13 (36.1)	15 (84.2)	11.26 (-11.13, 32.45)	57 (56.4)	116 (81.7)
Investigations	10 (26.3)	16 (87.4)	4 (11.1)	5 (28.1)	15.20 (-3.18, 31.86)	24 (23.8)	37 (26.0)

	Controlled 200mg b.i.d. Safety Set					Broad 200mg b.i.d. Safety Set	
	LNP023 200mg b.i.d.		Placebo		LNP023 200mg b.i.d. vs. Placebo	LNP023 200mg b.i.d.	
System organ class	N=38 n (%)	Total exp=18.3 PY m (OccR)	N=36 n (%)	Total exp=17.8 PY m (OccR)	Difference in % (95% CI)	N=101 n (%)	Total exp=142.0 PY m (OccR)
Gastrointestinal disorders	5 (13.2)	7 (38.3)	7 (19.4)	7 (39.3)	-6.29 (-23.10, 10.99)	22 (21.8)	34 (23.9)
Blood and lymphatic system disorders	4 (10.5)	4 (21.9)	1 (2.8)	2 (11.2)	7.75 (-5.23, 19.70)	13 (12.9)	14 (9.9)
Nervous system disorders	3 (7.9)	3 (16.4)	5 (13.9)	6 (33.7)	-5.99 (-20.65, 9.07)	12 (11.9)	13 (9.2)
Ear and labyrinth disorders	3 (7.9)	3 (16.4)	0	0 (0.0)	7.89 (-3.23, 17.97)	5 (5.0)	5 (3.5)
Skin and subcutaneous tissue disorders	2 (5.3)	3 (16.4)	0	0 (0.0)	5.26 (-4.75, 14.49)	9 (8.9)	13 (9.2)
Psychiatric disorders	0	0 (0.0)	2 (5.6)	4 (22.5)	-5.56 (-15.24, 4.45)	5 (5.0)	6 (4.2)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	0	0 (0.0)	2 (5.6)	2 (11.2)	-5.56 (-15.24, 4.45)	3 (3.0)	3 (2.1)

Besides the AEs related to infections and investigations, the analysis of AEs per Preferred Term (PT, see Table 31 below) revealed some numerical differences between iptacopan and placebo, e.g. for headache, but the number of affected subjects was low (often 2 vs. 1 subject) so that no reliable conclusions can be drawn. A comparably high number of patients presented with increased serum CK. The MAH explained that this was due to physical exercise. The CK values are further discussed in the section on laboratory findings.

Table 31: (CO) Most common TEAEs by PT (≥ 5% of patients in any treatment group) for C3G studies (Controlled 200 mg b.i.d. Safety Set and Broad 200 mg b.i.d. Safety Set)

	Controlled 200 mg b.i.d. Safety Set				Broad 200 mg b.i.d. Safety Set	
	LNP023 200 mg b.i.d.		Placebo		LNP023 200 mg b.i.d.	
Preferred terms	N=38 n (%)	Total exp=18.3 PY m (OccR)	N=36 n (%)	Total exp=17.8 PY m (OccR)	N=101 n (%)	Total exp=142.0 PY m (OccR)
Number of patients with ≥ 1 event	29 (76.3)	78 (426.3)	24 (66.7)	59 (331.3)	78 (77.2)	385 (271.0)
COVID-19	8 (21.1)	8 (43.7)	6 (16.7)	6 (33.7)	27 (26.7)	30 (21.1)
Blood creatine phosphokinase increased	5 (13.2)	5 (27.3)	1 (2.8)	1 (5.6)	8 (7.9)	10 (7.0)
Nasopharyngitis	4 (10.5)	5 (27.3)	1 (2.8)	1 (5.6)	12 (11.9)	15 (10.6)
Cough	2 (5.3)	2 (10.9)	1 (2.8)	1 (5.6)	7 (6.9)	7 (4.9)
Anaemia	2 (5.3)	2 (10.9)	0	0 (0.0)	6 (5.9)	6 (4.2)
Headache	2 (5.3)	2 (10.9)	1 (2.8)	2 (11.2)	6 (5.9)	6 (4.2)
Blood creatinine increased	2 (5.3)	2 (10.9)	0	0 (0.0)	5 (5.0)	5 (3.5)
Otitis media	2 (5.3)	3 (16.4)	0	0 (0.0)	3 (3.0)	5 (3.5)
Viral infection	2 (5.3)	2 (10.9)	0	0 (0.0)	3 (3.0)	3 (2.1)

	Controlled 200 mg b.i.d. Safety Set				Broad 200 mg b.i.d. Safety Set	
	LNP023 200 mg b.i.d.		Placebo		LNP023 200 mg b.i.d.	
Preferred terms	N=38 n (%)	Total exp=18.3 PY m (OccR)	N=36 n (%)	Total exp=17.8 PY m (OccR)	N=101 n (%)	Total exp=142.0 PY m (OccR)
Aspartate aminotransferase increased	2 (5.3)	2 (10.9)	0	0 (0.0)	2 (2.0)	2 (1.4)
Diarrhoea	1 (2.6)	1 (5.5)	0	0 (0.0)	7 (6.9)	7 (4.9)
Vomiting	1 (2.6)	1 (5.5)	1 (2.8)	1 (5.6)	6 (5.9)	7 (4.9)
Nausea	1 (2.6)	1 (5.5)	2 (5.6)	2 (11.2)	4 (4.0)	4 (2.8)

Update with D90 response:

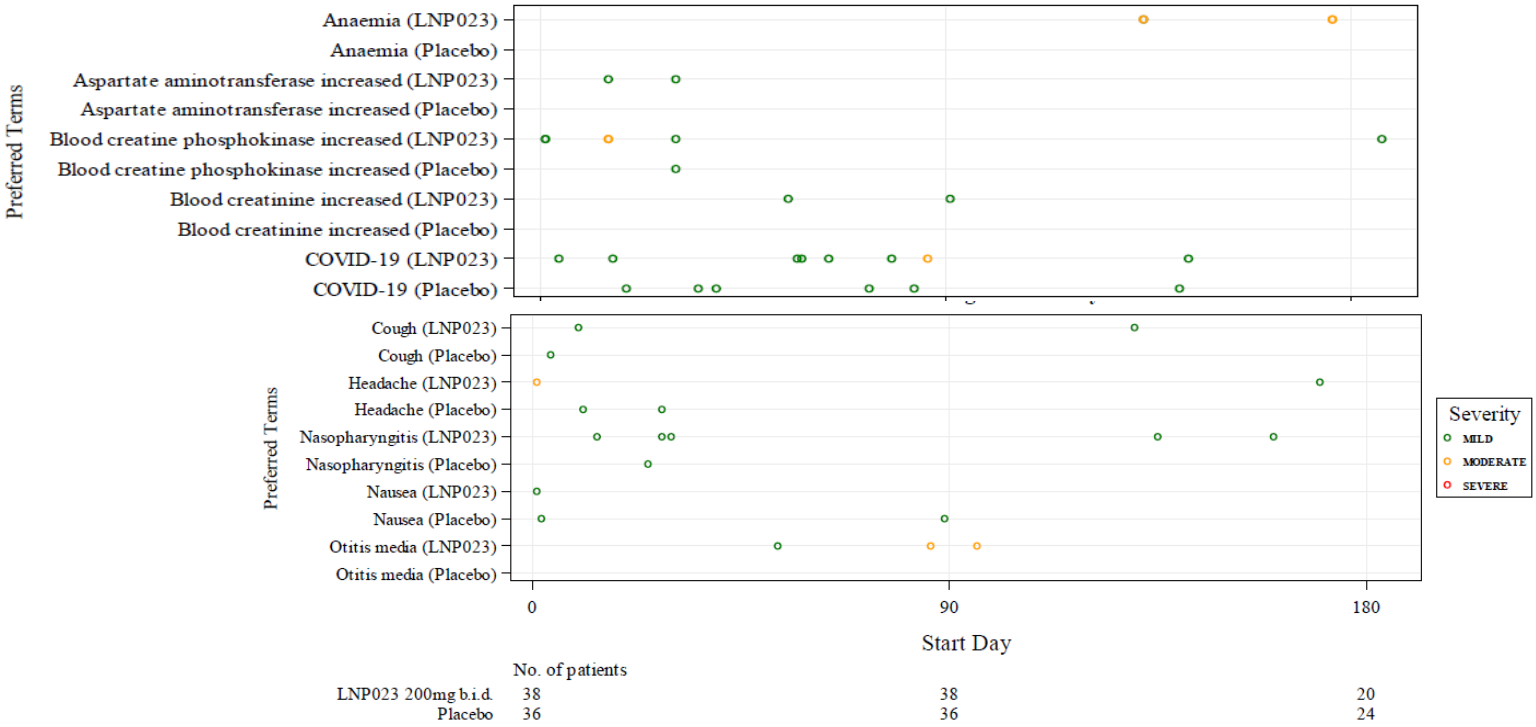
The evaluation of the newly observed AEs by preferred terms (PT) in the ongoing open-label extension phase are tabulated below. No meaningful changes in the occurrence rate (OccR, right column in the Table 32 below) were observed compared to the previous evaluation.

Table 32: The most frequent treatment emergent adverse events (>=5% patients in any treatment arm), by preferred terms - C3G studies; Controlled 200mg b.i.d. Safety Set and Broad 200mg b.i.d. Safety Set

	Broad 200mg b.i.d. Safety Set	
	LNP023 200mg b.i.d.	
	N=101 n (%)	Total exp=189.8 PY m (OccR)
Number of patients with at least one event	86 (85.1)	506 (266.5)
COVID-19	30 (29.7)	35 (18.4)
Blood creatine phosphokinase increased	11 (10.9)	14 (7.4)
Nasopharyngitis	14 (13.9)	18 (9.5)
Headache	9 (8.9)	9 (4.7)
Cough	8 (7.9)	8 (4.2)
Anaemia	6 (5.9)	6 (3.2)
Upper respiratory tract infection	6 (5.9)	6 (3.2)
Blood creatinine increased	5 (5.0)	6 (3.2)
Otitis media	5 (5.0)	8 (4.2)
Aspartate aminotransferase increased	3 (3.0)	3 (1.6)
Respiratory tract infection viral	3 (3.0)	3 (1.6)
Vomiting	8 (7.9)	10 (5.3)
Diarrhoea	7 (6.9)	7 (3.7)
Hyperkalaemia	6 (5.9)	12 (6.3)
Nausea	4 (4.0)	4 (2.1)
Hypercholesterolaemia	3 (3.0)	3 (1.6)
Renal impairment	6 (5.9)	7 (3.7)

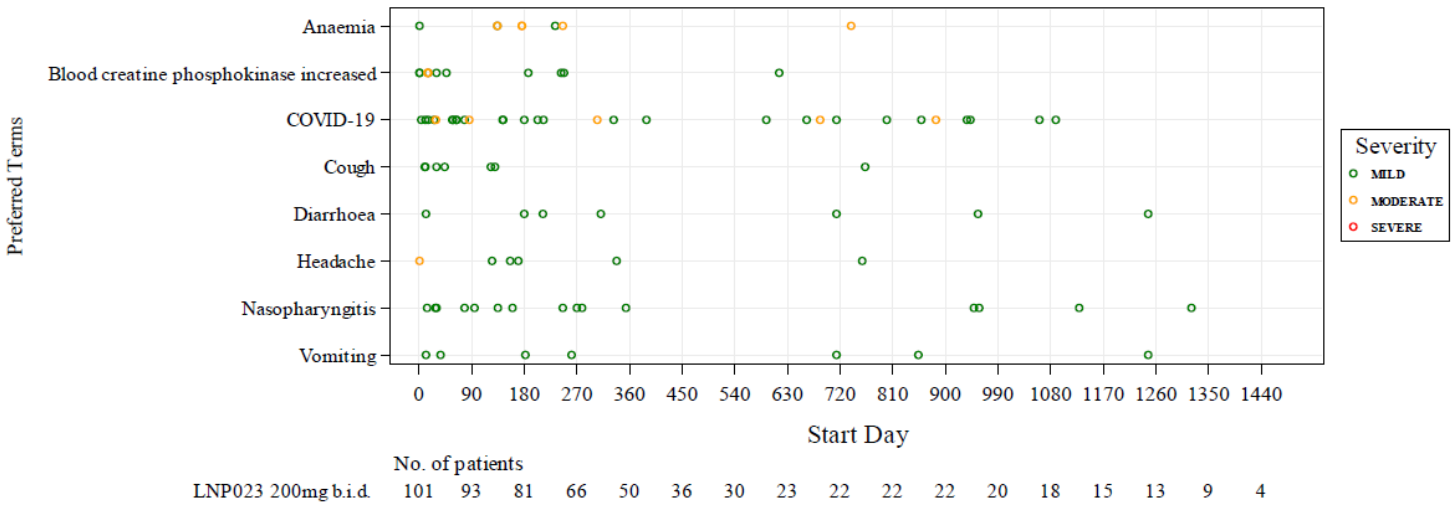
The Figure 44 below depicts the observed AEs by severity and by time of occurrence in the placebo-controlled period of study APPEAR-C3G. Reassuringly, in most cases the severity was mild Moderate severity was observed for events of anaemia and increased serum CK. As discussed in the section on laboratory findings, iptacopan in general did not lead to a decrease in haemoglobin and related parameters.

Figure 44: Dot plot of the most frequent treatment emergent adverse events (>= 5% patients in either treatment arm) by treatment, preferred term, and time - C3G studies; Controlled 200mg b.i.d. Safety Set



In the uncontrolled dataset (Figure 45 below), again most reported AEs were mild in severity.

Figure 45: Broad 200mg b.i.d. Safety Set; Dot plot of the most frequent treatment emergent adverse events (>= 5% patients) by preferred term and time - C3G studies



Serious adverse event/deaths/other significant events

Deaths

Across the three C3G studies, up to the cut-off dates, one death was reported:

A patient, originally from Study X2202, died on Day 501. Post-mortem examination revealed no obvious cause of death. The cause of death was presumed to be cardiac arrhythmia that was not considered to be related to iptacopan by the Investigator. Evidence of cardiac arrhythmia included arteriolo-nephrosclerosis, a clinical history of C3G, hypertension, focal myocardial scar, and a clinical history of hypocalcemia. The patient had pre-existing conditions of anxiety, palpitations, and hyperparathyroidism. Possible confounders for the event included concurrent condition of hypocalcaemia and concomitant medications including methylphenidate (potential ADRs of tachycardia and arrhythmia), venlafaxine (potential ADRs of tachycardia and arrhythmia) as well as trazodone (warning for QT prolongation).

SAEs

The MAH provided narratives of all SAEs reported in the C3G studies including the uncontrolled extension periods.

- Four events of infection in three patients (pneunomia and/or sepsis with Streptococcus pneumoniae in two patients, Pneumocystis jirovecii pneumonia in one patient) were suspected to be related to iptacopan by the investigator. All events resolved with antibiotic therapy.
- Two events (in two patients) of C3G progression, requiring haemodialysis, were reported. They were not suspected to be related to iptacopan (actually, they reflect treatment failure)
- All other events were not suspected related by the investigator. These events included cardiac and gastrointestinal events as well as a few other infections (a pneumococcus-negative pneumonia, pericarditis and urinary tract infections).

Other significant events (or adverse event of special interests)

AEs of special interest (AESI)

Infections caused by encapsulated bacteria

Infections with encapsulated bacteria are a known side effect of complement inhibition. Therefore, vaccination is a prerequisite for treatment with iptacopan. In the placebo-controlled data set, 2 patients in the iptacopan group vs. 1 patient in the placebo group reported this type of infection. In the uncontrolled data set, such an infection occurred in six patients, see Table 33 below.

Table 33: Overview of AESIs for C3G studies (Controlled 200 mg b.i.d. Safety Set and Broad 200 mg b.i.d. Safety Set)

	Controlled 200 mg b.i.d. Safety Set				Broad 200 mg b.i.d. Safety Set	
	LNP023 200 mg b.i.d.		Placebo		LNP023 200 mg b.i.d.	
Safety topic* **Preferred term**	**N=38 n (%)**	**Total exp=18.3 PY m (OccR)**	**N=36 n (%)**	**Total exp=17.8 PY m (OccR))**	**N=101 n (%)**	**Total exp=142.0 PY m (OccR)**
Infections caused by encapsulated bacteria	2 (5.3)	3 (16.4)	1 (2.8)	1 (5.6)	6 (5.9)	9 (6.3)
Otitis media	2 (5.3)	3 (16.4)	0	0 (0.0)	3 (3.0)	5 (3.5)
Pneumonia pneumococcal	0	0 (0.0)	0	0 (0.0)	2 (2.0)	2 (1.4)
Cellulitis	0	0 (0.0)	0	0 (0.0)	1 (1.0)	1 (0.7)
Pneumococcal sepsis	0	0 (0.0)	0	0 (0.0)	1 (1.0)	1 (0.7)
Urethritis gonococcal	0	0 (0.0)	1 (2.8)	1 (5.6)	0	0 (0.0)

n: number of patients with at least one event; m: number of AE episodes; Total exposure in patient-years is computed as (sum of the duration of on-treatment periods over patients, in days)/365.25.
OccR = occurrence rate (number of episodes per 100 patient-years) is calculated as 100*(m divided by the total exposure in patient-years

Update with D90 Response:

Also for the events of infections with encapsulated bacteria, an AE of special interest, an update was provided to include further events from the ongoing open-label extension studies. Reassuringly, the occurrence rate (OccR, right column of the Table 34 below), i.e. the number of events per 100 patient-years (PY) did not relevantly change compared to the previous safety evaluation.

Table 34: Treatment emergent adverse events of special interest by safety topic and preferred term - C3G studies, Controlled 200mg b.i.d. Safety Set and Broad 200mg b.i.d. Safety Set

	Broad 200mg b.i.d. Safety Set	
	LNP023 200mg b.i.d.	
	N=101 n (%)	Total exp=189.8 PY m (OccR)
Infections caused by encapsulated bacteria	9 (8.9)	15 (7.9)
Otitis media	5 (5.0)	8 (4.2)
Pneumonia pneumococcal	2 (2.0)	2 (1.1)
Cellulitis	1 (1.0)	1 (0.5)
Otitis media acute	1 (1.0)	2 (1.1)
Pneumococcal sepsis	1 (1.0)	1 (0.5)
Streptococcal bacteraemia	1 (1.0)	1 (0.5)
Urethritis gonococcal	0	0 (0.0)

Other infections (serious and/or severe)

Again, the number of affected patients was low, precluding meaningful conclusions. For discussion of the serious events, see section on SAEs below.

Thyroid changes

This AESI was defined based on non-clinical findings. One event of increased serum TSH was reported in the placebo group. No differences in mean serum levels of TSH, T3, T4 and rT3 between placebo and iptacopan were observed.

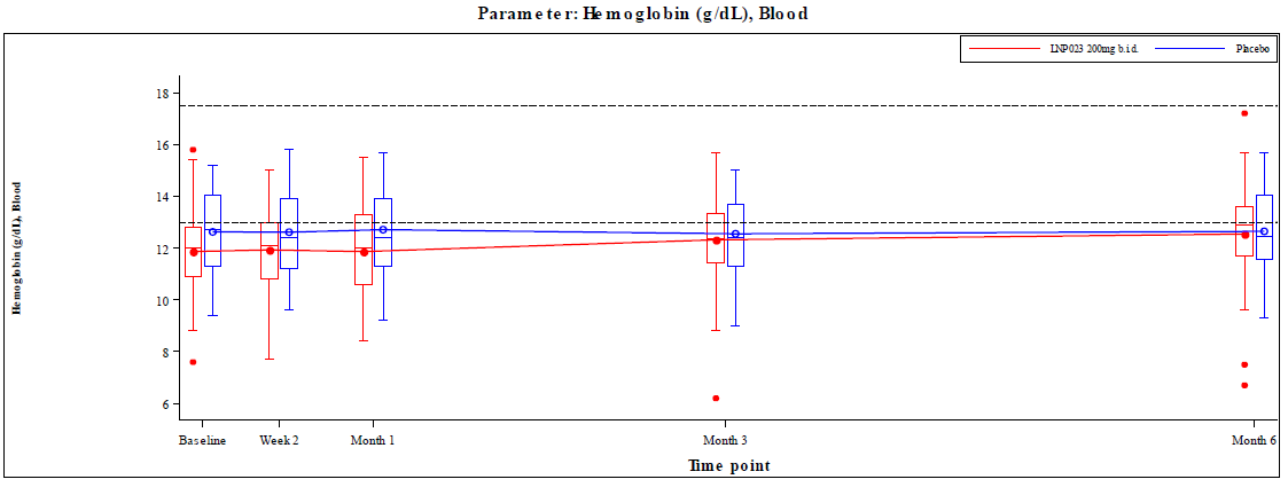
Laboratory findings

In the following, salient laboratory findings are presented and findings that are related to adverse events.

Haematology

Six events of anaemia in iptacopan-treated patients were reported as AEs. Most of these events were moderate in intensity. However, the mean **haemoglobin** level in blood was not affected by iptacopan, see Figure 46 below. The same is true for related haematological parameters such as erythrocyte count or haematocrit.

Figure 46: Haematology: Box plot of haemoglobin by time and treatment - C3G studies; Controlled 200mg b.i.d. Safety Set

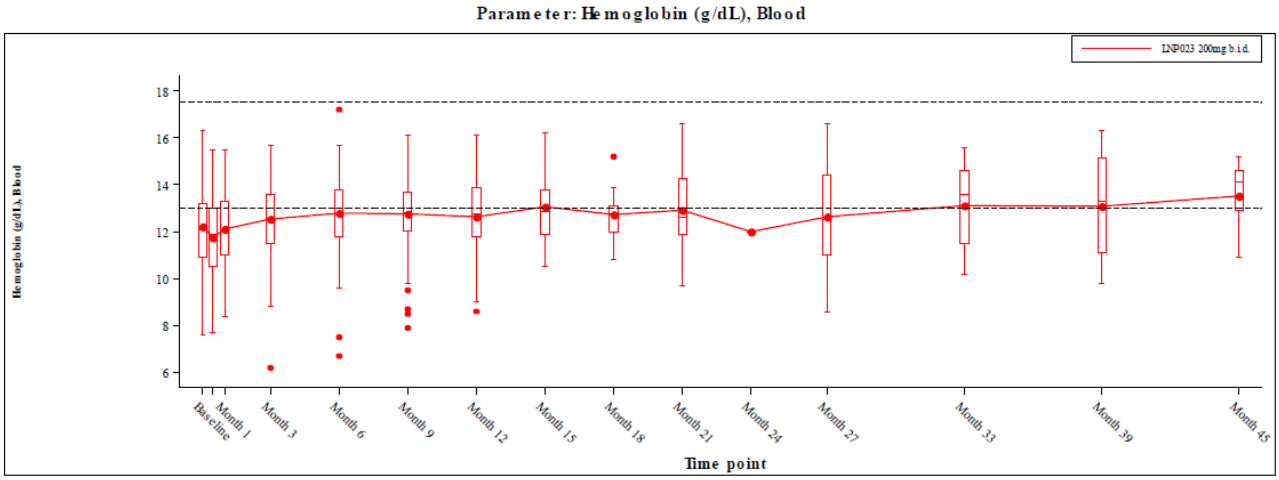


No. of observations

LNP023 200mg b.i.d.	38	35	35	36	33
Placebo	36	35	35	35	32

In the long term, blood haemoglobin slightly increased with time in the iptacopan-treated patients, see Figure 47 below. Placebo data are not available for this period. If real, the Hb increase could be related to improved kidney function.

Figure 47: Haematology: Box plot of haemoglobin by time - C3G studies; Broad 200mg b.i.d. Safety Set



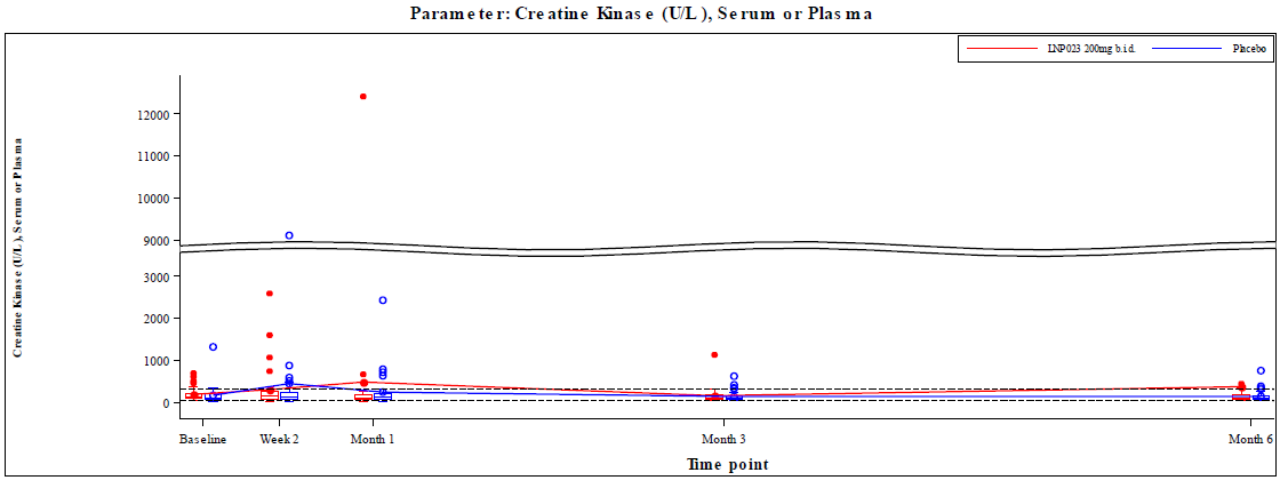
No. of observations

LNP023 200mg b.i.d.	97	86	64	57	64	50	34	10	20	2	20	17	16	9

Serum chemistry

In the pooled iptacopan-treated groups, increased **CK** was reported as AE in eight patients. The applicant explained this by intense physical exercise. Mean serum CK did not increase with iptacopan compared to placebo and did not increase over time in the long term, see figures below.

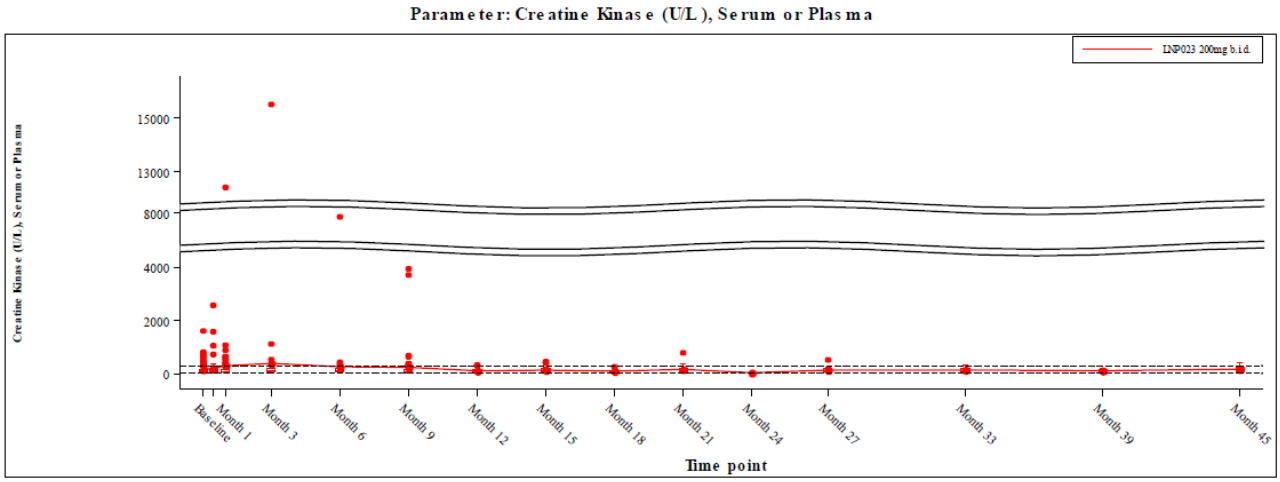
Figure 48: Chemistry: Box plot of serum creatine kinase (CK) by time and treatment - C3G studies; Controlled 200mg b.i.d. Safety Set



No. of observations

LNP023 200mg b.i.d.	38	35	36	35	33
Placebo	36	35	34	35	35

Figure 49: Chemistry: Box plot of serum creatine kinase (CK) by time - C3G studies; Broad 200mg b.i.d. Safety Set

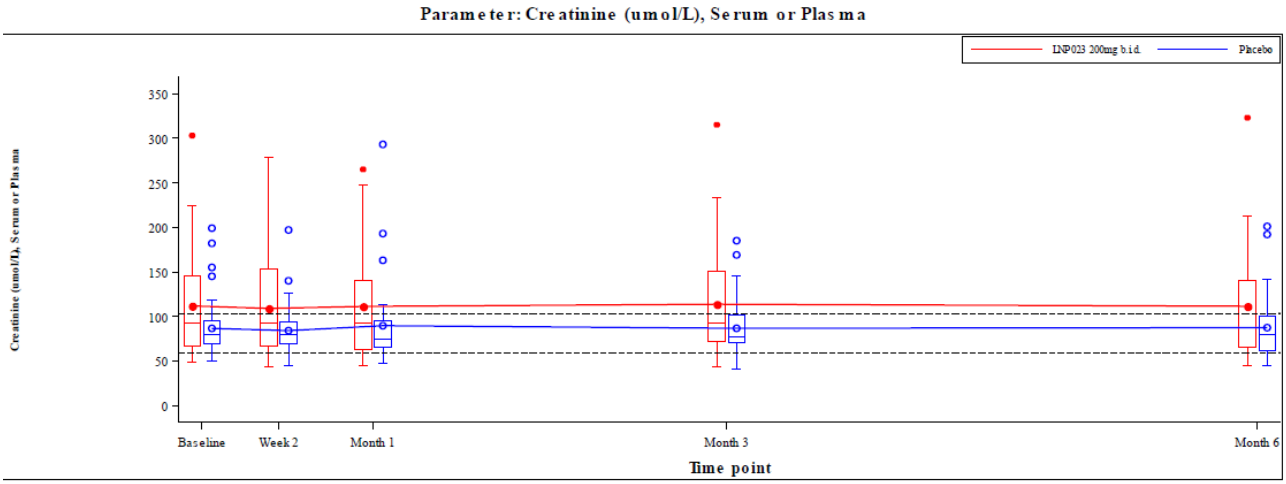


No. of observations

LNP023 200mg b.i.d.	98	87	64	57	64	50	33	7	21	1	20	18	16	9

In the placebo-controlled period, mean serum **creatinine** was not altered with iptacopan compared to placebo, see Figure 50 below. In fact, creatinine was slightly higher in the iptacopan group from baseline onwards, throughout the placebo-controlled period. This could be due to the fact that patients in the iptacopan group had a more progressed disease at baseline (see efficacy section).

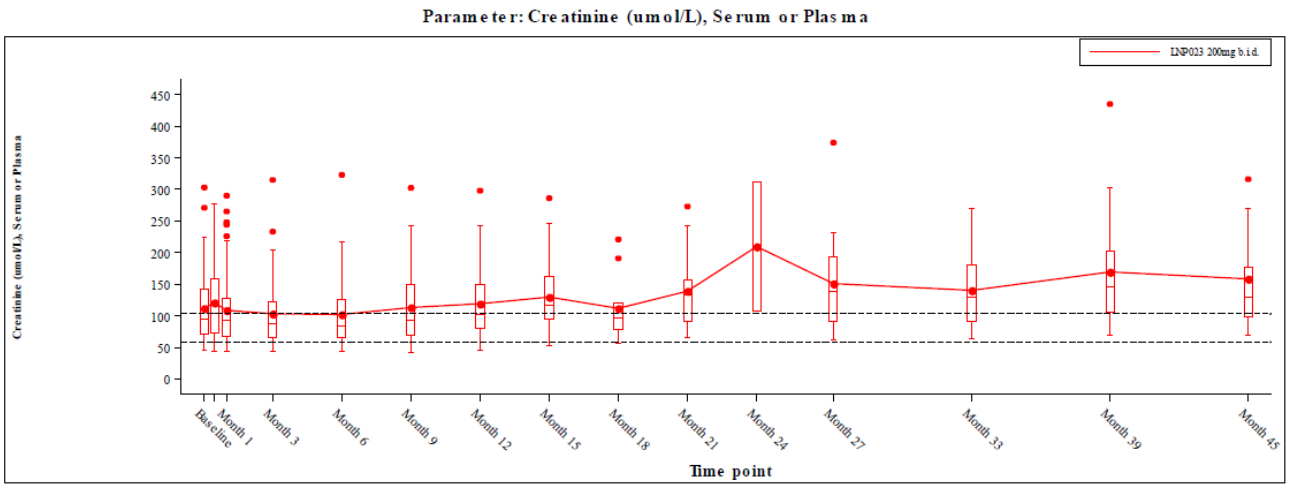
Figure 50: Chemistry: Box plot of serum creatinine by time and treatment - C3G studies; Controlled 200mg b.i.d. Safety Set



No. of observations					
LNP023 200mg b.i.d.	38	36	37	35	33
Placebo	36	35	35	35	35

In the long term, serum creatinine slightly increased during iptacopan treatment, see Figure 51 below. This could be related to disease progression.

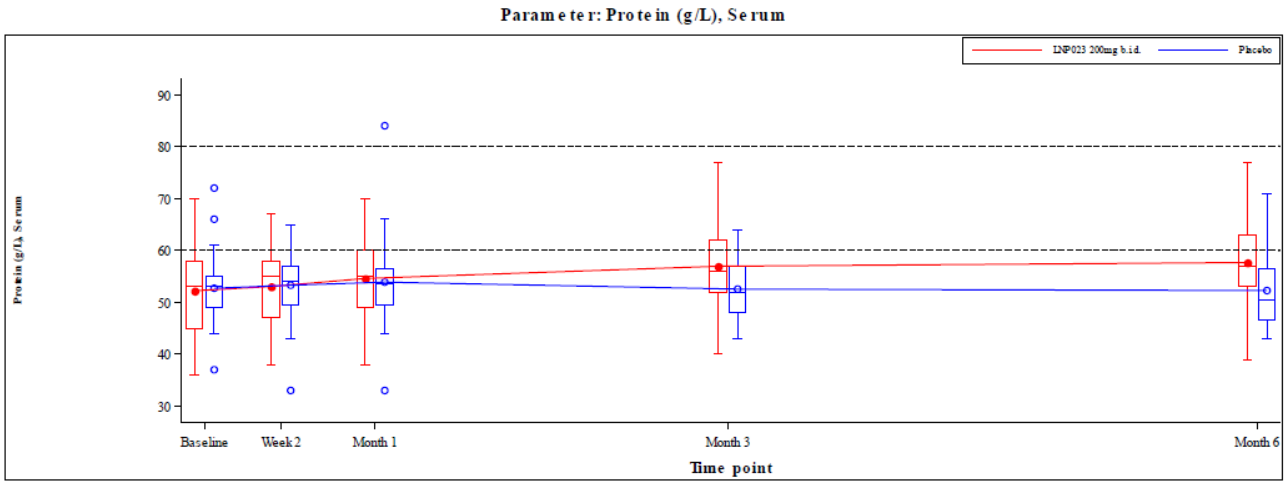
Figure 51: Chemistry: Box plot of serum creatinine by time - C3G studies; Broad 200mg b.i.d. Safety Set



No. of observations														
LNP023 200mg b.i.d.	98	89	64	57	64	50	35	10	21	2	20	18	16	9

A slight increase over time in mean **serum protein** concentration was observed with iptacopan compared to placebo as shown in the following two figures. Serum protein increased up to Month 12 with iptacopan and reached low normal values. This effect, if real, could be related to the decrease in renal protein loss with iptacopan.

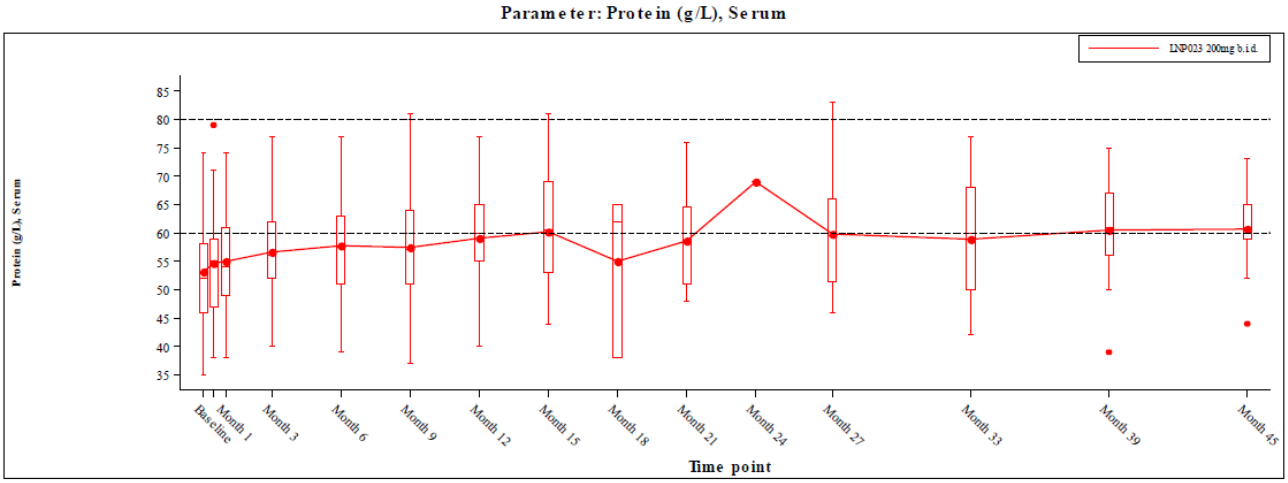
Figure 52: Chemistry: Box plot of serum protein by time and treatment - C3G studies; Controlled 200mg b.i.d. Safety Set



No. of observations

LNP023 200mg b.i.d.	33	31	31	30	29
Placebo	33	32	32	32	32

Figure 53: Chemistry: Box plot of serum protein by time - C3G studies; Broad 200mg b.i.d. Safety Set



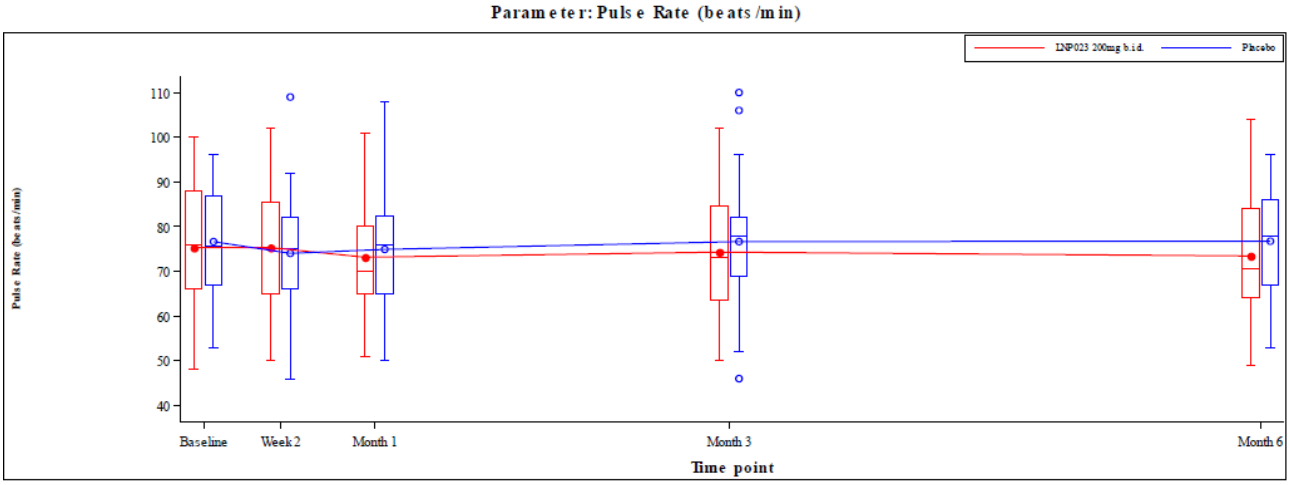
No. of observations

LNP023 200mg b.i.d.	93	83	59	52	59	45	30	3	20	1	20	18	16	9

Vital signs

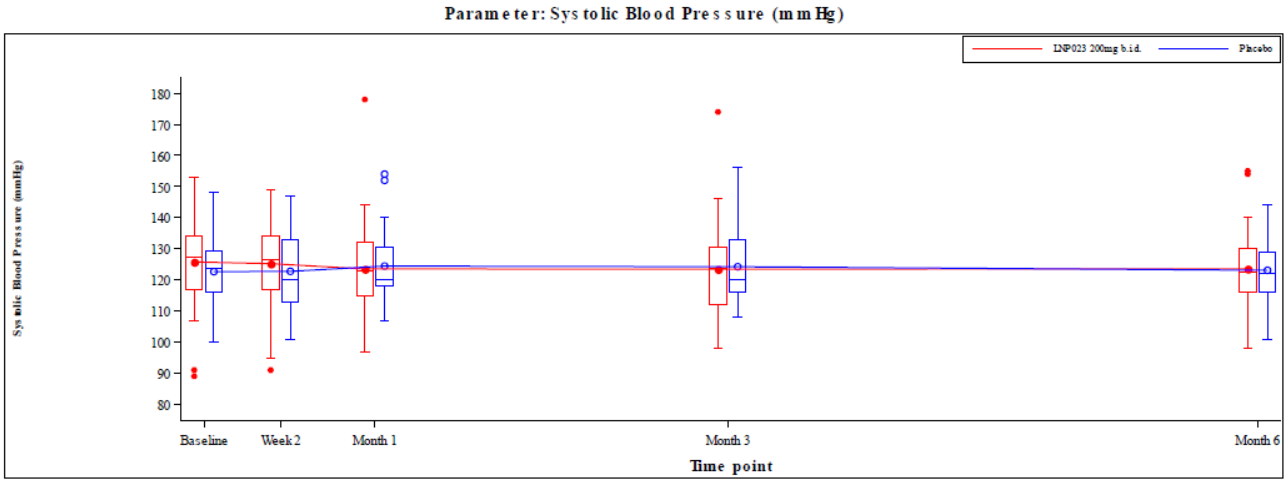
Iptacopan had no effect on heart rate (HR) and blood pressure (BP) during the placebo-controlled period, see figures below.

Figure 54: Box plot of blood pressure and heart rate by time and treatment - C3G studies; Controlled 200mg b.i.d. Safety Set



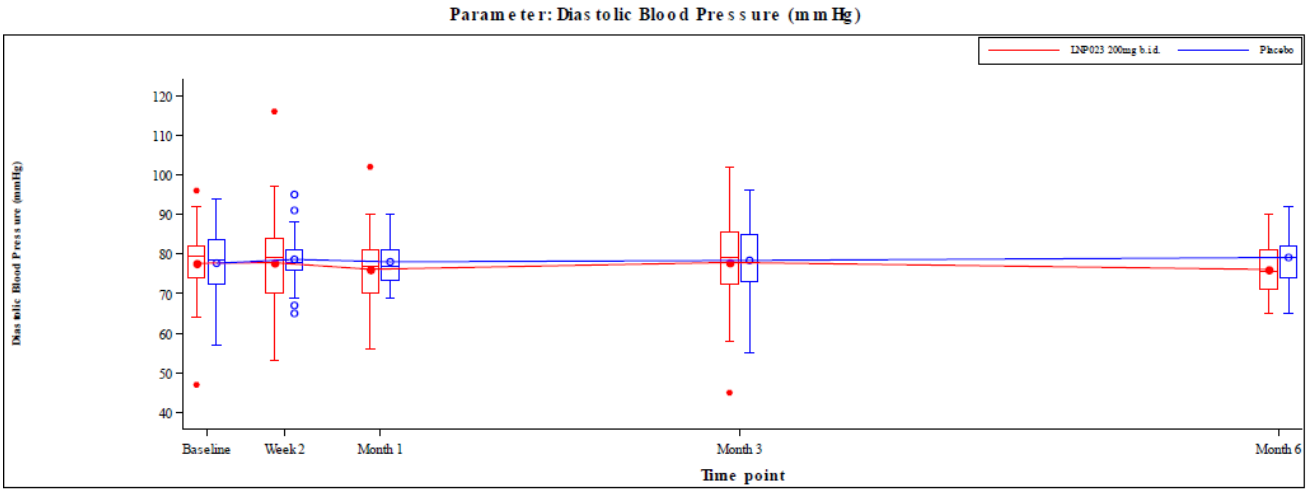
No. of observations

LNP023 200mg b.i.d.	38	36	37	36	34
Placebo	36	35	36	35	35



No. of observations

LNP023 200mg b.i.d.	38	36	37	36	34
Placebo	36	35	36	35	35

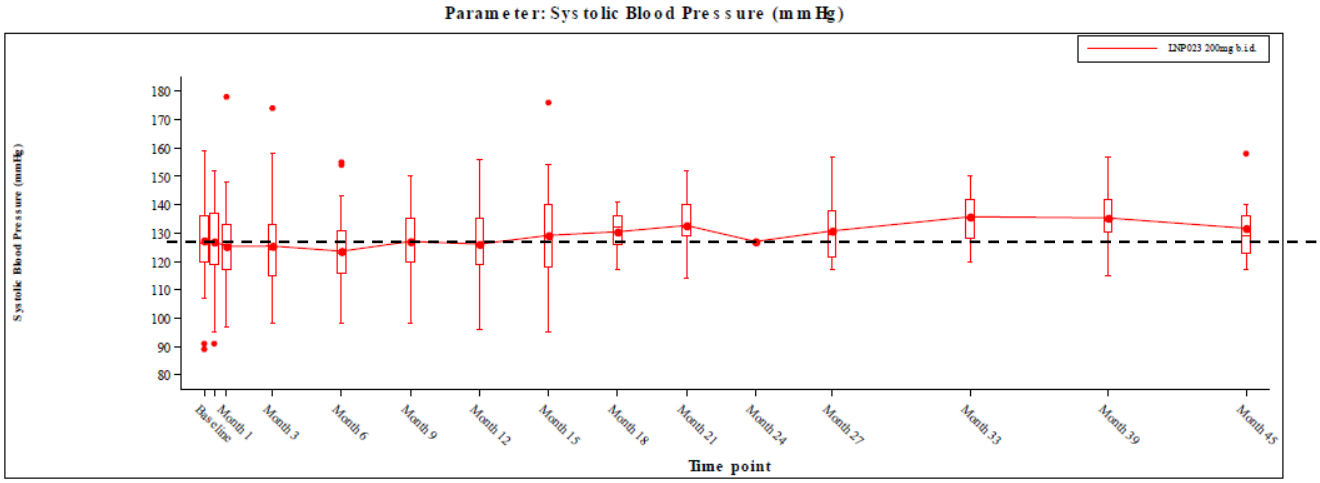


No. of observations

LNP023 200mg b.i.d.	38	36	37	36	34
Placebo	36	35	36	35	35

Also in the long term, there was no major change in BP or HR from baseline. As an example, systolic BP is shown in the Figure 55 below

Figure 55: Box plot of systolic blood pressure and heart rate by time point - C3G studies; Broad 200mg b.i.d. Safety Set

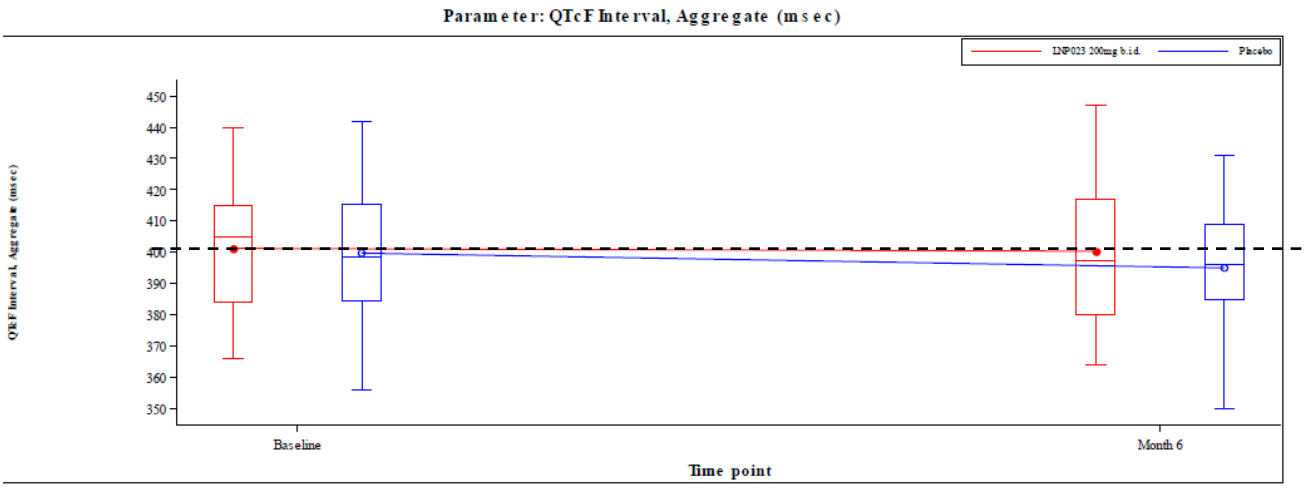


No. of observations

LNP023 200mg b.i.d.	98	93	63	56	64	50	35	9	21	1	20	19	16	9

No hints for QTc prolongation was detected (see Figure 56 below). Notably, iptacopan does not alter heart rate so that any artificial effects by over- or under-correction for HR do not play a role.

Figure 56: Box plot of QTc intervals by time and treatment - C3G studies; Controlled 200mg b.i.d. Safety Set



No. of observations		
LNP023 200mg b.i.d.	36	34
Placebo	36	35

Safety in special populations

There were no notable differences in the safety profile of iptacopan exhibited by intrinsic factor subgroup analyses (age, sex, race, baseline eGFR and baseline UPCR). However, the assessments were limited by small subgroup sample sizes

Safety related to drug-drug interactions and other interactions

Subgroup analysis based on the use of concomitant immunosuppressive therapies was performed in C3G patients to evaluate if iptacopan increases the risk of infections in these patients. In the Controlled safety set, there was no evidence showing that the risks of Infections and infestations (SOC) was increased with iptacopan treatment compared to placebo in patients on concomitant immunosuppressive therapies.

Discontinuation due to adverse events

In the Controlled safety set, TEAEs leading to study treatment interruption were reported in 10.5% and 11.1% of patients in the iptacopan and placebo groups, respectively. The most reported TEAE leading to interruption of iptacopan treatment was COVID-19 (reported in 4 patients, 10.5%).

In the Broad safety set, iptacopan dose was reduced for one recurrent C3G patient to 100 mg b.i.d., in accordance with Study B12001B protocol guidance, for 23 days due to non-serious tonsillar hypertrophy which was suspected to be study treatment related by the Investigator, was treated with ceftriaxone, and resolved after 14 days. The dose was subsequently increased back to 200 mg b.i.d. The patient discontinued iptacopan treatment due to progression of recurrent C3G (following a further dose reduction to 100 mg b.i.d. for 7 days).

In total 8.9% of Broad safety set patients reported a total of 22 TEAEs that required study iptacopan treatment interruption. In C3G patients (N=90), 6.7% of patients had a total of 17 TEAEs that required iptacopan treatment interruption:

- One C3G patient had an interruption of iptacopan treatment on 2 separate occasions:
  - The first interruption in iptacopan treatment was due to the concurrent events of:
    - Blood culture positive SAE (causality suspected by Investigator)
    - COVID-19 and respiratory syncytial virus positive (both non-serious, both moderate, concomitant drug/therapy received for both events, both resolved after 19 days, causality not suspected by Investigator for both events)
  - The second interruption in iptacopan treatment was due to the concurrent SAEs of pneumococcal sepsis, pneumonia pneumococcal, septic shock (all causality suspected by Investigator), and acute left ventricular failure (causality not suspected by the Investigator). The other events (non-serious) reported concurrently such as vitamin D deficiency, cardiomyopathy, acute kidney injury, hyponatremia and microcytic anemia were not suspected to be related to iptacopan by the Investigator
- One C3G patient had an interruption in iptacopan treatment due to the SAE of drug abuse (causality not suspected by the Investigator)
- One C3G patient had an interruption in iptacopan treatment due to the SAE of acute kidney injury (causality not suspected by the Investigator)
- Three C3G patients had iptacopan treatment interrupted due to 1 event each of COVID-19 (all non-serious, all mild, concomitant drug/therapy received for all events, resolved after 6 days, 24 days and 10 days respectively, causality not suspected by Investigator for all 3 events)

In recurrent C3G patients (N=11), 27.3% of patients had a total of 5 TEAEs that required iptacopan treatment interruption:

- One recurrent C3G patient had an interruption of iptacopan treatment due to the concurrent SAEs (causality suspected by the Investigator) of pneumonia pneumococcal, acute respiratory distress syndrome and septic shock
- One recurrent C3G patient had an interruption in iptacopan treatment due the SAE of pyelonephritis (causality not suspected by the Investigator)
- One recurrent C3G patient had an interruption in iptacopan treatment due to COVID-19 (non-serious, mild, concomitant drug/therapy not required, resolved after 42 days, causality not suspected by Investigator).

Post marketing experience

First approval for iptacopan was obtained in the US on 05 December 2023 and in the EU on 17 May 2024. Post-marketing safety data was assessed and discussed in the first Periodic Safety Update Report (PSUR); data lockpoint: 04-Jun-2024. Based on this assessment it was considered that the benefit-risk profile of iptacopan remained unchanged for the approved indication (treatment of PNH).

2.5.1. Discussion on clinical safety

The safety database of iptacopan in the C3G population is limited. Placebo-controlled data are only available in 36 or 38 patients per group (iptacopan and placebo) for 6 months. Uncontrolled data are available for a longer period, up to 50 months (extension study ongoing). However, with uncontrolled data, it is difficult to obtain a relationship between iptacopan and a certain type of AE. Safety information is also available from use of iptacopan in PNH. However, as discussed in the initial MAA for PNH, the most salient side effects of iptacopan, i.e. headache, blood pressure increase heart rate decrease and increase in serum cholesterol, were specific to the pathophysiology of PNH. Indeed, these effects were not observed in the C3G population. In the C3G population, AEs of infection as well as anaemia and increase in serum CK were observed more frequently with iptacopan than with placebo. The MAH explained that CK increase was related to physical activity. This explanation is plausible since the increases were reversible and there was no persistent increase in mean serum CK with iptacopan compared to baseline or compared to placebo. Anaemia was present already at baseline in some subjects. During iptacopan treatment, blood haemoglobin (Hb) values tended to increase slightly. Thus, there is no hint that iptacopan adversely affects Hb; the events of anaemia reported in the studies can also be related to the underlying kidney disease.

Regarding infections, it is known that complement inhibition can increase the frequency of infections with encapsulated bacteria. Hence, vaccination was required for study participation. The largest difference between iptacopan and placebo was observed for nasopharyngitis (4 pts. vs. 1 pt.). Infections with encapsulated bacteria were followed as AEs of special interest. In the controlled study period, there were two cases of otitis media in the iptacopan group vs. none in the placebo group. In the complete dataset, also including the uncontrolled extension periods, six participants reported a total of nine events of infection with encapsulated bacteria, including four severe events (in three pts.). Most of them were pneumococcal pneumonia and/or sepsis. In C3G clinical studies, 1/101 (0.99%) patients with C3G reported serious pneumococcal infection with pneumonia and sepsis while receiving treatment with iptacopan; as per study protocol the patient had been vaccinated against *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* type B and recovered following treatment with antibiotics. Iptacopan treatment was interrupted and restarted after recovery. Pneumococcal infections were included in under the adverse reactions in the Product information. All events resolved with appropriate therapy.

The MAH was asked during the procedure why some infections were considered related to iptacopan by the investigator and others were not. A bias due to expectation (because complement inhibitors are known to be related to certain types of infection) should be excluded. The MAH acknowledged the possibility of such a bias but argued that it would be conservative in respect to safety evaluation which was considered acceptable by the CHMP. Assuming a relationship too often would be rather unfavourable for the safety profile of iptacopan. In the worst-case scenario, one would assume that all infections with encapsulated bacteria are related to iptacopan. But even in this worst-case scenario, the safety profile of iptacopan remains acceptable since the number of events was rather low, and all events responded to anti-infective treatment.

Thus, the iptacopan studies in C3G patients did not reveal new safety concerns.

However, information on long-term safety, particular in the C3G indication, is limited to date. Differences in the safety profile of iptacopan in C3G patients compared to use in other indications cannot be excluded, and safety data for long-term use of iptacopan in combination with RAS inhibitors are also missing. The MAH will submit post authorisation the safety evaluations of the ongoing C3G long-term study CLNP023B12001B on long-term safety, tolerability and efficacy of iptacopan in patients with C3G, recurrent C3G as described in the risk management plan (category 3 study).

2.5.2. Conclusions on clinical safety

Safety information in the C3G programme was limited by the low number of participants in the controlled study (APPEAR-C3G, first part). Information from uncontrolled extension studies is less informative due to the lack of comparator. Reassuringly, neither the controlled nor the uncontrolled study periods revealed hints for relevant safety concerns of iptacopan. Safety information is also available from the PNH programme; notably, in PNH patients, adverse events occurred that were related to the pathophysiology of PNH and that therefore are not relevant for C3G.

Since C3G is a rare disease, it is acceptable that the safety information is limited and will be complemented post authorisation as described in the risk management plan.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version 2.3 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.3 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 2.3 with the following content:

Safety concerns

Important identified risks	• Infections caused by encapsulated bacteria
Important potential risks	• Serious haemolysis following discontinuation of iptacopan (PNH indication) • Malignancies
Missing information	• Use in pregnant patients • Long-term safety (>2 years)

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
CLNP023C12001B Long-term safety and tolerability of iptacopan in patients with Paroxysmal Nocturnal Hemoglobinuria (PNH). Status: Ongoing	The purpose of this study is to evaluate the long-term safety, tolerability and efficacy of iptacopan in patients with PNH and to provide continued access to patients who have completed the treatment extension period (without tapering down) of the Phase II and Phase III trials and derived benefit from iptacopan treatment.	Infections caused by encapsulated bacteria, Serious haemolysis following discontinuation of iptacopan, Malignancies, Long-term safety (>2 years)	Final report submission	31-May-2029
CLNP023C12003 PASS in iptacopan-treated PNH patients using IPIG Registry data Status: Planned	The purpose of this study is to characterize the identified and potential risks of iptacopan in the real-world clinical practice. Further study objectives are to provide additional data for the missing information (use in pregnancy and long-term safety) and to evaluate effectiveness of additional risk minimization measures (aRMMs) related to the required and recommended vaccinations in the iptacopan-treated PNH population. This study will use data collected through the International PNH Intere st Group (IPIG) registry (IPIG Registry). The aim of the IPIG registry is to develop an international database to prospectively collect observational data on patients with PNH (regardless of treatment received) covering clinical outcomes, patient reported outcomes, and health-resource utilization on all enrolled patients, as well as long term safety	Infections caused by encapsulated bacteria, Serious haemolysis following discontinuation of iptacopan, Malignancies, Use in pregnant patients, Long-term safety (>2 years)	Annual update	Progress reports on enrollment and intermediate analysis results to be provided annually with the PSUR.
			Final report submission	31-Mar-2030

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	data. According to the IPIG Registry protocol, Novartis will only have access to the data from PNH patients treated with iptacopan. The iptacopan PASS (a secondary analysis of the data collected in the IPIG Registry) will thus be a single-arm study with no internal comparator.			
CLNP023B12001B Extension study to evaluate the long-term efficacy, safety and tolerability of iptacopan (LNP023) in C3G and IC-MPGN patients. Status: Ongoing	The purpose of this study is to evaluate the long-term safety, tolerability and efficacy of iptacopan in patients with C3G, recurrent C3G or IC-MPGN and to provide continued iptacopan access to patients who have completed the Phase II and Phase III trials	Infections caused by encapsulated bacteria, malignancies, use in pregnant patients, long-term safety (>2 years)	Final Study Report	31-Dec-2034

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Infections caused by encapsulated bacteria	**Routine risk communication** Risk addressed in SmPC Sections: - Contraindications (Section 4.3) - Warning and Precautions (Section 4.4) - Undesirable Effects (Section 4.8) Risk addressed in Package Leaflet (PL) - Section 2 and 4 SmPC section 4.3 and 4.4 where advice is given on vaccination/prophylactic antibiotic requirements. - SmPC section 4.4 where recommendation for monitoring of early signs and symptoms of infections is given. Legal status: Prescription only medicine **Additional risk minimization measures:** • Healthcare professional guide • Patient/caregiver guide • Patient safety card • Controlled access system	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study CLNP023C12001B **Final study report date** 31-May-2029 CLNP023C12003, PASS in iptacopan-treated patients using IPIG Registry data **Final study report date** 31-Mar-2030 Study CLNP023B12001B **Final study report date** 31-Dec-2034

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines)	
Serious haemolysis following discontinuation of iptacopan (PNH indication)	**Routine risk communication** Risk addressed in SmPC Sections: - Posology and administration (Section 4.2) - Warning and Precautions (Section 4.4) Risk addressed in PL - Section 3 SmPC section 4.2 where description of the risk, along with treatment guidance is provided. - SmPC section 4.4 where monitoring of PNH manifestations after discontinuation is discussed. Calendarized packaging to aid in patient adherence to the dosing schedule. Legal status: Prescription only medicine **Additional risk minimization measures:** • Healthcare professional guide • Patient/caregiver guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study CLNP023C12001B **Final study report date** 31-May-2029 CLNP023C12003, PASS in iptacopan-treated patients using IPIG Registry data **Final study report date** 31-Mar-2030
Malignancies	**Routine risk communication** Legal status: Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study CLNP023C12001B **Final study report date** 31-May-2029 CLNP023C12003, PASS in iptacopan-treated patients using registry data **Final study report date** 31-Mar-2030 Study CLNP023B12001B **Final study report date** 31-Dec-2034
Use in pregnant patients	**Routine risk communication** Missing information addressed in SmPC sections - Fertility, pregnancy and lactation (Section 4.6) **-** Preclinical safety data (Section 5.3) Missing information addressed in PL - Section 2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Preclinical data and risks of pregnancy in PNH patients described. Lack of data on iptacopan in pregnancy and need for a risk-benefit assessment stated. Legal status: Prescription only medicine **Additional risk minimization measures:** None	CLNP023C12003, PASS in iptacopan-treated patients using IPIG Registry data **Final study report date** 31-Mar-2030 Study CLNP023B12001B **Final study report date** 31-Dec-2034
Long-term safety (>2 years)	**Routine risk communication:** Legal status: Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study CLNP023C12001B **Final study report date** 31-May-2029 CLNP023C12003, PASS in iptacopan-treated patients using IPIG Registry data: **Final study report date** 31-Mar-2030 Study CLNP023B12001B **Final study report date** 31-Dec-2034

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.6, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

Please refer to the full PI in attachment.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable, as changes due to the introduction of the new C3G indication are minimal and are not considered to affect readability.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

C3G is an ultra-rare (incidence 1-2 per 1 million people) complement-mediated kidney disease caused by dysregulation of the complement AP in plasma and in the glomerular microenvironment, resulting in accumulation of complement proteins such as C3 in the glomeruli. This dysregulation is mediated by acquired autoantibodies and/or genetic variants inducing overstimulation of the AP while subsequent deposition of complement proteins and their cleavage products results in proliferative glomerulonephritis and capillary-wall remodelling of the glomerulus with the formation of double contours. These structural changes lead to progressive loss of kidney function and ultimately, kidney failure.

Based on findings seen only under electron microscopy, C3G is classified into two slightly distinct histopathologic entities, namely C3 glomerulonephritis (C3GN) and dense deposit disease (DDD). C3G that develops in the patient's native kidneys is referred to as native C3G whereas, when it reoccurs in a patient post-kidney transplantation, it is called recurrent C3G.

Patients often present with haematuria (presence of blood in urine), sub-nephrotic or nephrotic range proteinuria, arterial hypertension, peripheral oedema, loss of appetite, sleep problems, and fatigue.

The new indication reads as follows (wording as proposed by the Applicant):

"Fabhalta is indicated for the treatment of adult patients with complement 3 glomerulopathy (C3G) in combination with a renin-angiotensin system (RAS) inhibitor, or in patients who are RAS-inhibitor intolerant, or for whom a RAS inhibitor is contraindicated (see section 5.1)."

3.1.2. Available therapies and unmet medical need

There is no approved treatment and no standard of care for C3G; hence, iptacopan could address an unmet medical need. Practice points from the "Kidney Disease: Improving Global Outcomes" (KDIGO 2021) Work Group relied primarily on expert opinion with some support from retrospective studies (Goodship et al, 2017). Therapeutic options are angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), which have anti-proteinuric and anti-hypertensive effects and reduce intraglomerular pressure as well as immunosuppressives (corticosteroids, mycophenolate mofetil, mycophenolate sodium, calcineurin inhibitors, rituximab, cyclophosphamide). The immunosuppressive drug mycophenolic acid (administered as mycophenolate mofetil or mycophenolate sodium) has been used with some success when combined with steroids but the results in these uncontrolled studies were mixed (Bomback et al 2018, Bomback et al 2012, Avasare et al 2018). Further, anti-complement therapies eculizumab and ravulizumab are used off-label. The anti-complement drug eculizumab targets the terminal complement cascade and has shown limited efficacy in C3G patients (Gurkan et al 2013, Welte et al 2018). While kidney transplantation is a potential treatment option when kidney failure develops, persistent AP dysregulation (unaffected by kidney transplantation) will result in recurrence of C3G in 55-85% of recipients.

3.1.3. Main clinical studies

Use of iptacopan in C3G is mainly supported by:

- 74 adult C3G patients who completed the 6-month randomized, double-blind, placebo-controlled part of the pivotal Phase 3 Study CLNP023B12301 (**APPEAR-C3G**). Studied patients had histologically confirmed native C3G, proteinuria at baseline of >1g/g, and a baseline eGFR ≥30ml/min/1.73m^2; 73 patients who completed the 6-month open-label period.

Supportive evidence came from:

- completed phase 2 study X2202: 27 adult patients with C3G (n=16) or recurrent C3G (n=11) who completed 3 months of treatment; this study was open-label, non-controlled.

- ongoing long-term extension study CLNP023B12001B (66 months). Patients who completed APPEAR-C3G and Study X2202 and rolled over into the open-label, non-controlled Study B12001B as of the data cut-off date of 01-Oct-2023. As per CHMP request during the review, selected long-term data were submitted as of the data cut-off date of 06-May-2024.

3.2. Favourable effects

- APPEAR-C3G met its primary objective of demonstrating superiority of iptacopan over placebo in proteinuria reduction. There was a statistically significant (1-sided p=0.0014) and clinically meaningful relative reduction in 24h UPCR of 35.1% (95% CI: 13.8%, 51.1%) following 6 months of treatment with iptacopan compared to placebo. The adjusted geometric mean ratios to baseline of 24h UPCR at Day 180 in the iptacopan and placebo arms were 0.70 (95% CI: 0.572, 0.852) and 1.08 (95% CI: 0.881, 1.313), respectively (i.e., reduction of 24h UPCR from baseline with iptacopan was 30% compared to an increase of 8% with placebo). Baseline imbalances in UPCR and eGFR across the two treatment arms did not affect the primary efficacy results. Subgroup analyses showed consistent treatment effects in favor of iptacopan.
- In the iptacopan arm, the proportion of participants with nephrotic range proteinuria decreased from 55.3% at baseline to 31.6% at Day 180 compared to an increase of 30.6% at baseline to 41.7% at Day 180 in the placebo group.
- The reduction in 24h UPCR with iptacopan treatment was sustained to Day 360 in a subset of participants initially randomized to iptacopan (−40%, n=37). Additionally, the reduction of 24h UPCR in a subset of participants originally randomized to placebo and who were transitioned to open-label iptacopan at Day 180 was 27% (n=34) at Day 360 compared to the Day 1 baseline.
- The reduction in geometric mean of FMV UPCR in participants randomized to the iptacopan arm was 34% at Day 180 (n=38) and this was sustained up to Day 360 (n=35) with a 38% reduction compared to baseline. The reduction in geometric mean of FMV UPCR in participants originally randomized to placebo and who were transitioned to open-label iptacopan at Day 180, was 34% at Day 360 (n=33) compared to the Day 1 baseline. A rapid reduction of FMV UPCR was observed in the iptacopan arm (Day 1 to Day 14) and was replicated in the placebo arm (Day 180 to Day 210) after initiation of iptacopan at Day 180.
- The adjusted mean changes from baseline in eGFR at the Day 180 visit in the iptacopan arm and the placebo arm were 1.30 mL/min/1.73m^2 (95% CI: −2.136, 4.726) and –0.86 mL/min/1.73m^2 (95% CI: −4.357, 2.635), respectively. A numerical improvement of 2.16 mL/min/1.73m^2 (95% CI: −2.749, 7.061) in eGFR was observed with iptacopan vs. placebo treatment at 6 months; this did not achieve statistical significance (multiplicity adjusted 1-sided p=0.3241). In a pre-specified analysis of all study participants combined (iptacopan plus placebo arms), the mean pre-treatment annualized

eGFR slope showed rapid decline with −7.57 mL/min/1.73m^2/year. Following the commencement of iptacopan treatment, there was stabilization of annualized eGFR slope at +1.44 mL/min/1.73m^2/year, which equated to a predicted preservation of eGFR of 9.01 mL/min/1.73m^2/year (p <0.0001) compared with the scenario where iptacopan had not been commenced and eGFR continued to deteriorate at the pre-treatment rate. To meet the composite renal endpoint, participants had to achieve a >50% reduction in 24h UPCR and stabilization of eGFR (defined as a ≤ 15% decrease). Iptacopan therapy resulted in a statistically significant 7-fold increase in the odds (OR=7.15, 1-sided p=0.0083, multiplicity adjusted 1-sided p=0.0166) of participants meeting the composite renal endpoint at Day 180 compared to placebo. The difference in the proportions of participants in the iptacopan and placebo arms was 0.23 (95% CI: 0.072, 0.394). These results were primarily driven by the 24h UPCR component while most participants achieved eGFR stabilization in both treatment arms *(see also uncertainities and limitations of favorable effects).*

- Iptacopan reduced glomerular C3 deposition by an adjusted mean difference for iptacopan vs. placebo of −1.88 in the C3 deposit score at Day 180 (1-sided p=0.0053).

  Important favourable effect in supportive study X2201 (phase 2 study which included 11 patients with recurrent C3G= Cohort B)

  Cohort A: Iptacopan reduced UPCR (45% reduction from baseline to Week 12, two-sided p=0.0003), and stabilized kidney function (eGFR, SCR, CrCL).

  Cohort B (recurrent disease): proteinuria and eGFR remained largely unchanged, starting from normal BL values (proteinuria at baseline 0.21 g/g, mean change from baseline -0.61g/g). C3 deposit score improved by -2.50 at week 12 compared to BL.

3.3. Uncertainties and limitations about favourable effects

The benefit of proteinuria reduction is moderated by a smaller than expected effect size (35% vs placebo). However, consistent findings in additional analyses on proteinuria (proteinuria determination in FMV urine, change in the proportion of patients with nephrotic range proteinuria) support the clinical relevance of the observed effect size of the primary endpoint.

Some uncertainty as regards eGFR related results in APPEAR-C3G remained. First, there was no clear explanation for the acute positive effect on eGFR. As total and chronic slope were largely similar, the impact on the iptacopan treatment effect over the longer-term was considered low. Second, the eGFR slope increase in the placebo arm of 4.56 mL/min/1.73m2/year could not be explained. It has to be recognised, in case of an interventional effect, this would likewise have added to iptacopan action. This uncertainty impairs the robustness of the pre-/on-study eGFR slope comparisons.

No clear change in the histologic total activity score in favour of iptacopan could be shown (difference in the histological total activity score with iptacopan −1.95, 95% CI: −2.691, −1.201; with placebo −1.11, 95% CI: −1.831, −0.394; mean difference of −0.83 at Day 180, not statistically significant, 1-sided p=0.0579). However, major improvement in histopathology during the six months period could not be expected; little could be concluded from 12 Month histopathology data, as a renal biopsy was performed in six patients only. The few data available showed a stable histologic activity score up to 12 Months.

Improvement of kidney function did not translate into an improvement in the patient's key symptom fatigue (mean FACIT-Fatigue scores at baseline were in the normal range in the iptacopan arm 42.4, SD 10.08 and in the placebo arm 41.9, SD 8.91; adjusted mean difference of change from baseline in the FACIT-Fatigue total score in the iptacopan and placebo arms was −2.60 (1-sided p=0.9310).

The benefit in subgroups (with lower degrees of baseline proteinuria, with recurrent C3G) had been discussed during the procedure.

The subgroup analysis separating at a proteinuria of 1.8g/g at baseline showed maintained proteinuria lowering efficacy in patients with baseline proteinuria below 1.8g/g. The subset with baseline proteinuria below 1.8 g/g was small (n=5 in the iptacopan group; n=8 in the placebo group), representing 18% of the overall APPEAR-C3G population. The geometric mean (CI) was 0.84 (0.27-2.60) in this subgroup. As regards the effect on a deceleration of eGFR decline, the smaller between-treatment difference with regard to eGFR decline in patients with lower-grade proteinuria was explained by a slower eGFR decline in the placebo group in non-nephrotic range patients. To sum up, iptacopan seems to be effective (proteinuria reduction, stabilization of eGFR) regardless of the level of baseline proteinuria. As only 10% of C3G patients present with proteinuria below 1g/g according to natural history data, the APPEAR-C3G population seemed largely representative for the broad target population. Overall, treatment with iptacopan should start once the diagnosis C3G is made in order to prevent further damage to the kidney.

Iptacopan is also expected to work likewise in recurrent C3G as it shares a common disease pathophysiology with native C3G. These patients are at risk of allograft loss and have a high medical need for eGFR decline decelerating therapy. While mechanistic findings (reduction of C3 deposit score, biomarkers reflective of alternative pathway activation) showed beneficial effects in recurrent disease, results for proteinuria reduction and deceleration of eGFR decline were less clear (uncontrolled study X2202). Due to the sparsity of data, these were also explored on an individual patient level. Overall, with iptacopan UPCR and eGFR essentially remained stable for up to 48 months in patients with recurrent disease. There were two drop-outs with renal deterioration, but these subjects had several additional conditions that could have contributed to renal damage.

In addition, some uncertainty remained with regard to the impact of concomitant immunosuppressive therapy (the effect size of proteinuria reduction was about 3-fold larger in patients without concomitant use of immunosuppressive agents in APPEAR-C3G). The relatively small effect size on proteinuria reduction of 14.5% in the IS-treated subset has to be seen in the light of prior unresponsiveness to prolonged background therapy. The most likely explanation is the more aggressive and treatment-resistant nature of C3G in IS-treated patients; this was supported by an analysis in IS-treated placebo patients, who showed a 20% increase in 24-hour UPCR while IS-untreated placebo patients showed a 4% decrease over the six month double-blind period in APPEAR-C3G; a switch from placebo to iptacopan at Day 180 led to a reversal of the aforementioned 20% increase in UPCR from Day 180 to Day 360 (adjusted geometric mean ratio to baseline decreased from 1.20 (95% CI: 0.92, 1.57) at Day 180 to 0.97 (95% CI: 0.72, 1.30) at Day 360). This decrease upon iptacopan initiation is considered a benefit, especially when contrasting it to the prior increase in proteinuria despite treatment with optimized SoC (immunosuppressive agents and RASi agents).

Remaining uncertainty as regards treatment of patients with proteinuria below 1g/g, patients with recurrent disease, and patients with concomitant IS therapy is reflected in the product information.

3.4. Unfavourable effects

In the placebo-controlled period of the phase 3 study APPEAR-C3G, 30 patients (78.9%) in the iptacopan group vs. 24 pts (66.7%) in the placebo group suffered at least one AE. This difference was mainly driven by infections and by investigations. Among the infections, cases of nasopharyngitis and COVID-19 were most frequent. The most frequent abnormal laboratory investigation was increased serum CK. However, CK increase was transient, and the MAH reported that the events were linked to physical activity.

Regarding patients suffering at least one serious AE (SAE), there was also a numerical imbalance, disfavouring iptacopan. Reassuringly, the absolute number of cases was low, 3 (7.9%) in the iptacopan

group vs. 1 (2.8%) in the placebo group. Further SAEs were reported in the uncontrolled studies or study periods, among them cases of infection with encapsulated bacteria, a known side effect of complement inhibitors. The latter events were in most cases suspected by the investigator to be related to treatment. The other SAEs were not suspected to be related. All infections resolved, with antibiotic treatment if necessary.

Notably, several types of AEs that were observed with iptacopan in patients with paroxysmal nocturnal haemoglobinuria (PNH) were not observed in C3G patients, e.g. headache, blood pressure increase or increase in serum cholesterol. The MAH suspected a relation of these AEs to PNH pathophysiology, and this appears to be true.

During the assessment, the MAH has submitted an updated safety evaluation, now encompassing 189.8 patient-years (PY) of 200 mg bid iptacopan. The first evaluation encompassed 142.0 PY. The new data came from the open-label, uncontrolled extension phases. Reassuringly, the occurrence rate of events (i.e. episodes per 100 PY) did not relevantly change in the new compared to the previous evaluation.

3.5. Uncertainties and limitations about unfavourable effects

The safety evaluation is limited by the low number of patients and the relatively short duration of treatment in the placebo-controlled study phase. Without a control group, it remains unclear whether certain types of AEs are related to iptacopan, are due to the underlying disease or are chance findings. It is reassuring that most AEs in the uncontrolled studies or study periods were mild in intensity and that no specific pattern of AEs occurred which would be unlikely to come from the underlying disease or by chance.

With the low number of patients and events in the controlled study period, the assessment of the investigator on the relationship of an AE to iptacopan becomes particularly important. Regarding SAEs of infection, some of them were considered related whereas others were not. A bias in the investigators' judgement cannot be excluded, because of the fact that infections by encapsulated bacteria are a known side effect of complement inhibitors. However, even in the worst-case scenario (assuming that all infections with encapsulated bacteria were related to iptacopan the safety profile of iptacopan remains acceptable since the number of events was low and they responded to anti-infective treatment.

Limited safety information is generally acceptable for a rare disease. Data on long-term safety of iptacopan, particularly in combination with ACEi/ARB are awaited from ongoing follow-up study CLNP023B12001B which is a category 3 study described in the RMP.

3.6. Effects Table

Table 35: Effects Table for iptacopan in C3G, APPEAR-C3G study (data cut-off: 07-Nov-2023)*

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Proteinuria reduction	24-hour UPCR-change from BL at Month 6 (primary endpoint)[1]	% reduction from BL; Geometric adjusted mean	-30.2% (-42.8, -14.8%)	+7.6% (-11.9,31.3)	-relative reduction in proteinuria of -35.1%(13.8, 51.1; p=0.014); effect size moderate; below the effect size for which lowering of the risk for kidney failure has been reported. -robustness supported by consistent results in sensitivity analysis adjusting for baseline imbalances in UPCR and eGFR/in subgroups -sustained reduction of 27%	Study APPEAR-C3G

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					(compared to day 1) up to day 360 in the subset randomised initially to iptacopan -consistent 32.6% UPCR reduction in FMV UPCR at Day 180 vs. placebo; sustained throughout Day 360 in participants initially randomized to iptacopan (−42%) at Day 360). In the placebo arm, FMV UPCR decreased by 35% at Day 360 compared to baseline following the switch to open-label iptacopan treatment. -proportion of patients with nephrotic range proteinuria decreased from 55.3% at baseline to 31.6% at Day 180 compared to an increase of 30.6% at baseline to 41.7% at Day 180 in the placebo group	
eGFR improvement	eGFR change from BL to day 180	ml/min/1.73m^2	1.30 mL/min/1.73m2 (95% CI: −2.136, 4.726)	−0.86 mL/min/1.73m2 (95% CI: −4.357, 2.635)	-adjusted mean difference 2.16 (-2.75, 7.06) -no statistical significance (multiplicity adjusted 1-sided p=0.3241[3]).	APPEAR-C3G
eGFR-slope	eGFR slope stabilisation	ml/min/1.73m2			post-treatment difference +3.05 (-6.82, 12.92)	APPEAR-C3G
	pre-treatment eGFR slope per year		-10.75	-7.64		
	post-treatment eGFR slope per year at day		-0.03	-3.08	Post-treatment difference 6.17 (-4.41, 16.74); slope increase with placebo +4.56 unclear (no change in concomitant therapy);	
	change in pre versus post treatment eGFR slope per year		10.73 (3.23, 18.23)	4.56 (2.90,12.02)		
Structural change in renal biopsy	Histology total activity score	Score change from BL	−1.95 (−2.69, −1.20)	−1.11 (−1.83, -0.39)	Adjusted mean difference: −0.83 (−1.87, 0.21) p=0.2895[3]	APPEAR-C3G
C3 deposition in renal biopsy	C3 deposit score	Score change from BL	−0.78 (-1.81, 0.25)	1.09 (0.11, 2.08)	Adjusted mean difference: −1.88 (−3.30, −0.45), unadjusted 1-sided p=0.0053 Renal biopsies samples may be not representative for the entirety of renal tissue.	
Unfavourable Effects						
Infections by		Pts with event	6	-		Broad safety data set

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
encapsulated bacteria						including uncontrolled studies and study periods
		Events	9	-		

Notes:
1 For the primary endpoint analysis, log transformed ratio to baseline was analyzed using a MMRM including treatment, visit, corticosteroid or mycophenolic acid treatment at randomization (yes vs. no) as fixed effects, treatment*visits as interaction term and log (baseline UPCR) as covariate. Results were back-transformed and expressed as geometric means.
2 Marginal proportion can be interpreted as the population average probability of being a responder in each treatment group; p-value obtained from a logistic regression model considering treatment and CS or MPA treatment at randomization (yes vs. no) as factors.
3Multiplicity adjusted 1-sided p values; for the composite renal endpoint, the p-value is associated with OR=7.145 (95% CI: 1.429, 35.723).
*Please refer to Table 22 for a summary of efficacy results from APPEAR-C3G with a data cut-off date of 06-May-2024.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

The key benefit of iptacopan is the reduction in proteinuria, with a statistically significant 35% relative reduction compared to placebo at Month 6 in patients receiving RASi background treatment for C3G. This reduction was fully sustained through Month 12 (40% reduction from BL). The reduction in proteinuria went along with a reduction in the proportion of patients with nephrotic range proteinuria at 6 months (from 55.3% to 31.6%, 23.7% decrease), while the proportion increased in placebo (from 30.6% to 41.7%, 11.1% increase). The robustness of the effect on proteinuria was strengthened by consistent findings in FMV urine samples as well by the phase 2 study X2202, Cohort A which showed proteinuria reduction in the same range.

As proteinuria is not considered acceptable as a sole marker of efficacy, other important benefits of iptacopan over placebo were a numerical increase in eGFR change from baseline compared to placebo and a stabilization of eGFR slope compared with the pre-treatment rate of progression. Reduction in glomerular C3-deposition, normalisation of C3 levels and reductions in sC5b-9 indicated that iptacopan effectively inhibits AP dysregulation, which are desirable mechanistic actions.

Importance of unfavourable effects

The most important unfavourable effect of complement inhibitors is an increased risk for infection with encapsulated bacteria. Hence, patients have to be vaccinated before receiving iptacopan. There were some cases of infection with this type of bacteria in the iptacopan C3G programme. Reassuringly they all could be controlled by appropriate therapy. Given the severity of the underlying disease, the risk for suffering a (treatable) infection is acceptable.

3.7.2. Balance of benefits and risks

Iptacopan treatment showed a clinically meaningful reduction in proteinuria. This was supported by a larger stabilisation of eGFR with iptacopan compared to placebo. Longer-term data showed sustained proteinuria reduction and a stable eGFR trajectory. Stable eGFR is considered a benefit given the progressive decline in eGFR shown in the systematically collected pre-treatment data as well as in natural history data (which also link a halt of the eGFR decline to renal outcome benefit). The clinical efficacy was furthermore mechanistically supported by reduction of biomarkers reflective of alternative pathway activation and by a clear reduction of C3 deposition.

The efficacy demonstrated with iptacopan on the prevention of irreversible renal function loss in patients with C3G outweighs the unfavourable effects which is in particular the manageable risk for infection.

3.8. Conclusions

The overall B/R of Falbhalta in the treatment of patients with C3G is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include, in combination with a renin-angiotensin system (RAS) inhibitor, the treatment of adult patients with complement 3 glomerulopathy (C3G) for Fabhalta, based on interim analysis results from study CLNP023B12301 (APPEAR-C3G) and supported by additional evidence of efficacy and safety data from Phase II study CLNP023X2202 (X2202) and Phase IIIb study CLNP023B12001B (C3G-REP). APPEAR-C3G is a Phase 3, multicenter, randomized, double-blind, parallel arm, placebo-controlled study to evaluate the efficacy and safety of iptacopan in patients with C3G. The study included a 6-month blinded, placebo-controlled period, followed by a 6-month period in which all patients receive open-label iptacopan (total study duration of 12 months). As a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8 and 5.1 of the SmPC are being updated. The Annex II and Package Leaflet are updated in accordance. Version 2.3 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and

any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of Fabhalta in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The educational programme is aimed at providing healthcare professionals (HCPs) and patients/caregivers with educational information on the following safety areas of interest:

- Infections caused by encapsulated bacteria
- Serious haemolysis following discontinuation of iptacopan in patients with PNH

The MAH shall ensure that in each Member State where Fabhalta is marketed, all HCPs and patients/caregivers who are expected to prescribe or use Fabhalta have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

Physician educational material:

- The Summary of Product Characteristics
- Guide for healthcare professionals
- **The Guide for healthcare professionals shall contain the following key messages:**
  - Fabhalta may increase the risk of serious infections with encapsulated bacteria, including *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae.*
  - Ensure patients are vaccinated against *N. meningitidis* and *S. pneumoniae* before starting treatment, and/or receive antibiotic prophylaxis until 2 weeks after vaccination.
  - Recommend vaccination against *H. influenzae* to patients where vaccines are available.
  - Ensure that Fabhalta is only dispensed after a written confirmation that the patient has received vaccination against *N. meningitidis* and *S. pneumoniae,* in accordance with current national vaccination guidelines, and/or is receiving prophylactic antibiotic.
  - Ensure prescribers or pharmacists receive annual reminders of mandatory revaccinations in accordance with current national vaccination guidelines (including *N. meningitidis*, *S. pneumoniae*, and, if appropriate, *H. influenzae*)
  - Monitor patients for signs and symptoms of sepsis, meningitis or pneumonia, such as: fever with or without shivers or chills, headache and a fever, fever and a rash, fever

with chest pain and cough, fever with breathlessness/fast breathing, fever with high heart rate, headache with nausea or vomiting, headache with a stiff neck or stiff back, confusion, body aches with flu-like symptoms, clammy skin, eyes sensitive to light. If bacterial infection is suspected, treat with antibiotics immediately.

- In patients with PNH, discontinuation of Fabhalta may increase the risk of serious haemolysis, therefore advice on adherence to the dosing schedule is important, as is close monitoring for signs of haemolysis following treatment discontinuation. If discontinuation of Fabhalta is necessary, alternative therapy should be considered. If haemolysis occurs after discontinuation of Fabhalta, restarting Fabhalta treatment should be considered. Possible signs and symptoms you need to look out for are: elevated lactate dehydrogenase (LDH) levels along with sudden decrease in haemoglobin or PNH clone size, fatigue, haemoglobinuria, abdominal pain, dyspnoea, dysphagia, erectile dysfunction or major adverse vascular events including thrombosis.
- Details about the PASS for patients with PNH and how to enter patients, if applicable.

The patient information pack:

- Package leaflet
- Patient/caregiver guide
- Patient safety card

- **The Patient/caregiver guide shall contain the following key messages:**
  - Treatment with Fabhalta may increase the risk of serious infections.
  - Doctors will inform you about which vaccinations are required prior to treatment and/or the need to receive antibiotic prophylaxis.
  - Signs and symptoms of serious infection are: fever with or without shivers or chills, headache and a fever, fever and a rash, fever with chest pain and cough, fever with breathlessness/fast breathing, fever with high heart rate, headache with nausea or vomiting, headache with a stiff neck or stiff back, confusion, body aches with flu-like symptoms, clammy skin, eyes sensitive to light.
  - Contact your doctor in case you experience any of the signs and symptoms above and seek immediate medical care at the nearest medical centre.
  - If you have PNH, discontinuation of Fabhalta may increase the risk of serious breakdown of red blood cells (haemolysis). It is important that you adhere to the scheduled treatment regimen. Possible signs and symptoms you need to look out for are: fatigue, blood in the urine, abdominal pain, shortness of breath, difficulty swallowing, erectile dysfunction or major adverse vascular events including thrombosis.
  - Tell your doctor before discontinuing Fabhalta.
  - If you miss a dose, take it as soon as you can, even if it is close to the next dose.
  - You will receive a patient safety card and will need to carry it with you and tell any treating healthcare professional that you are being treated with Fabhalta.
  - If you have any adverse reactions, including infections or serious haemolysis, it is important that you report them immediately.

- You will be informed of the details to enroll in the PASS if you have PNH.

- **Patient Safety Card:**
  - Statement that the patient is receiving Fabhalta.
  - Signs and symptoms of serious infection caused by encapsulated bacteria and warning to seek immediate treatment with antibiotics if bacterial infection is suspected.
  - Contact details where a healthcare professional can receive further information.

- **System for Controlled Access:**
  - The MAH shall ensure that in each Member State where Fabhalta is marketed, a system aimed to control access beyond the level of routine risk minimisation measures is in place. The following requirement needs to be fulfilled before the product is dispensed:
  - Submission of written confirmation of the patient's vaccination against *N. meningitidis* and *S. pneumoniae* infections and/or receipt of prophylactic antibiotic according to national guidelines.

- **Annual reminder of mandatory revaccinations:**
  - The MAH shall send to prescribers or pharmacists who prescribe/dispense Fabhalta an annual reminder in order that the prescriber/pharmacist checks if a revaccination (booster vaccination) against *N. meningitidis* and *S. pneumoniae* infections is required for their patients on treatment with Fabhalta, in accordance with current national vaccination guidelines.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Falbhalta-H-C-005764-II-001'

Attachments

1. Product information as adopted by the CHMP 27 February 2025.