Cardio-Renal-Metabolic Franchise

LNP023, a novel, oral complement alternative pathway Factor B inhibitor, safely and effectively reduces proteinuria in C3 glomerulopathy

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LNP023, a novel, oral complement alternative pathway Factor B inhibitor, safely and effectively reduces proteinuria in C3 glomerulopathy

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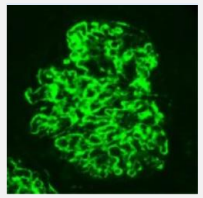
ASN 2020 Meeting – October 2020

Disclosures

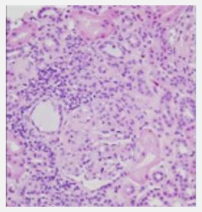
- Received fees for consultation / speakers bureau from Alexion Pharmaceuticals, Biocryst and Novartis.

C3 Glomerulopathy (C3G) - Background

- C3G is a rare disease caused by uncontrolled activation of the complement alternative pathway (AP) in the fluid phase

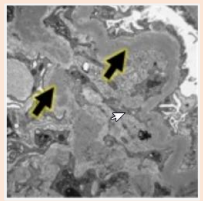


Defined by bright staining for C3 in renal biopsy (≥2X greater than any other immune reactant)

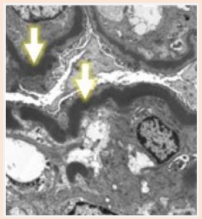


Patterns of inflammation on light microscopy including membrano-proliferative glomerulonephritis

- 2 subtypes based on appearance in electron microscopy findings



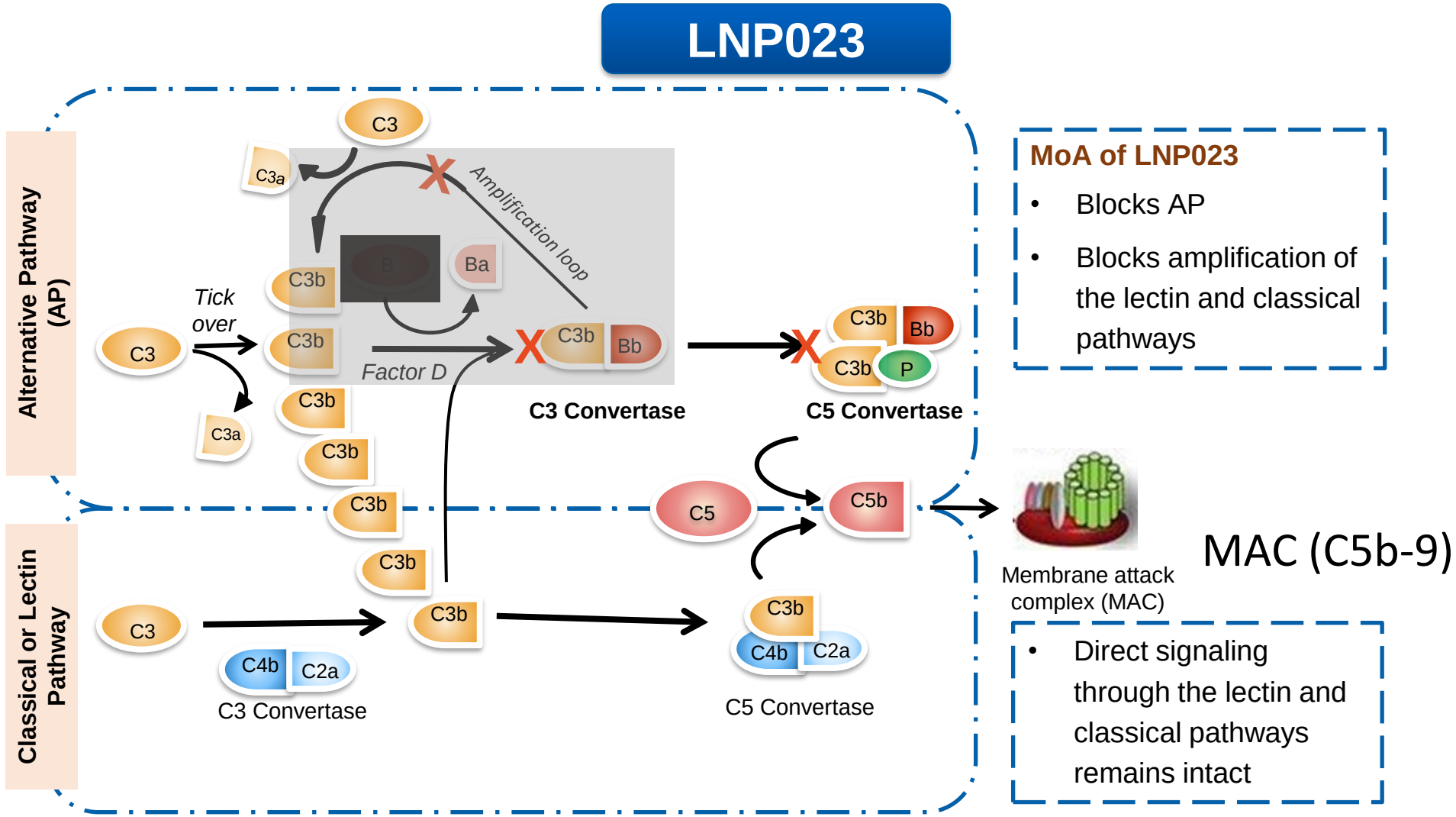
C3GN, with light, hump-like, and clustered deposits in the mesangium, subendothelial and/or subepithelial spaces (black arrows)



DDD, with linear dense deposits (white arrows)

- 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
- There are no approved therapies
- Spontaneous remission of C3G is uncommon, and ~50% of affected individuals develop end-stage renal disease (ESRD) within 10 years of diagnosis

LNP023 - Alternative pathway inhibitor



MoA of LNP023

- Blocks AP
- Blocks amplification of the lectin and classical pathways

- Direct signaling through the lectin and classical pathways remains intact

LNP023 in C3G Study design: NCT03832114

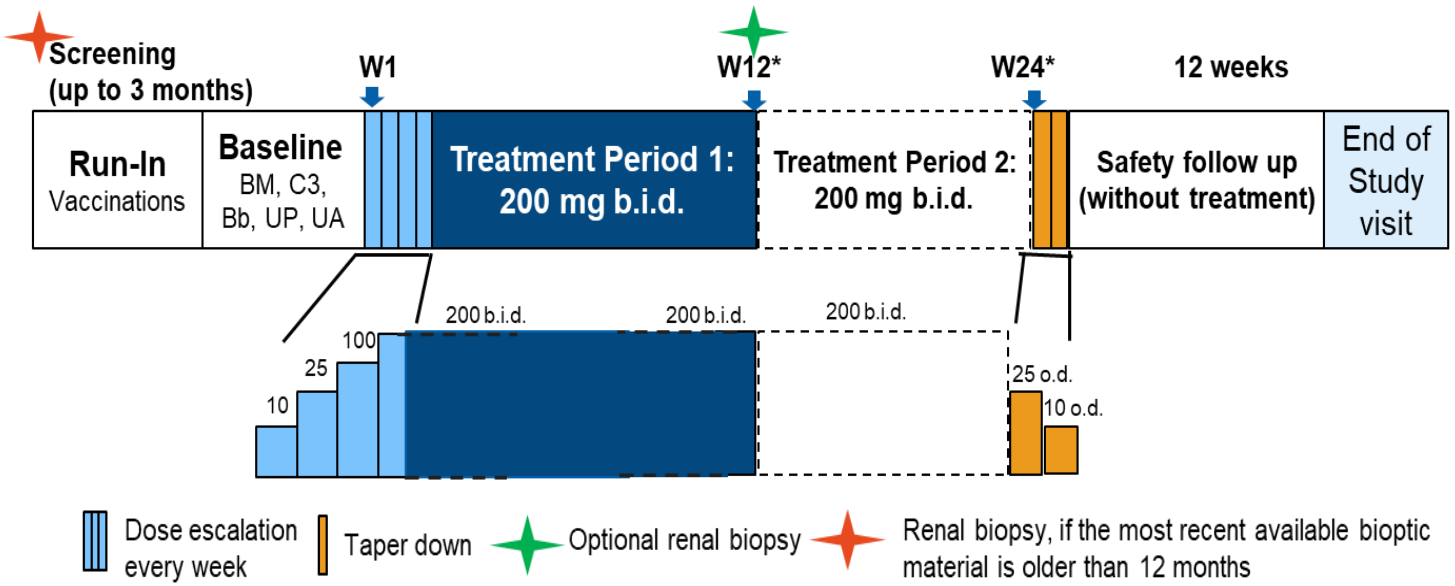
Open label, non-randomized study evaluating efficacy, safety and PK of LNP023

Primary objective:

- To evaluate the efficacy of LNP023 in reducing proteinuria at Week 12 measured as ratio to baseline of UPCR (derived from 24h urine sample)

Key secondary objectives:

- Relationship between LNP023 dose and pharmacodynamics / biomarkers
- Relationship between LNP023 dose and proteinuria
- Effect of LNP023 on renal function
- Safety and tolerability of LNP023



***Patient may roll-over in an extension study at this visit**

Key inclusion criteria

- Biopsy-proven C3G with eGFR ≥30 mL/min/1.73m^2
- Max tolerated ACEi or ARB
- UPCR >100mg/mmol or proteinuria ≥1 g/24h
- Reduced serum C3 level
- Vaccinated against meningococcal disease

Patient demographics

		12 patients (11 C3GN, 1 DDD)
Age (years)	Mean (SD)	26.1 (12.1)
	Range	18 – 59
Gender (N)	Male / Female	10 / 2
Race (N)	Caucasian / Other	12 / 0
Weight (kg)	Mean (SD)	68.2 (9.0)
Body Mass Index (kg/m^2)	Mean (SD)	22.2 (2.7)
Estimated GFR (mL/min/1.73m^2)	Geo-mean (CV%)	57.9 (65.46)
	Median	56.2
	Range	28 – 134
Urine protein:creatinine ratio (g/mol)	Geo-mean (CV%)	397.4 (56.0)
	Median	359
	Range	221-1019

Pharmacokinetics of LNP023

PK parameter (Unit)	LNP023 10mg b.i.d. N= 7	LNP023 25mg b.i.d. N= 6	LNP023 100mg b.i.d. N= 6	LNP023 200mg b.i.d. N= 6
AUC_{last} (hr*ng/mL)	4030 ± 556 (13.8%)	6180 ± 2310 (37.4%)	15200 ± 5840 (38.4%)	22300 ± 11100 (49.9%)
C_{max} (ng/mL)	700 ± 104 (14.8%)	1060 ± 407 (38.5%)	2580 ± 1120 (43.6%)	3990 ± 1770 (44.4%)
C_{min} (ng/mL)	297 ± 97.5 (32.8%)	493 ± 146 (29.6%)	1210 ± 451 (37.2%)	1680 ± 729 (43.4%)
T_{max} (hr)	2.00 (1.00 - 6.00)	2.00 (1.00 - 6.00)	2.00 (0.500 - 4.00)	2.00 (1.00 - 4.00)

Statistics are Mean ± SD (CV%); For T_{max}: Median (Min-Max)

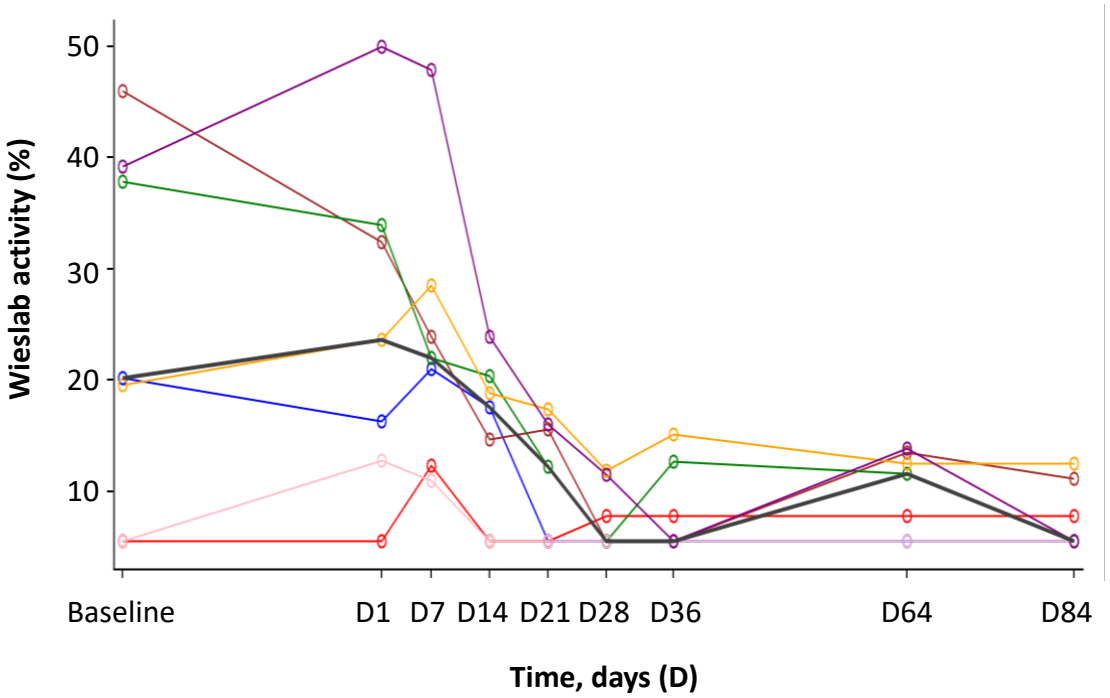
PK Summary

- Overall, PK profile consistent with FIH study with AUC and C_{max} almost identical – no impact on safety margins
- Under-proportional dose/exposure relationship with on average slightly lower exposure compared with healthy volunteers.
- Variability increased with dose
- Only doses of 100 and 200 mg bid reached the C_0 target trough level ≥900 ng/mL (PK/PD model prediction)

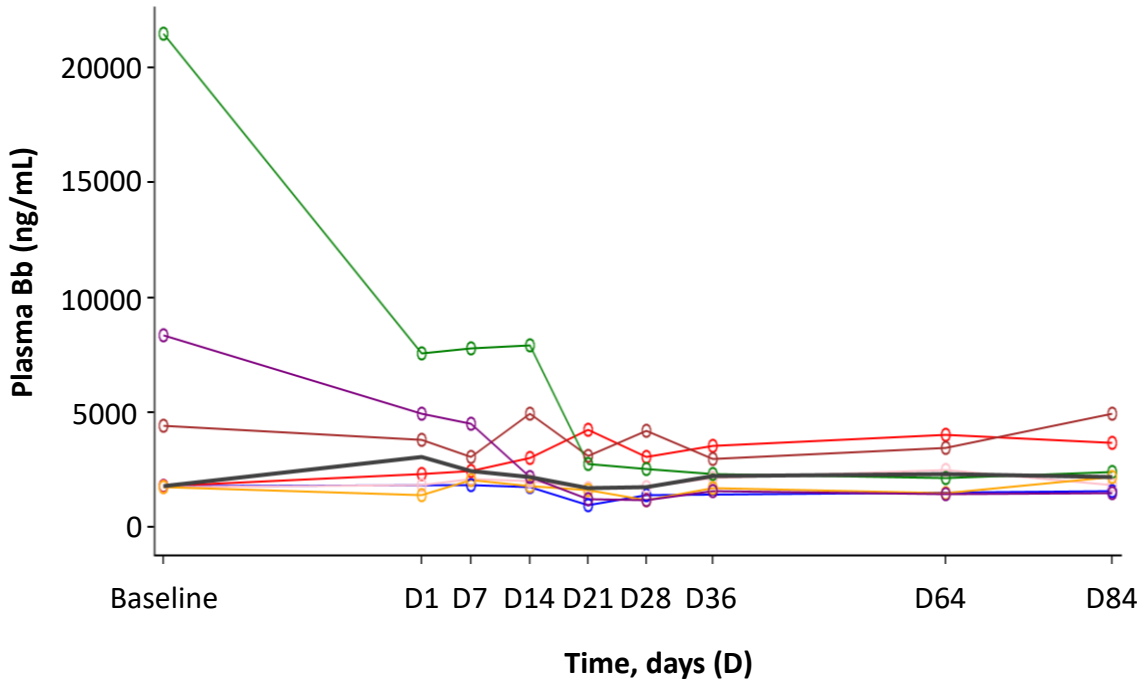
Biomarkers of complement activity (N=7)

- LNP023 reduces complement alternative pathway activity (Wieslab and Bb)

Evolution of Wieslab activity over time



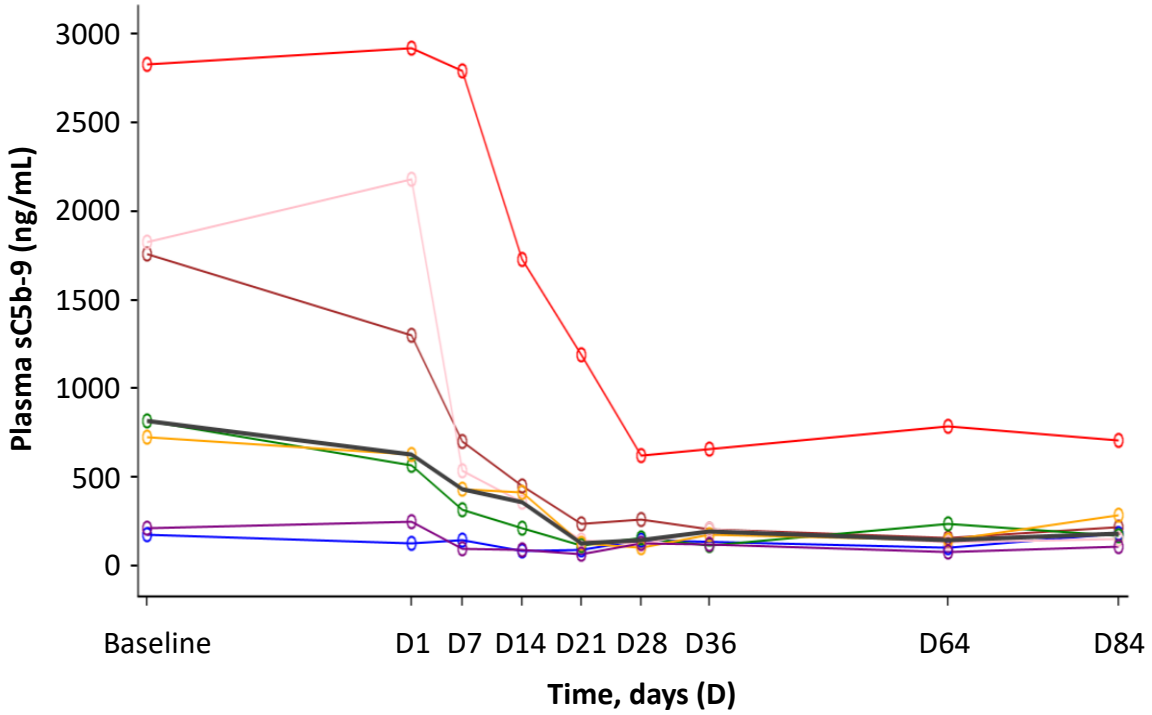
Evolution of plasma Bb levels over time



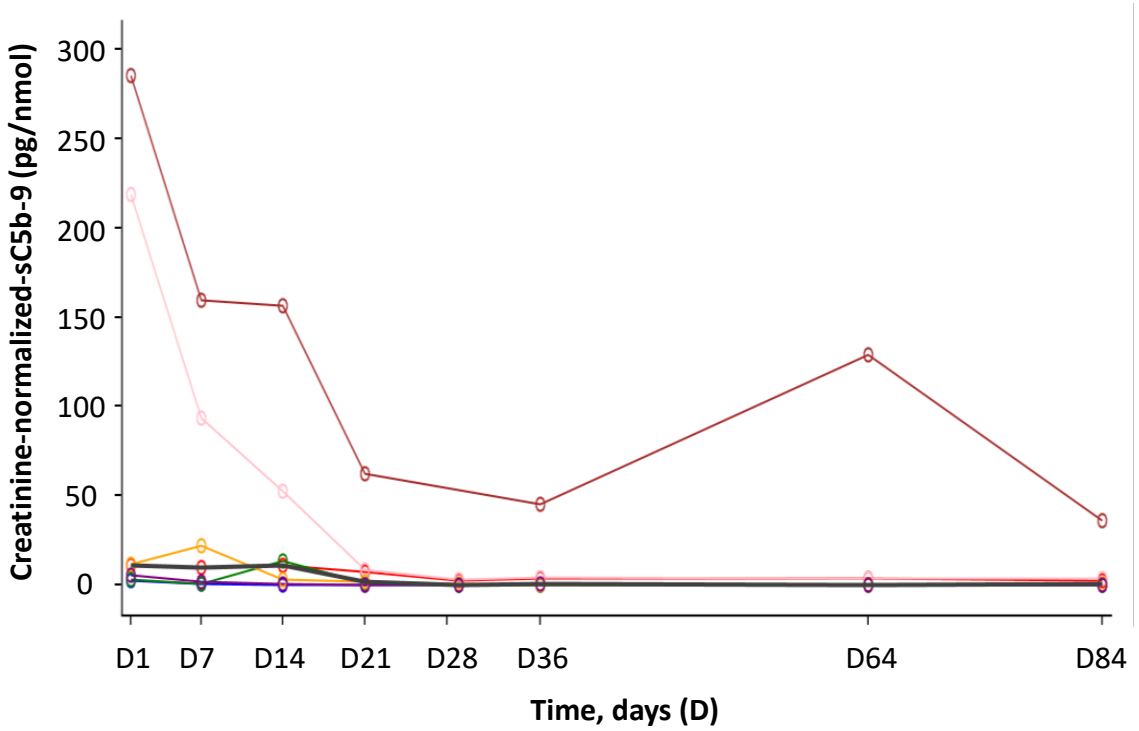
Strong reduction of sC5b-9 (and normalization) only in patients with elevated baseline levels (N=7)

- LNP023 reduces plasma and urine sC5b9 levels

Evolution of plasma sC5b-9 levels over time

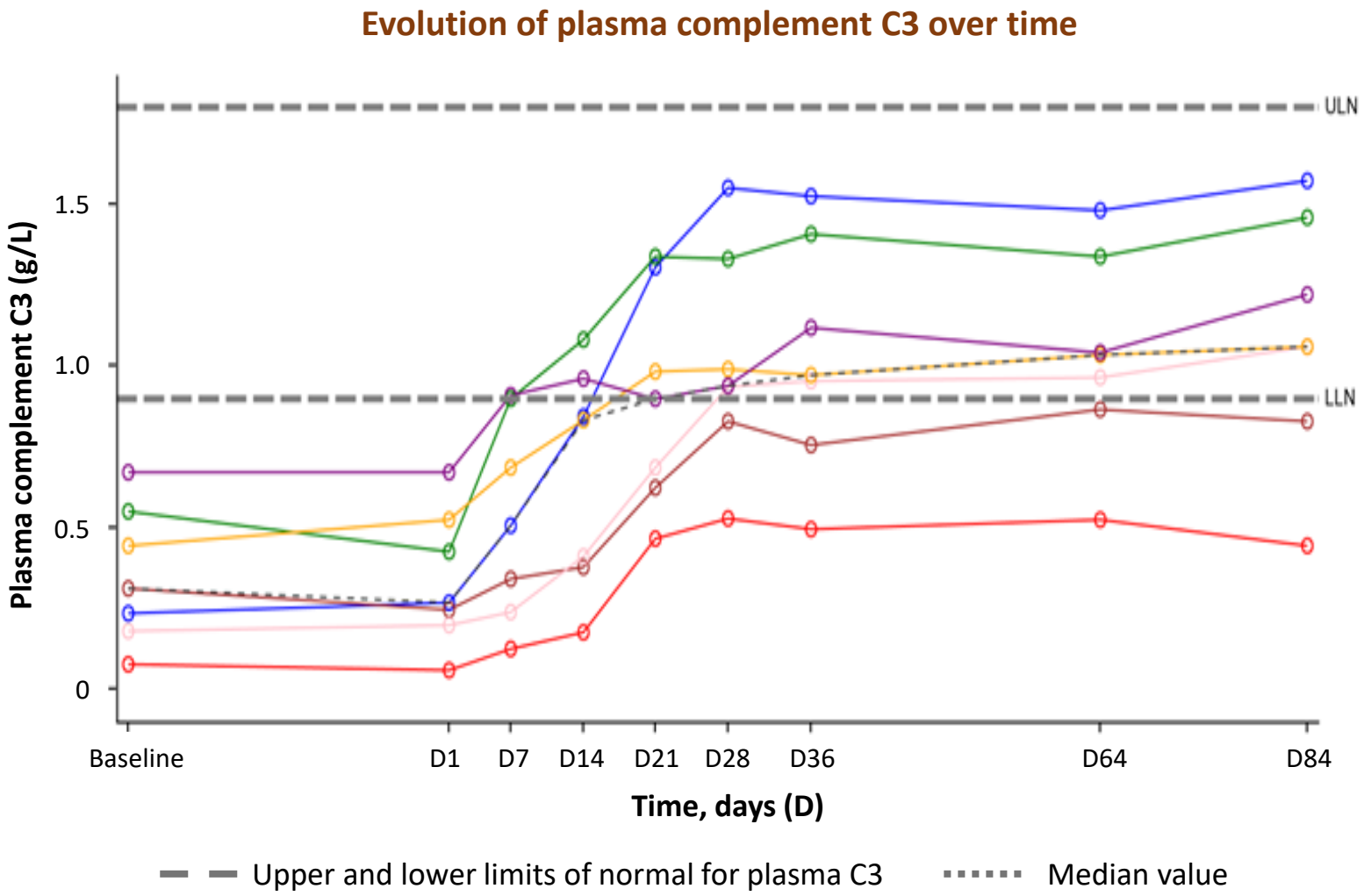


Evolution of urine sC5b-9 levels over time



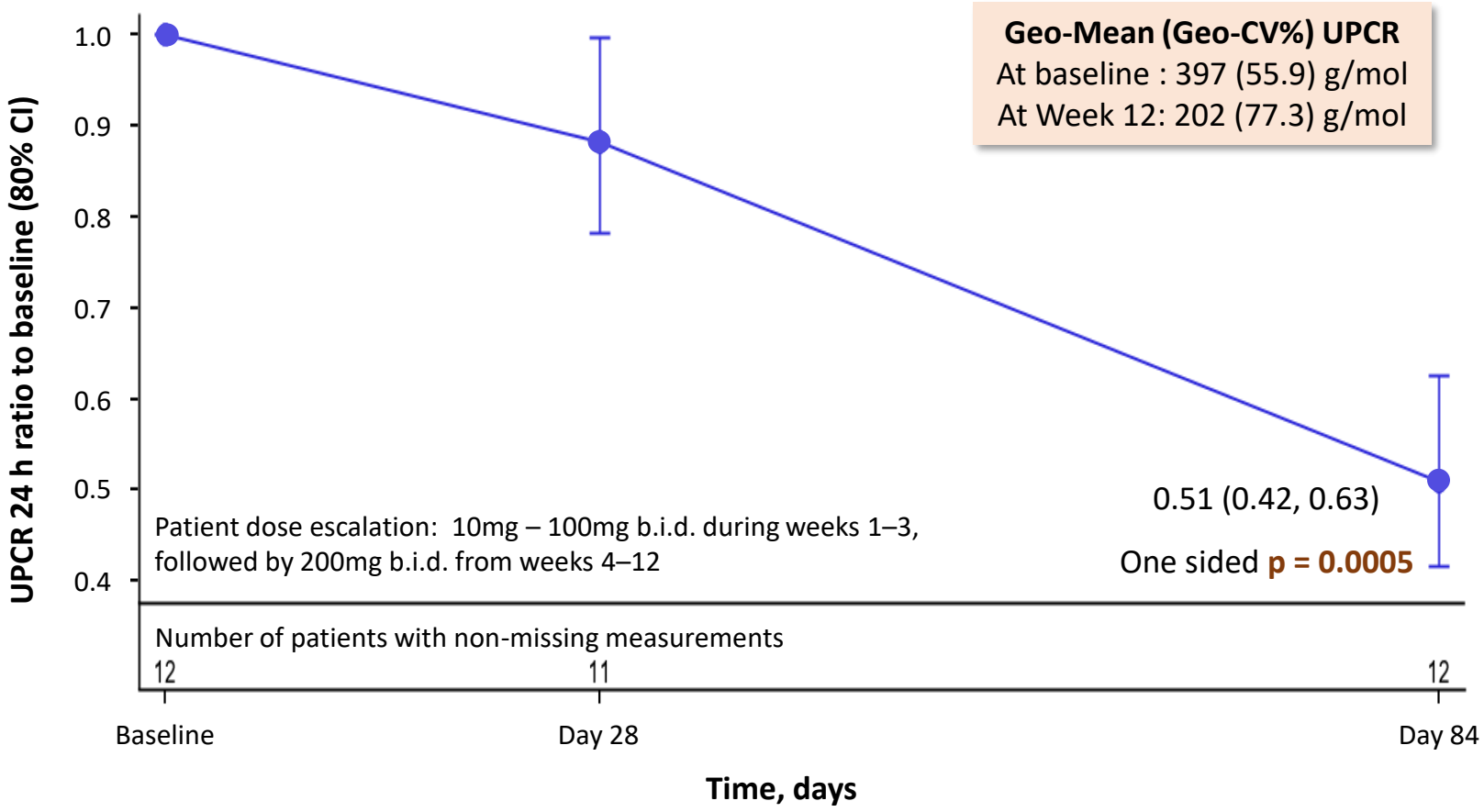
Elevated sC5b-9 plasma levels compared with healthy volunteers (FIH data: maximum levels in healthy volunteers ~230 ng/mL).

Uniform improvement in plasma C3 levels with normalization in 71% (N=7)

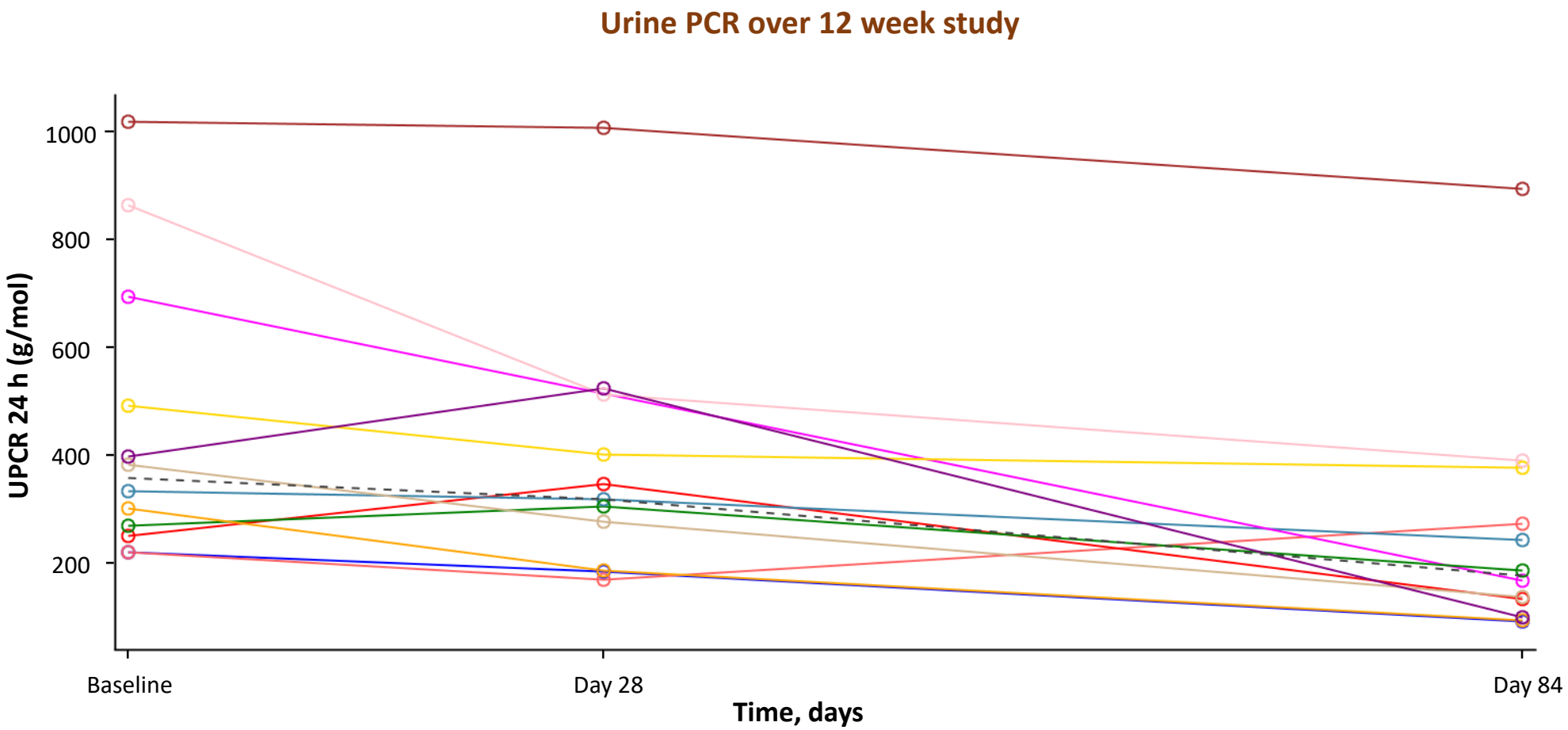


Primary endpoint : 49% reduction in UPCR (24h) from baseline

Adjusted geometric mean (80% CI) of ratio to baseline for UPCR (24h urine collection) over time (N=12)

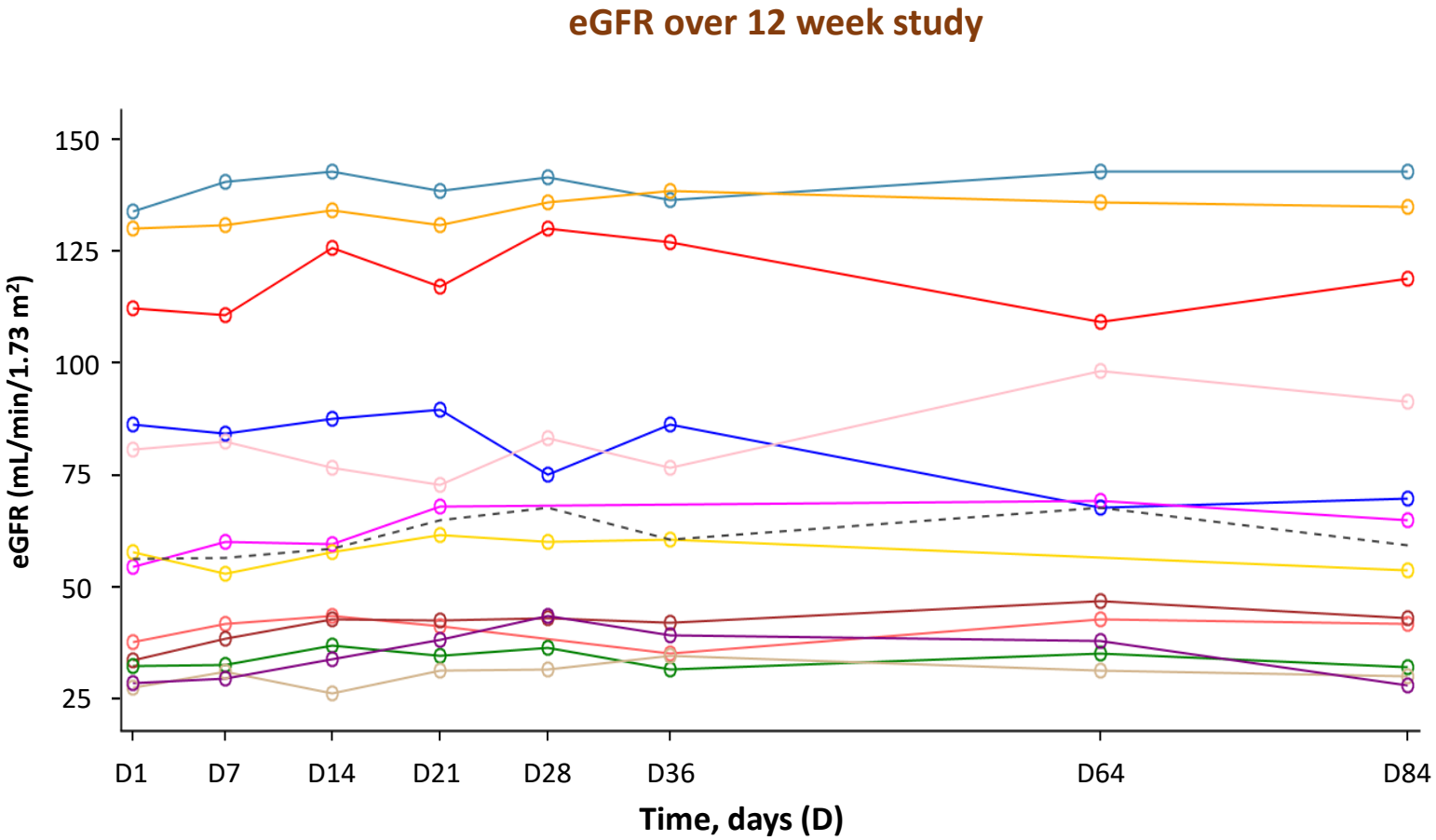


Individual patient data demonstrates fall in proteinuria across range of proteinuria (N=12)



Dotted line represents median value

Individual patient data demonstrates eGFR stability across a wide range of kidney function (N=12)

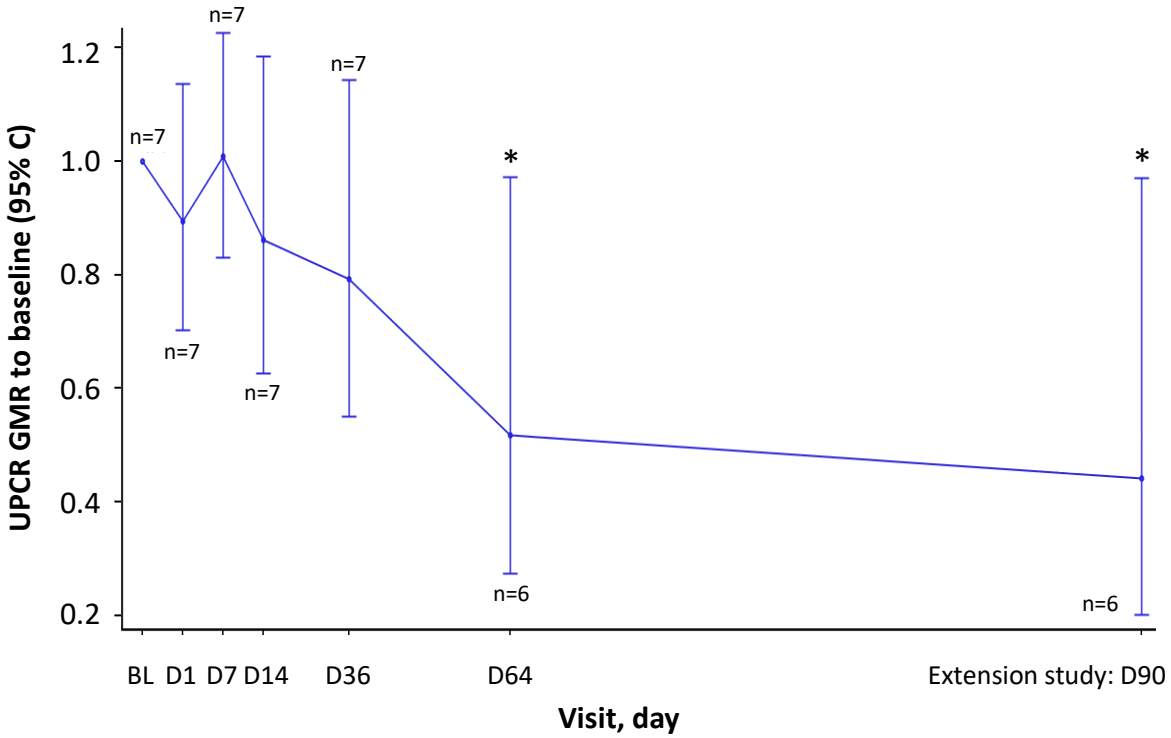


Adjusted arithmetic mean change from baseline (80% CI): 3.03 (-0.05, 6.11) ml/min/1.73m²

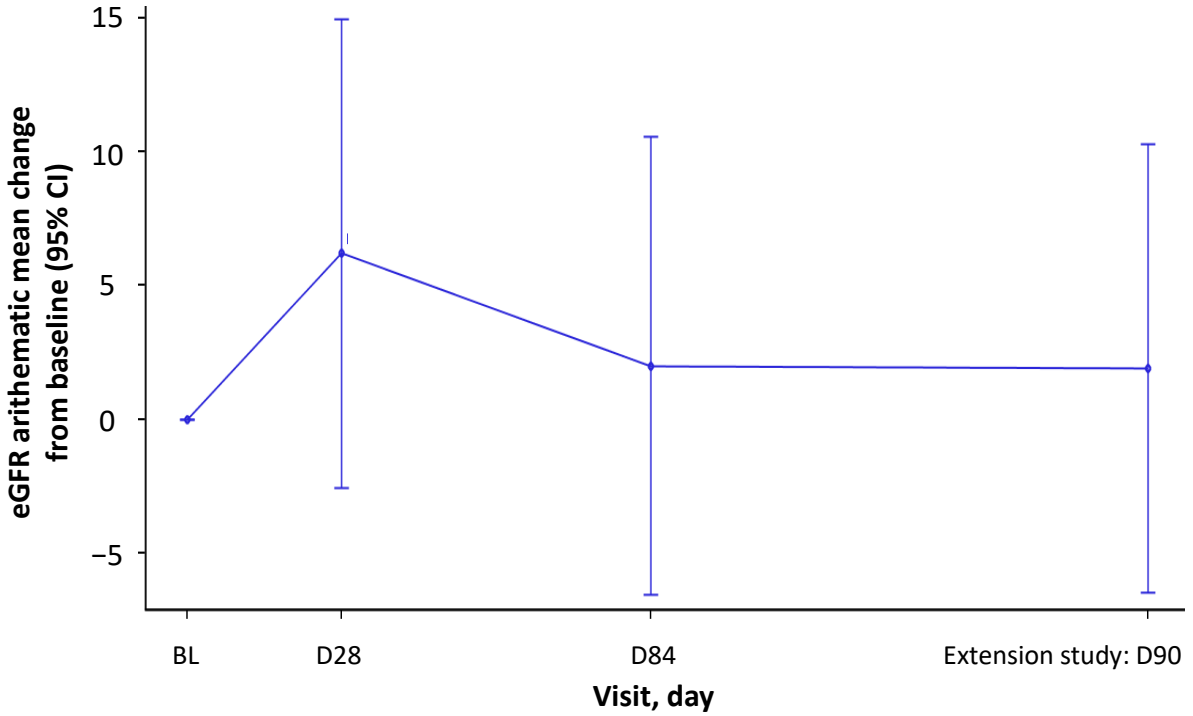
Baseline is defined as the last available assessment (ie., Day 1, 0 hr pre dose) prior to the first dose of study drug. Dotted line represents median value

Extending LNP023 treatment to 6 months results in 56% reduction in proteinuria compared with baseline and stability of eGFR

Unadjusted geometric mean (95% CI) ratio to baseline for UPCR (FMV urine collection) over time



Arithmetic mean (95% CI) eGFR change from baseline sensitivity analysis (n=7)



*p<0.05

Data from 7/12 patients who received an additional 3 months of LNP023 treatment in the extension study (total of 6 months follow-up): 6/7 had UPCR assessments at Month 6.

Safety

- No deaths were reported
- No SAEs were related to study medication
- No AEs leading to study drug discontinuation
- The majority of AEs were mild

Overall AE incidence*	Number, patients [N=16]
AE, Patients with AE	38, 13
Mild AE	31, 11
Moderate AE	6, 3
Severe AE	1, 1
Study drug-related AE	2, 2
Serious AE (not related to study drug)	1, 1
AE leading to discontinuation of study treatment	0
Study-drug related AE leading to discontinuation of study treatment	0

* includes all 16 patients enrolled as of 13-Jul-2020, but excludes any S/AE reported from extension study

Summary

- LNP023 doses of 100 and 200 mg bid reached the C_0 target trough level ≥900 ng/mL expected to provide full target inhibition
- Inhibition of AP activity was demonstrated in both blood and urine complement markers upon treatment with LNP023, with maximal effects observed at 100 to 200 mg bid
- LNP023 at final dose levels of 200 mg bid demonstrated a 49% reduction in UPCR from baseline to Week 12 as well as stabilization of renal function (eGFR)
- LNP023 monotherapy was well tolerated with no new or unexpected safety findings