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Renal & Metabolism Franchise

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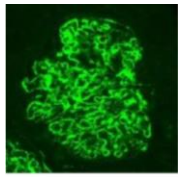
Disclosures

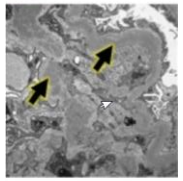
1. Trial NCT03832114 was sponsored by the Novartis Institutes of Biomedical Research
2. The presentation does include discussion of not (yet) approved experimental / development compounds under clinical investigation

C3 Glomerulopathy (C3G): Background

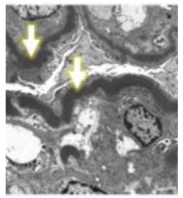
Disease-specific characteristic IF, EM & LM biopsy images in C3 glomerulopathy



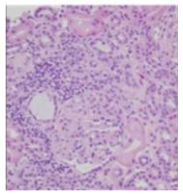
IF shows bright staining for C3, which must be at least two orders of magnitude greater than any other immune reactant



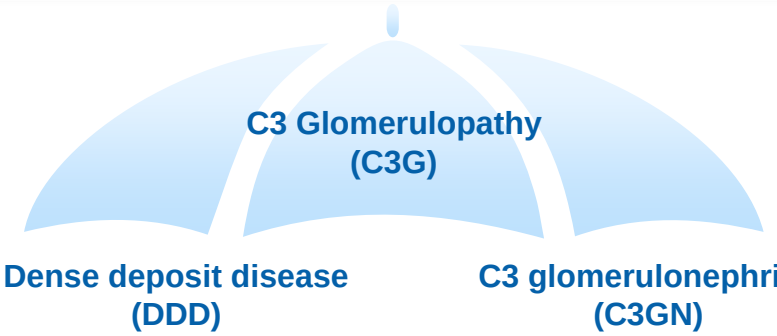
EM of a glomerulus with **C3GN** (black arrows) showing light, hump-like, and clustered deposits in the mesangium and in the subendothelial and/or subepithelial spaces



EM of a glomerulus with **DDD** (white arrows). Note that the DDD deposits appear denser and more ribbon-like than the C3GN deposits



LM showing mesangial proliferation with obliteration of glomerular capillaries and a robust inflammatory infiltrate



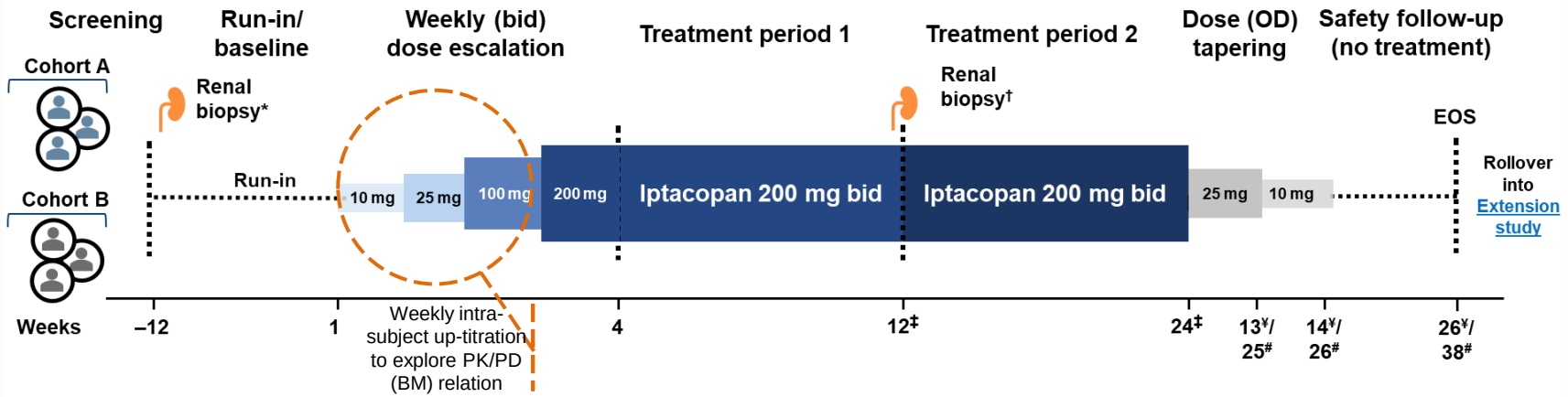
- C3G is a rare, complement-mediated renal disease caused by uncontrolled activation of the complement alternative pathway (AP) in the fluid phase without any approved therapy
- Symptomatic therapy consists of ACE inhibitors and ARBs. C3G affects individuals of all ages, with a median age at diagnosis of 23 years
- Individuals with C3G typically present with hematuria, proteinuria, and low levels of the complement component C3
- Spontaneous remission of C3G is uncommon, and ~50% of affected individuals develop end-stage kidney failure within 10 years of diagnosis, occasionally developing the late comorbidity of impaired visual acuity (drusen)
- EM is used to distinguish between C3GN and DDD, a clinically relevant distinction
- In **C3GN** there are light, hump-like and clustered deposits, which are found in the mesangium or in the subendothelial and/or subepithelial spaces
- In **DDD**, the deposits are darker, denser, segmental, discontinuous, ribbon-like, or diffuse and are most frequently located in the lamina densa of the glomerular basement membrane

ACE, angiotensin converting enzyme inhibitors; ARB, angiotensin-receptor blockers; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; EM, electron microscopy; LM, light microscopy.

Phase 3 enabling 2-cohort proof-of-concept in C3G[1,2]

An open-label, non-randomized study on efficacy, pharmacokinetics, pharmacodynamics, safety, and tolerability of LNP023 in two patient populations with C3 glomerulopathy [NCT03832114]

Phase 2



Primary endpoint	• **Cohort A**: Change from baseline in proteinuria (Urine Protein to Creatinine concentration Ratio [UPCR]) at Week 12 • **Cohort B**: Change from baseline in C3 deposit score (based on IF microscopy) at Week 12

Phase 3

APPEAR-C3G (NCT04817618)

1) Early interim analysis (IA)
2) 2 parallel patient cohorts
3) Extension study
4) Natural history study

*Not required for Cohort A unless most recent biopsy material >12 months old
†Optional for Cohort A
‡Patient may rollover into a separate extension study (CLNP023B2001B) at Week 12
¥For patients entering safety follow-up period following completion of 12 weeks of Treatment period 1
#For patients entering safety follow-up period following completion of 24 weeks of treatment (treatment periods 1 and 2)
bid, twice daily; C3G, C3 glomerulopathy; EOS, end of study; IA, interim analysis; IF, immunofluorescence; od, once daily; PD, pharmacodynamics; PK, pharmacokinetics; UPCR, urinary protein to creatinine ratio.

1. https://clinicaltrials.gov/ct2/show/NCT03832114 (Last Accessed 14 February 2021). 2. Novartis: Data on file.

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Key study objectives, endpoints and population

Primary objectives

Cohort A: To evaluate the efficacy of iptacopan (LNP023) in reducing proteinuria at Week 12 measured as ratio to baseline of UPCR

Cohort B: To assess histopathological changes in kidney biopsies at Week 12 measured as change from baseline in C3 deposit score

Key inclusion criteria

- Male and female patients 18 years old or older
- At screening and baseline, patients must weigh at least 35 kg to participate in the study, and must have a BMI within the range of 18–38 kg/m^2
- Patients must have C3G as confirmed by renal biopsy within 12 months prior to enrollment
- Estimated GFR (CKD-EPI formula) ≥30 mL/min for patients on a maximum recommended or maximum tolerated dose of ACEI or ARB
- Previous vaccination against *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*

For Cohort A (native kidneys)

- C3G patients with reduced C3 levels at screening (defined as less than 0.90 × lower limit of the lab normal range)
- UPCR ≥100 mg/mmol sampled from first morning void (or ≥1 g/24h total urinary protein excretion from a 24h collection) at run-in or baseline

For Cohort B (recurrent C3G post KTx)

- Transplantation of a kidney allograft >90 days before screening visit
- Patients need to be on a stable dose of immunosuppressive regimen for at least 90 days prior to Day 1
- If applicable, induction treatment after allotransplantation needs to be completed >30 days before screening visit
- No histological/laboratory/clinical signs of allo-rejection
- Normal or elevated urinary protein excretion at screening or at baseline

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin-receptor blockers; BMI, body mass index; C3G, C3 glomerulopathy; CKD-EPI, chronic kidney disease epidemiology collaboration; GFR, glomerular filtration rate; KTx, kidney transplant; UPCR, urine protein to creatinine concentration ratio.

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Patient demographics and baseline characteristics

All subjects completed the study

		Cohort A N=16	Cohort B N=11
Age (years)	Mean (SD)	26.1 (10.57)	34.5 (18.32)
	Median (Range)	22.0 (18–59)	31.0 (18–70)
Gender - n(%)	Male	10 (63)	8 (73)
Ethnicity - n(%)	American Indian or Alaska Native		1 (9)
	Black or African Americans		1 (9)
	White	16 (100)	9 (82)
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)
UPCR 24h (g/mol)	Mean (SD)	454.0 (242.16)	112.3 (178.05)
	Geo-mean	**401.9**	36.2
	CV% geo-mean	53.64	310.78
	Median (Range)	**391 (199–1019)**	24 (9–445)

C3, complement 3 protein; DDD, dense deposit disease; SD, standard deviation; UPCR, urine protein to creatinine concentration ratio.

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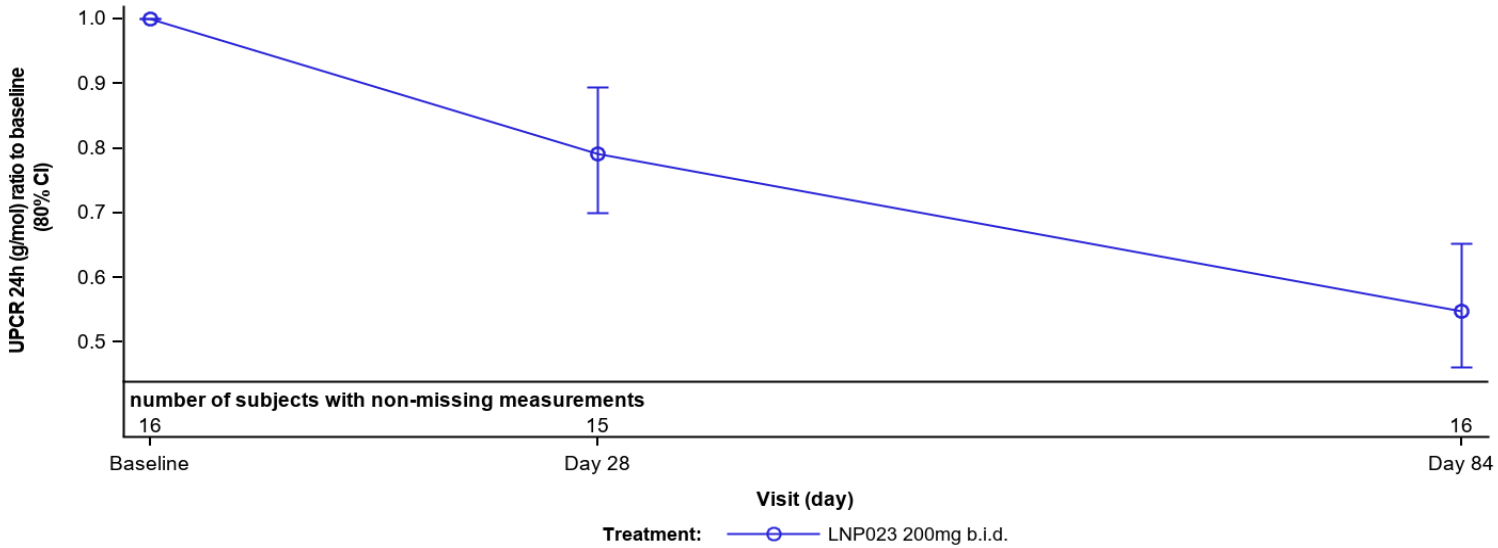
Cohort A primary endpoint achieved with 45% reduction in UPCR 24h (g/mol) vs Baseline

Adjusted geometric mean (80% CI) of ratio to baseline for UPCR (24h urine collection)



MMRM of the log transformed ratio to baseline in UPCR

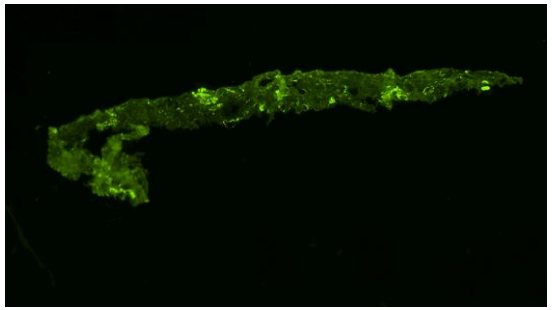
Cohort	Timepoint	N	n	Unadjusted geometric mean ratio to baseline (CV%)	Adjusted geometric mean ratio to baseline (80% CI)*	p-value*
Cohort A	Day 28	16	15[#]	0.80 (34.9)	0.79 (0.70, 0.89)	0.0219
	Day 84	16	16	0.55 (54.4)	0.55 (0.46, 0.65)	**0.0003**

N = number of all subjects included in the analysis (i.e., with at least one post-baseline value of the outcome variable); **n** = number of subjects with non-missing measurements; ***** calculated from two-sided test.
Evaluation was not done for a patient. Model includes the log ratio to baseline in UPCR as the dependent variable, baseline log transformed UPCR and time point (as study day relative to the start of study treatment, Day 28/29 and Day 84/85) as fixed effects

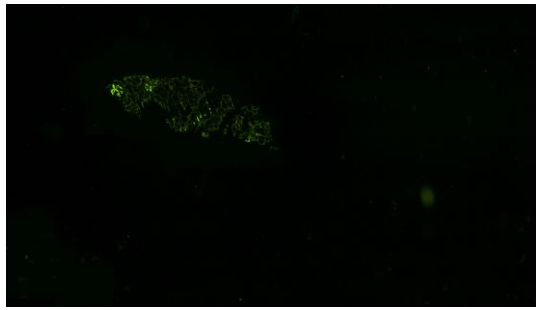
CI, confidence interval; CV, coefficient of variation; MMRM, mixed model repeated measures; UPCR, urine protein to creatinine concentration ratio.

Cohort B primary endpoint achieved with significant C3 Deposit Scores reduction vs Baseline

Kidney Biopsy BL → W12 C3 Deposit Score (ID 4003002)

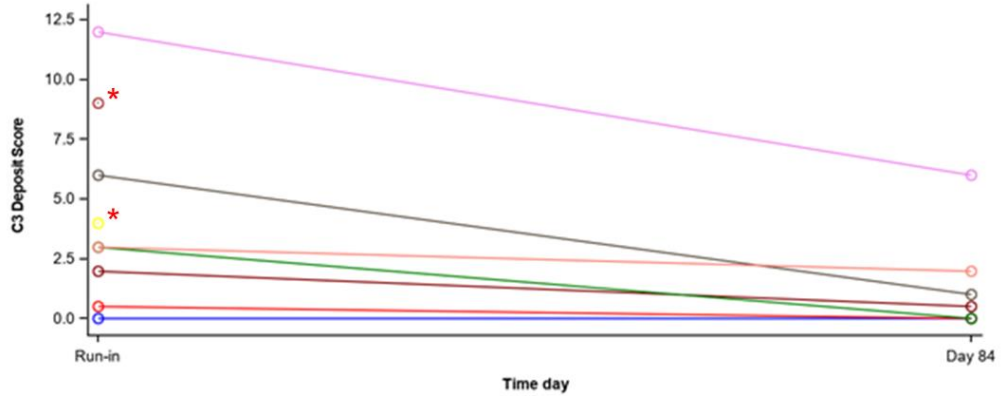


Baseline Bx



Week 12 Bx

Individual plots for total C3 Deposit Score (Bx)



* subjects with only baseline values

Wilcoxon signed rank test estimate for the median difference of C3 Deposit Score

		Medians		Difference		
N	n	Median Baseline	Median Week 12	Shift Location	80% CI	p-value
7	7	3.00	0.50	-10.5	-2.5 (-3.75, -0.75)	**0.0313**

The Wilcoxon signed rank test used for C3 Deposit Score data at Week 12 timepoint to compare the median difference of change from baseline between periods. A two-sided 80% confidence interval for the median difference was calculated. Extent was considered to be segmental for patient 6001002 due to not clear biopsy. **N** = number of all subjects included in the analysis (i.e., with at least one post-baseline value of the outcome variable); **n** = number of subjects with non-missing measurements.

BL, baseline; Bx, biopsy-proven; C3, complement 3 protein; CI, confidence interval.

Safety summary Cohorts A and B

Iptacopan treatment was well tolerated without drug-related SAE

	Cohort A (native kidneys)			Cohort B (post KTx)		
	Run-in N=16 nE, nS (%)	Dose-escalation* N=16 nE, nS (%)	200 mg bid N=16 nE, nS (%)	Run-in N=11 nE, nS (%)	Dose-escalation* N=11 nE, nS (%)	200 mg bid N=11 nE, nS (%)
AE, Subjects with AE	21, 8 (50.0)	9, 6 (37.5)	15, 8 (50.0)	10, 2 (18.2)	8, 5 (45.5)	18, 6 (54.5)
AE of mild intensity	15, 6 (37.5)	8, 6 (37.5)	14, 8 (50.0)	2, 1 (9.1)	6, 4 (36.4)	13, 6 (54.5)
AE of moderate intensity	5, 3 (18.8)	1, 1 (6.3)	1, 1 (6.3)	5, 2 (18.2)	2, 1 (9.1)	5, 4 (36.4)
AE of severe intensity	1, 1 (6.3)	0	0	3, 1 (9.1)	0	0
SAE	**2, 2 (12.5)**	**0**	**0**	**2, 1 (9.1)**	**0**	**3, 2 (18.2)**
Study drug-related AE	0	0	2, 2 (12.5)	0	1, 1 (9.1)	3, 2 (18.2)
SAE drug related	**0**	**0**	**0**	**0**	**0**	**0**
AE leading to study drug interruption	0	0	0	0	0	1, 1 (9.1)
AE leading to study drug discontinuation	0	0	0	0	0	0
SAE leading to study drug discontinuation	0	0	0	0	0	0
Non-SAE leading to study drug discontinuation	0	0	0	0	0	0

***** = LNP023 10, 25 and 100 mg bid; **N** = number of subjects studied; **nE** = number of AE events in the category; **nS** = number of subjects with at least one AE in the category; **%** is based on the number of subjects.
Only adverse events occurring at or after first drug intake are included.

AE, adverse event; SAE, serious adverse event.

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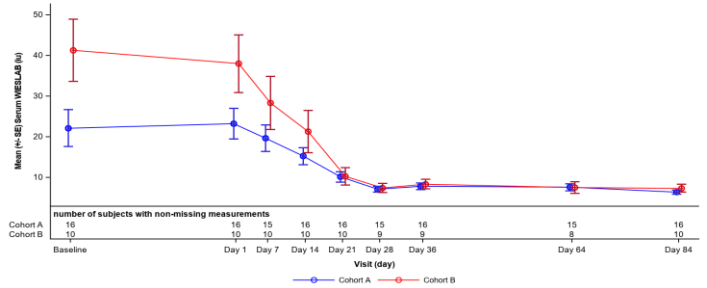
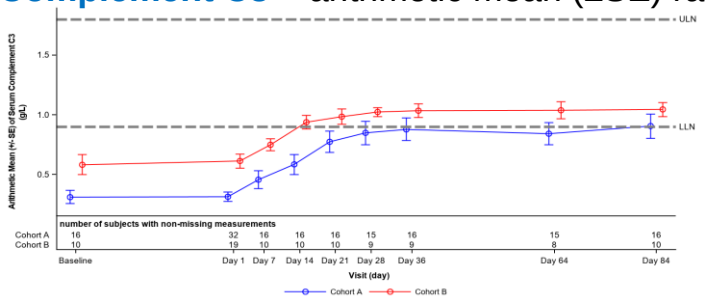
Summary and conclusion

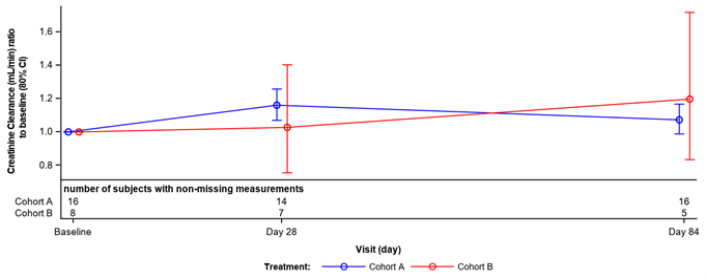
Wieslab – arithmetic mean (±SE) raw



Complement C3 – arithmetic mean (±SE) raw



CrCl – adjusted geo mean (±SE) ratio to BL



- Chronic iptacopan monotherapy with sequential, intra-subject dose increments at Week 1, 2, and 3 with dose levels of 10, 25, 100, and 200 mg bid) is well tolerated without unexpected safety findings in patients with native C3G (Cohort A) as well as in patients post kidney transplantation (Tx) with recurrent disease (Cohort B)
- In patients with native C3G (**Cohort A**), iptacopan at final dose levels of 200 mg bid demonstrates a 45% reduction in UPCR from baseline to Week 12 (primary endpoint; **p=0.0003**)
- In patients with recurrent C3G post kidney Tx (**Cohort B**), iptacopan at final dose levels of 200 mg bid demonstrates a reduction in C3 Deposit Scores (i.e., immunofluorescence) in kidney biopsies at Week 12 compared to baseline (**p=0.0313**)
- Complement C3 is low as evidence of abnormal AP hyperactivity in C3G patients; inhibition of AP activity, and improvement in C3 has been demonstrated with maximal effects observed at 100 to 200 mg bid
- Renal function measured as CrCl was stabilized in both Cohorts with a ratio from baseline to Week 12 (adjusted geo mean) of +1.07 and +1.20 mL/min for Cohort A and B, respectively

AP, alternative complement pathway; bid, twice daily; BL, baseline; C3G, C3 glomerulopathy; CrCl, creatinine clearance; SE, standard error; Tx, transplant; UPCR, urine protein to creatinine concentration ratio.

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