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Clinical Trial Results Website

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Generic Drug Name

iptacopan

Trial Indication(s)

IgA nephropathy

Protocol Number

CLNP023X2203

Protocol Title

An adaptive seamless randomized, double-blind, placebo-controlled, dose ranging study to investigate the efficacy and safety of LNP023 in primary IgA nephropathy patients

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: February 2018 (Actual)
Primary Completion Date: December 2020 (Actual)
Study Completion Date: June 2021 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was a multicenter, randomized, double-blind, dose-ranging, parallel-group study with an adaptive design (Part 1 informed the design adaptations for Part 2). In Part 1, three doses of LNP023 (10 mg, 50 mg, and 200 mg) vs. placebo control were compared; In Part 2, four doses of LNP023 (10 mg, 50 mg, 100 mg, and 200 mg) vs. placebo control were compared. The study comprised a run-in phase in order that patients were on stable and maximally tolerated dose of Angiotensin-converting-enzyme inhibitor (ACEi) or Angiotensin II Receptor Blockers (ARB) for at least 90 days, a 90 days treatment phase in Part 1; a 180 days treatment phase in Part 2 and a 90 days follow-up phase in both Parts 1 and 2.

Centers

57 centers in 25 countries/regions: United Kingdom(5), Sweden(2), Taiwan(3), Singapore(2), Australia(2), Thailand(3), Norway(3), Belgium(3), Netherlands(1), Denmark(2), Finland(1), Germany(2), Argentina(2), China(4), Turkey(4), Japan(5), Hong Kong(1), Czech Republic(1), France(1), Israel(3), Korea, Republic of(1), Malaysia(1), Colombia(1), India(2), Brazil(2)

Objectives:

The primary objective of the study was to evaluate the dose response relationship of LNP023 on the reduction in proteinuria versus placebo after 90 days of treatment.

The secondary objectives were: to evaluate the safety and tolerability of LNP023, to assess the effect of LNP023 on renal function, to assess the pharmacokinetics (PK) of LNP023, to assess the effect of LNP023 on alternative complement pathway, to estimate the lowest dose that provides maximal reduction of proteinuria.

Test Product (s), Dose(s), and Mode(s) of Administration

Part 1 - Patients were randomized (ratio 3:2:2:3) to one of the four treatment arms and treated orally b.i.d. for 90 days: Placebo, LNP023 10 mg, LNP023 50 mg, LNP023 200 mg

Part 2 - Based on IA1 results and decisions, patients were randomized to one of the five treatment arms and treated orally b.i.d. for 180 days: Placebo, LNP023 10 mg, LNP023 50 mg, LNP023 100 mg, LNP023 200 mg.

Statistical Methods

The primary endpoint was analyzed using the Multiple Comparison Procedure (MCP) methodology, which consists of a two-stage approach:

Firstly, the change from baseline in log transformed (natural log, base of e) UPCR at multiple time points (baseline, day 30, and day 90) was analyzed using a Mixed Model of Repeated Measures (MMRM) model. The model included treatment, time point (as study day relative to start of study treatment), study part (Part 1 or Part 2), and ancestry (Asian/non-Asian) as fixed effects, and baseline log UPCR as a fixed covariate. Treatment by time point and time point by baseline log UPCR were included as interaction terms. Time point was included as a repeated factor with an unstructured covariance matrix to allow adjustment for correlations between time points within patients.

Secondly, the global hypothesis was tested for the Day 90 time point using the generalized MCP-Mod approach at the one-sided 10% significance level, to assess whether LNP023 is different from placebo.

The secondary variables supporting the secondary objectives were evaluated on both Parts 1 and 2 combined data up to Day 90 and on Part 2 data up to Day 180. Secondary endpoints were: log ratio to baseline in UPCR (from 24h urine collection) up to Day 180 only (as up to Day 90 was the primary endpoint), log ratio to baseline in UPCR (from FMV), change from baseline in eGFR, change from baseline in serum creatinine, log ratio to baseline in 24h-UP, log ratio to baseline in 24h-UA, log ratio to baseline in UACR, hematuria.

The secondary variables (except hematuria) were each analyzed with the MMRM model as used in the first step of analysis of the primary variable, considering measurements up to Day 90. For all secondary variables (except hematuria), the MMRM was repeated considering measurements up to Day 180. Shift tables from baseline of Hematuria levels at Day 90 and Day 180 were produced.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

• Female and male patients above 18 years of age with a biopsy-verified IgA nephropathy and where the biopsy was performed within the prior three years.

• Patients must weigh at least 35 kg to participate in the study, and must have a body mass index (BMI) within the range of 15 - 38 kg/m2. BMI = Body weight (kg) / [Height (m)]2

• Measured Glomerular Filtration Rate (GFR) or estimated GFR (using the CKD-EPI formula) ≥30 mL/min per 1.73 m2

• Urine protein ≥1 g/24hr at screening and ≥0.75 g / 24h after the run- in period

• Vaccination against Neisseria meningitidis types A, C, Y and W-135 is required at least 30 days prior to first dosing with LNP023. Vaccination against N. meningitidis type B, S. pneumoniae and H. influenzae should be conducted if available and acceptable by local regulations, at least 30 days prior to first dosing with LNP023

• All patients must have been on supportive care including a maximally tolerated dose of ACEi or ARB therapy for the individual, antihypertensive therapy or diuretics for at least 90 days before dosing

Exclusion criteria

1. Presence of crescent formation in ≥50% of glomeruli assessed on renal biopsy
2. Patients previously treated with immunosuppressive agents such as cyclophosphamide or mycophenolate mofetil (MMF), or cyclosporine, systemic corticosteroids exposure within 90 days prior to start of LNP023/Placebo dosing
3. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days, whichever is longer; or longer if required by local regulations
4. All transplanted patients (any organ, including bone marrow)
5. History of immunodeficiency diseases, or a positive HIV (ELISA and Western blot) test result.
Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV). A positive HBV surface antigen (HBsAg) test, or if standard local practice, a positive HBV core antigen test, excludes a patient. Patients with a positive HCV antibody test should have HCV RNA levels measured. Subjects with positive (detectable) HCV RNA should be excluded
6. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study. The Investigator should make this determination in consideration of the subject's medical history and/or clinical or laboratory evidence of any of the following:

• A history of invasive infections caused by encapsulated organisms, e.g. meningococcus or pneumococcus
• Splenectomy
• Inflammatory bowel disease, peptic ulcers, severe gastrointestinal disorder including rectal bleeding;
• Major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection;
• Pancreatic injury or pancreatitis;
• Liver disease or liver injury as indicated by abnormal liver function tests. ALT (SGPT), AST (SGOT), GGT, alkaline phosphatase and serum bilirubin will be tested.
• Any single parameter of ALT, AST, GGT, alkaline phosphatase or serum bilirubin must not exceed 3 x upper limit of normal (ULN)
• PT/INR must be within the reference range of normal individuals
• Evidence of urinary obstruction or difficulty in voiding any urinary tract disorder other than IgNA that is associated with hematuria at screening and before dosing; [If necessary, laboratory testing may be repeated on one occasion (as soon as possible) prior to randomization, to rule out any laboratory error]
7. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
8. A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening or baseline:
• PR > 200 msec
• QRS complex > 120 msec
• QTcF > 450 msec (males)
• QTcF > 460 msec (females)
• History of familial long QT syndrome or known family history of Torsades de Pointes
• Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of the study
9. History of severe allergic reactions as per Investigator decision
10. Plasma donation (> 200mL) within 30 days prior to first dosing.
11. Donation or loss of 400 mL or more of blood within eight (8) weeks prior to initial dosing, or longer if required by local regulation
12. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 1 week after stopping of investigational drug. Highly effective contraception methods include:
• Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
• Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
• Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be

the sole partner for that subject.
• Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure <1%), for example hormone vaginal ring or transdermal hormone contraception
In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.
If local regulations deviate from the contraception methods listed above and require more extensive measures to prevent pregnancy, local regulations apply and will be described in the ICF.
Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
13. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in-situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
14. History of any porphyria metabolic disorder
15. History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during screening and baseline.
16. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes

Participant Flow Table

Part 1

	LNP023 10 mg BID	LNP023 50 mg BID	LNP023 100 mg BID - Part 2	LNP023 200 mg BID	Placebo	Total
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day	Placebo identical to LNP023 taken orally twice a day	
Started	9	8	0	15	14	46
Completed	9	8	0	15	14	46

Not Completed	0	0	0	0	0	0

Part 2

	LNP023 10 mg BID	LNP023 50 mg BID	LNP023 100 mg BID - Part 2	LNP023 200 mg BID	Placebo	Total
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day	Placebo identical to LNP023 taken orally twice a day	
Started	11	11	22	11	11	66
Completed	11	10	22	11	10	64
Not Completed	0	1	0	0	1	2
Adverse Event	0	1	0	0	1	2

Baseline Characteristics

	LNP023 10 mg BID	LNP023 50 mg BID	LNP023 100 mg BID - Part 2	LNP023 200 mg BID	Placebo	Total
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day	Placebo identical to LNP023 taken orally twice a day	
Number of Participants [units: participants]	20	19	22	26	25	112

Age Continuous (units: years) Mean ± Standard Deviation						
	39.2±12.42	36.6±8.42	36.0±13.15	42.5±15.76	39.4±11.00	38.9±12.58
Sex: Female, Male (units:) Count of Participants (Not Applicable)						
Female	11	6	11	11	7	46
Male	9	13	11	15	18	66
Race/Ethnicity, Customized (units: Participants) Count of Participants (Not Applicable)						
Asian	10	9	12	12	11	54
White	10	9	10	13	13	55
Black or African American	0	1	0	1	0	2
American Indian or Alaska Native	0	0	0	0	1	1
Age, Customized (units:) Count of Participants (Not Applicable)						
18 years - <65 years	20	19	21	24	25	109
65 years - <85 years	0	0	1	2	0	3
Urine Protein to Creatinine Ratio (UPCR)[1] (units: g/mol) Mean ± Standard Deviation						
	214.1±122.29	188.2±90.38	203.4±98.29	151.0±109.46	146.6±61.62	177.9±100.02
Estimated Glomerular Filtration Rate (eGFR) (units: mL/min/1.73m^2) Mean ± Standard Deviation						

	66.0±28.51	53.8±22.73	67.0±31.75	57.9±28.92	65.7±32.60	62.2±29.30
Supine Blood Pressure (units: mmHg) Mean ± Standard Deviation						
Systolic	134.4±11.65	122.6±12.15	125.0±11.30	125.7±11.66	125.5±11.37	126.5±11.89
Diastolic	84.1±7.65	76.9±8.41	80.0±10.40	79.7±7.62	78.2±7.32	79.6±8.26
Prior use of ACEi and/or ARB[2] (units: Participants) Count of Participants (Not Applicable)						
	19	19	22	26	25	111

[1] From 24 hour urine collection
[2] Prior use of angiotensin converting enzyme inhibitor and/or angiotensin receptor blocker

Primary Outcome Result(s)

MCP-Mod estimates of the ratio to baseline of urine protein to creatinine ratio (UPCR) (g/mol) - Parts 1 and 2 at Day 90

(Time Frame: Baseline, Days 30 and 90)

	LNP023 10 mg BID	LNP023 50 mg BID	LNP023 100 mg BID - Part 2	LNP023 200 mg BID	Placebo
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day	Placebo identical to LNP023 taken orally twice a day
Number of Participants Analyzed [units: participants]	19	19	22	26	25
MCP-Mod estimates of the ratio to baseline of					

urine protein to creatinine ratio (UPCR) (g/mol) - Parts 1 and 2 at Day 90 (units: Ratio to baseline) Number (80% Confidence Interval)					
	0.85 (0.77 to 0.93)	0.80 (0.73 to 0.87)	0.76 (0.70 to 0.81)	0.69 (0.61 to 0.77)	0.88 (0.80 to 1.00)

Statistical Analysis

Groups	LNP023 10 mg BID, LNP023 50 mg BID, LNP023 100 mg BID - Part 2, LNP023 200 mg BID, Placebo
P Value	0.038
Method	Other Multiple Comparison Procedure-Modeling

Statistical Analysis

Groups	LNP023 10 mg BID, Placebo
Other Ratio to placebo (of ratio to baseline)	0.99
80 % Confidence Interval 2-Sided	0.86 to 1.00

Statistical Analysis

Groups	LNP023 50 mg BID, Placebo

Other Ratio to placebo (of ratio to baseline)	0.94
80 % Confidence Interval 2-Sided	0.76 to 0.98

Statistical Analysis

Groups	LNP023 100 mg BID - Part 2, Placebo
Other Ratio to placebo (of ratio to baseline)	0.87
80 % Confidence Interval 2-Sided	0.72 to 0.96

Statistical Analysis

Groups	LNP023 200 mg BID, Placebo
Other Ratio to placebo (of ratio to baseline)	0.77
80 % Confidence Interval 2-Sided	0.66 to 0.92

Secondary Outcome Result(s)

Mixed Model of Repeated Measures (MMRM) of the change from baseline for Estimated Glomerular Filtration Rate (eGFR) - Parts 1 and 2 at Day 90

(Time Frame: Baseline, Days 8, 15, 30 and 90)

	LNP023 10 mg BID	LNP023 50 mg BID	LNP023 100 mg BID - Part 2	LNP023 200 mg BID	Placebo
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day	Placebo identical to LNP023 taken orally twice a day
Number of Participants Analyzed [units: participants]	20	19	22	26	25
Mixed Model of Repeated Measures (MMRM) of the change from baseline for Estimated Glomerular Filtration Rate (eGFR) - Parts 1 and 2 at Day 90 (units: mL/min/SSA) Mean ± Standard Error					
Day 90	-0.06 ± 1.760	2.49 ± 1.859	0.23 ± 1.821	2.42 ± 1.545	-3.34 ± 1.606

Statistical Analysis

Groups	LNP023 10 mg BID, Placebo
Mean Difference (Final Values)	3.28
80 % Confidence Interval 2-Sided	0.210 to 6.344

Statistical Analysis

Groups	LNP023 50 mg BID, Placebo

Mean Difference (Final Values)	5.83
80 % Confidence Interval 2-Sided	2.642 to 9.010

Statistical Analysis

Groups	LNP023 100 mg BID - Part 2, Placebo
Mean Difference (Final Values)	3.56
80 % Confidence Interval 2-Sided	0.427 to 6.700

Statistical Analysis

Groups	LNP023 200 mg BID, Placebo
Mean Difference (Final Values)	5.76
80 % Confidence Interval 2-Sided	2.882 to 8.638

Mixed Model of Repeated Measures (MMRM) of the change from baseline for Serum Creatinine - Parts 1 and 2 at Day 90

(Time Frame: Baseline, Days 8, 15, 30 and 90)

	LNP023 10 mg BID	**LNP023 50 mg BID**	**LNP023 100 mg BID - Part 2**	**LNP023 200 mg BID**	**Placebo**
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day	Placebo identical to LNP023 taken

					orally twice a day
Number of Participants Analyzed [units: participants]	20	19	22	26	25
Mixed Model of Repeated Measures (MMRM) of the change from baseline for Serum Creatinine - Parts 1 and 2 at Day 90 (units: umol/L) Mean ± Standard Error					
	-2.55 ± 3.488	-2.60 ± 3.665	0.76 ± 3.555	-3.47 ± 3.043	6.65 ± 3.150

Statistical Analysis

Groups	LNP023 10 mg BID, Placebo
Mean Difference (Final Values)	-9.20
80 % Confidence Interval 2-Sided	-15.253 to -3.145

Statistical Analysis

Groups	LNP023 50 mg BID, Placebo
Mean Difference (Final Values)	-9.25
80 % Confidence Interval 2-Sided	-15.499 to -3.000

Statistical Analysis

Groups	LNP023 100 mg BID - Part 2, Placebo
Mean Difference (Final Values)	-5.89
80 % Confidence Interval 2-Sided	-12.040 to 0.260

Statistical Analysis

Groups	LNP023 200 mg BID, Placebo
Mean Difference (Final Values)	-10.12
80 % Confidence Interval 2-Sided	-15.763 to -4.471

Shift table from baseline for Hematuria levels - Parts 1 and 2 at Day 90

(Time Frame: Baseline, Days 8, 15, 30 ,60 and 90)

	<9 rbc/hpf, Day 90	>=9 to =<50 rbc/hpf, Day 90	>50 rbc/hpf, Day 90
Arm/Group Description	Low-grade hematuria	Intermediate-grade hematuria	Higher-grade hematuria
Number of Participants Analyzed [units: participants]	56	10	1

Shift table from baseline for Hematuria levels - Parts 1 and 2 at Day 90
(units: participants)

LNP023 10mg <9, baseline=8	7	1	0
LNP023 10mg >=9 to =<50, baseline=4	1	3	0
LNP023 10mg >50, baseline=0	0	0	0
LNP023 50mg <9, baseline=13	13	0	0
LNP023 50mg >=9 to =<50, baseline=2	1	1	0
LNP023 50mg >50, baseline=0	0	0	0
LNP023 100mg <9, baseline=6	6	0	0
LNP023 100mg >=9 to =<50, baseline=4	4	0	0
LNP023 100mg >50, baseline=3	2	1	0
LNP023 200mg <9, baseline=6	6	0	0
LNP023 200mg >=9 to =<50, baseline=8	6	2	0
LNP023 200mg >50, baseline=0	0	0	0
Placebo <9, baseline=8	6	2	0
Placebo >=9 to =<50, baseline=5	4	0	1
Placebo >50, baseline=0	0	0	0

Mixed Model of Repeated Measures (MMRM) of the ratio to baseline in 24hour urine protein (UP) - Parts 1 and 2 to Day 90

(Time Frame: Baseline, Days 30 and 90)

	LNP023 10 mg BID	LNP023 50 mg BID	LNP023 100 mg BID - Part 2	LNP023 200 mg BID	Placebo
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day	Placebo identical to LNP023 taken orally twice a day
Number of Participants Analyzed [units: participants]	19	19	22	26	25
Mixed Model of Repeated Measures (MMRM) of the ratio to baseline in 24hour urine protein (UP) - Parts 1 and 2 to Day 90 (units: Ratio to baseline) Geometric Mean (80% Confidence Interval)					
	0.80 (0.661 to 0.965)	0.89 (0.740 to 1.070)	0.61 (0.509 to 0.729)	0.70 (0.601 to 0.823)	0.84 (0.713 to 0.987)

Statistical Analysis

Groups	LNP023 10 mg BID, Placebo
Other Ratio to placebo (of ratio to baseline)	0.95
80 % Confidence Interval 2-Sided	0.742 to 1.222

Statistical Analysis

Groups	LNP023 50 mg BID, Placebo
Other Ratio to placebo (of ratio to baseline)	1.06
80 % Confidence Interval 2-Sided	0.830 to 1.356

Statistical Analysis

Groups	LNP023 100 mg BID - Part 2, Placebo
Other Ratio to placebo (of ratio to baseline)	0.73
80 % Confidence Interval 2-Sided	0.569 to 0.928

Statistical Analysis

Groups	LNP023 200 mg BID, Placebo
Other Ratio to placebo (of ratio to baseline)	0.84
80 % Confidence Interval 2-Sided	0.669 to 1.050

Mixed Model of Repeated Measures (MMRM) of the ratio to baseline of 24 hour urine albumin (UA) - Parts 1 and 2 to Day 90

(Time Frame: Baseline, Days 30 and 90)

	LNP023 10 mg BID	LNP023 50 mg BID	LNP023 100 mg BID - Part 2	LNP023 200 mg BID	Placebo

Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day	Placebo identical to LNP023 taken orally twice a day
Number of Participants Analyzed [units: participants]	19	19	22	26	25
Mixed Model of Repeated Measures (MMRM) of the ratio to baseline of 24 hour urine albumin (UA) - Parts 1 and 2 to Day 90 (units: Ratio to baseline) Geometric Mean (80% Confidence Interval)					
	0.79 (0.648 to 0.964)	0.93 (0.763 to 1.122)	0.61 (0.504 to 0.734)	0.73 (0.623 to 0.865)	0.82 (0.693 to 0.973)

Statistical Analysis

Groups	LNP023 10 mg BID, Placebo
Other Ratio to placebo (of ratio to baseline)	0.96
80 % Confidence Interval 2-Sided	0.741 to 1.250

Statistical Analysis

Groups	LNP023 50 mg BID, Placebo

Other Ratio to placebo (of ratio to baseline)	1.13
80 % Confidence Interval 2-Sided	0.872 to 1.458

Statistical Analysis

Groups	LNP023 100 mg BID - Part 2, Placebo
Other Ratio to placebo (of ratio to baseline)	0.74
80 % Confidence Interval 2-Sided	0.574 to 0.957

Statistical Analysis

Groups	LNP023 200 mg BID, Placebo
Other Ratio to placebo (of ratio to baseline)	0.89
80 % Confidence Interval 2-Sided	0.706 to 1.132

Mixed Model of Repeated Measures (MMRM) of the ratio to baseline in 24 hour urine albumin to creatinine (UACR) - Parts 1 and 2 to Day 90

(Time Frame: Baseline, Days 30 and 90)

	LNP023 10 mg BID	**LNP023 50 mg BID**	**LNP023 100 mg BID - Part 2**	**LNP023 200 mg BID**	**Placebo**

Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day	Placebo identical to LNP023 taken orally twice a day
Number of Participants Analyzed [units: participants]	19	19	22	26	25
Mixed Model of Repeated Measures (MMRM) of the ratio to baseline in 24 hour urine albumin to creatinine (UACR) - Parts 1 and 2 to Day 90 (units: Ratio to baseline) Geometric Mean (80% Confidence Interval)					
	0.85 (0.728 to 0.998)	0.89 (0.765 to 1.045)	0.66 (0.567 to 0.772)	0.74 (0.647 to 0.842)	0.87 (0.756 to 0.998)

Statistical Analysis

Groups	LNP023 10 mg BID, Placebo
Other Ratio to placebo (of ratio to baseline)	0.98
80 % Confidence Interval 2-Sided	0.794 to 1.214

Statistical Analysis

Groups	LNP023 50 mg BID, Placebo

Other Ratio to placebo (of ratio to baseline)	1.03
80 % Confidence Interval 2-Sided	0.835 to 1.269

Statistical Analysis

Groups	LNP023 100 mg BID - Part 2, Placebo
Other Ratio to placebo (of ratio to baseline)	0.76
80 % Confidence Interval 2-Sided	0.616 to 0.942

Statistical Analysis

Groups	LNP023 200 mg BID, Placebo
Other Ratio to placebo (of ratio to baseline)	0.85
80 % Confidence Interval 2-Sided	0.704 to 1.027

Mixed Model of Repeated Measures (MMRM) of the ratio to baseline in urine protein to creatinine (UPCR) from 1st morning void - Parts 1 and 2 at Day 90

(Time Frame: Baseline, Days 8, 15, 30, 60 and 90)

	LNP023 10 mg BID	**LNP023 50 mg BID**	**LNP023 100 mg BID - Part 2**	**LNP023 200 mg BID**	**Placebo**

Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day	Placebo identical to LNP023 taken orally twice a day
Number of Participants Analyzed [units: participants]	20	19	22	26	25
Mixed Model of Repeated Measures (MMRM) of the ratio to baseline in urine protein to creatinine (UPCR) from 1st morning void - Parts 1 and 2 at Day 90 (units: Ratio to baseline) Geometric Mean (80% Confidence Interval)					
	0.76 (0.638 to 0.908)	0.81 (0.674 to 0.970)	0.61 (0.509 to 0.725)	0.70 (0.598 to 0.815)	0.83 (0.704 to 0.970)

Statistical Analysis

Groups	LNP023 10 mg BID, Placebo
Other Ratio to placebo (of ratio to baseline)	0.92
80 % Confidence Interval 2-Sided	0.723 to 1.172

Statistical Analysis

Groups	LNP023 50 mg BID, Placebo

Other Ratio to placebo (of ratio to baseline)	0.98
80 % Confidence Interval 2-Sided	0.767 to 1.249

Statistical Analysis

Groups	LNP023 100 mg BID - Part 2, Placebo
Other Ratio to placebo (of ratio to baseline)	0.74
80 % Confidence Interval 2-Sided	0.577 to 0.937

Statistical Analysis

Groups	LNP023 200 mg BID, Placebo
Other Ratio to placebo (of ratio to baseline)	0.84
80 % Confidence Interval 2-Sided	0.678 to 1.052

Plasma Pharmacokinetics (PK) of Area Under the Curve at steady state (AUCtau,ss and AUClast,ss) at Day 30

(Time Frame: Baseline (0 hr), Day 15 (0 hr) Day 30 (0, 0.25, 0.5, 1, 2, 4, 6, 8 hrs), Days 60, 90, 135, 180 (0 hr))

	LNP023 10 mg BID	**LNP023 50 mg BID**	**LNP023 100 mg BID - Part 2**	**LNP023 200 mg BID**
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day

Number of Participants Analyzed [units: participants]	18	18	16	24
Plasma Pharmacokinetics (PK) of Area Under the Curve at steady state (AUCtau,ss and AUClast,ss) at Day 30 (units: hr*ng/mL) Mean ± Standard Deviation				
AUClast,ss	5820 ± 1750	13000 ± 2740	18400 ± 6040	27900 ± 9930
AUCtau,ss	8010 ± 2550	17700 ± 4250	24700 ± 8030	37100 ± 13500

Plasma Pharmacokinetics (PK) of pre-dose trough at steady state (Ctrough,ss) and maximum concentrations (Cmax,ss) at Day 30

(Time Frame: Baseline (0 hr), Day 15 (0 hr) Day 30 (0, 0.25, 0.5, 1, 2, 4, 6, 8 hrs), Days 60, 90, 135, 180 (0 hr))

	LNP023 10 mg BID	LNP023 50 mg BID	LNP023 100 mg BID - Part 2	LNP023 200 mg BID
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day
Number of Participants Analyzed [units: participants]	18	18	16	24
Plasma Pharmacokinetics (PK) of pre-dose trough at steady state (Ctrough,ss) and maximum concentrations (Cmax,ss) at Day 30 (units: hr*ng/mL) Mean ± Standard Deviation				
Ctrough,ss	515 ± 232	1130 ± 348	1510 ± 567	2200 ± 964
Cmax,ss	964 ± 264	2150 ± 480	3300 ± 1080	4940 ± 1770

Plasma Pharmacokinetics (PK) of time to maximum concentration at steady state (Tmax,ss) at Day 30

(Time Frame: Baseline (0 hr), Day 15 (0 hr) Day 30 (0, 0.25, 0.5, 1, 2, 4, 6, 8 hrs), Days 60, 90, 135, 180 (0 hr))

	LNP023 10 mg BID	LNP023 50 mg BID	LNP023 100 mg BID - Part 2	LNP023 200 mg BID
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day
Number of Participants Analyzed [units: participants]	18	18	16	24
Plasma Pharmacokinetics (PK) of time to maximum concentration at steady state (Tmax,ss) at Day 30 (units: hour) Median (Full Range)				
	2.00 (0.250 to 6.00)	2.00 (1.00 to 6.00)	2.00 (0.500 to 6.00)	2.00 (0.500 to 4.00)

Amount of LNP023 excreted into urine (Ae,ss) at Day 30

(Time Frame: Baseline and Day 30)

	LNP023 10 mg BID	LNP023 50 mg BID	LNP023 100 mg BID - Part 2	LNP023 200 mg BID
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day
Number of Participants Analyzed [units: participants]	16	14	14	22
Amount of LNP023 excreted into urine (Ae,ss) at Day 30 (units: mg)				

Mean ± Standard Deviation				
	1.72 ± 1.15	11.7 ± 5.84	30.9 ± 17.0	60.3 ± 27.1

Percent of LNP023 excreted into urine at Day 30

(Time Frame: Baseline and Day 30)

	LNP023 10 mg BID	LNP023 50 mg BID	LNP023 100 mg BID - Part 2	LNP023 200 mg BID
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day
Number of Participants Analyzed [units: participants]	16	14	14	22
Percent of LNP023 excreted into urine at Day 30 (units: percent of dose) Mean ± Standard Deviation				
	8.59 ± 5.77	11.7 ± 5.84	15.5 ± 8.50	15.1 ± 6.77

Renal clearance from plasma at steady state (CLr,ss) at Day 30

(Time Frame: Baseline and Day 30)

	LNP023 10 mg BID	LNP023 50 mg BID	LNP023 100 mg BID - Part 2	LNP023 200 mg BID
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day

Number of Participants Analyzed [units: participants]	16	14	14	22
Renal clearance from plasma at steady state (CLr,ss) at Day 30 (units: L/hr) Mean ± Standard Deviation				
	0.112 ± 0.0744	0.348 ± 0.179	0.719 ± 0.479	0.942 ± 0.540

Change from baseline in plasma levels of circulating fragment of Factor B (Bb) and soluble terminal complement complex (sC5b-9) biomarkers for Parts 1 and 2 to Day 90

(Time Frame: Baseline, Days 8, 15, 30, 60, 90)

	LNP023 10 mg BID	LNP023 50 mg BID	LNP023 100 mg BID - Part 2	LNP023 200 mg BID	Placebo
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day	Placebo identical to LNP023 taken orally twice a day
Number of Participants Analyzed [units: participants]	20	19	22	26	25
Change from baseline in plasma levels of circulating fragment of Factor B (Bb) and soluble terminal complement complex (sC5b-9) biomarkers for Parts 1 and 2 to Day 90 (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)					
Day 8 - Bb, n=14,16,13,25,19	76.7 (22.89%)	72.2 (22.86%)	71.4 (30.66%)	66.3 (28.15%)	102.7 (19.78%)
Day 15 - Bb, n=13,14,16,22,22	80.4 (32.59%)	74.1 (23.30%)	78.5 (33.35%)	72.9 (20.47%)	108.6 (23.19%)

Day 30 - Bb, n=16,17,18,26,24	76.4 (18.32%)	76.2 (23.62%)	76.8 (34.00%)	70.4 (28.96%)	99.3 (22.07%)
Day 60 - Bb, n=14,16,17,25,21	78.8 (20.26%)	75.2 (19.05%)	77.4 (35.23%)	72.8 (23.97%)	102.9 (24.07%)
Day 90 - Bb, n=17,16,17,25,21	90.5 (25.57%)	79.3 (22.47%)	77.6 (35.42%)	74.6 (23.91%)	102.7 (22.01%)
Day 8 sC5B-9, n=12,16,13,22,17	80.6 (12.29%)	69.6 (37.40%)	65.9 (24.05%)	75.8 (30.15%)	95.2 (22.01%)
Day 15 sC5B-9, n=13,14,16,21,21	79.4 (27.60%)	72.2 (33.86%)	78.4 (33.35%)	78.0 (32.06%)	99.4 (25.40%)
Day 30 sC5B-9, n=16,17,18,25,24	85.8 (23.88%)	68.6 (41.32%)	76.4 (25.97%)	69.8 (21.98%)	94.2 (24.96%)
Day 60 sC5B-9, n=14,16,17,24,20	84.6 (27.37%)	73.7 (31.99%)	74.9 (29.65%)	76.2 (29.80%)	95.7 (30.11%)
Day 90 sC5B-9, n=16,16,17,23,19	89.6 (28.66%)	73.8 (36.21%)	79.0 (22.82%)	75.0 (34.21%)	103.4 (21.52%)

Estimation of lowest dose providing maximal reduction of proteinuria

(Time Frame: Baseline up to Month 3)

	LNP023 10 mg BID	LNP023 50 mg BID	LNP023 100 mg BID - Part 2	LNP023 200 mg BID	Placebo
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day	Placebo identical to LNP023 taken orally twice a day
Number of Participants Analyzed [units: participants]	19	19	22	26	25
Estimation of lowest dose providing maximal reduction of proteinuria					

(units: Ratio to baseline) Number (80% Confidence Interval)					
Ratio to Baseline	0.85 (0.77 to 0.93)	0.80 (0.73 to 0.87)	0.76 (0.70 to 0.81)	0.69 (0.61 to 0.77)	0.88 (0.80 to 1.00)

Mixed Model of Repeated Measures (MMRM) of the change from baseline for Estimated Glomerular Filtration Rate (eGFR) - Part 2 up to Day 180

(Time Frame: Baseline, Days 8, 15, 30, 60, 90, 135 and 180)

	LNP023 10 mg BID	LNP023 50 mg BID	LNP023 100 mg BID - Part 2	LNP023 200 mg BID	Placebo
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day	Placebo identical to LNP023 taken orally twice a day
Number of Participants Analyzed [units: participants]	9	10	19	11	11
Mixed Model of Repeated Measures (MMRM) of the change from baseline for Estimated Glomerular Filtration Rate (eGFR) - Part 2 up to Day 180 (units: mL/min/SSA) Mean ± Standard Error					
Day 180	0.78 ± 1.977	-2.35 ± 1.995	-2.91 ± 1.359	-1.18 ± 1.798	-3.17 ± 1.868

Statistical Analysis

Groups	LNP023 10 mg BID, Placebo

Mean Difference (Final Values)	3.95
80 % Confidence Interval 2-Sided	0.420 to 7.472

Statistical Analysis

Groups	LNP023 50 mg BID, Placebo
Mean Difference (Final Values)	0.82
80 % Confidence Interval 2-Sided	-2.747 to 4.390

Statistical Analysis

Groups	LNP023 100 mg BID - Part 2, Placebo
Mean Difference (Final Values)	0.26
80 % Confidence Interval 2-Sided	-2.745 to 3.262

Statistical Analysis

Groups	LNP023 200 mg BID, Placebo
Mean Difference (Final Values)	1.98

80	
% Confidence Interval 2-Sided	-1.368 to 5.337

Mixed Model of Repeated Measures (MMRM) of the ratio to baseline protein to creatinine (UPCR) from 1st morning void - Part 2 up to Day 180

(Time Frame: Baseline, Days 8, 15, 30, 60, 90, 135 and 180)

	LNP023 10 mg BID	LNP023 50 mg BID	LNP023 100 mg BID - Part 2	LNP023 200 mg BID	Placebo
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day	Placebo identical to LNP023 taken orally twice a day
Number of Participants Analyzed [units: participants]	9	10	19	11	11
Mixed Model of Repeated Measures (MMRM) of the ratio to baseline protein to creatinine (UPCR) from 1st morning void - Part 2 up to Day 180 (units: Ratio to baseline) Geometric Mean (80% Confidence Interval)					
Day 180 n=9,9,18,11, 10	0.81 (0.599 to 1.108)	0.72 (0.534 to 0.976)	0.63 (0.507 to 0.784)	0.72 (0.544 to 0.949)	0.79 (0.590 to 1.047)

Statistical Analysis

Groups	LNP023 10 mg BID, Placebo

Other Ratio to placebo (of ratio to baseline)	1.04
80 % Confidence Interval 2-Sided	0.680 to 1.579

Statistical Analysis

Groups	LNP023 50 mg BID, Placebo
Other Ratio to placebo (of ratio to baseline)	0.92
80 % Confidence Interval 2-Sided	0.607 to 1.390

Statistical Analysis

Groups	LNP023 100 mg BID - Part 2, Placebo
Other Ratio to placebo (of ratio to baseline)	0.80
80 % Confidence Interval 2-Sided	0.558 to 1.153

Statistical Analysis

Groups	LNP023 200 mg BID, Placebo
Other Ratio to placebo (of ratio to baseline)	0.91

80
% Confidence Interval 0.614 to 1.362
2-Sided

Shift table from baseline for Hematuria levels - Part 2 at Day 180

(Time Frame: Baseline, Days 8, 15, 30, 60, 90, 135 and 180)

	<9 rbc/hpf	>=9 to =<50 rbc/hpf	>50 rbc/hpf
Arm/Group Description	Low-grade hematuria	Intermediate-grade hematuria	Higher-grade hematuria
Number of Participants Analyzed [units: participants]	10	19	11
Shift table from baseline for Hematuria levels - Part 2 at Day 180 (units: participants)			
LNP023 10mg <9, baseline=2	1	1	0
LNP023 10mg >=9 to =<50, baseline=3	2	1	0
LNP023 10mg >50, baseline=0	0	0	0
LNP023 50mg <9, baseline=5	5	0	0
LNP023 50mg >=9 to =<50, baseline=1	1	0	0
LNP023 50mg >50, baseline=0	0	0	0
LNP023 100mg <9, baseline=2	2	0	0
LNP023 100mg >=9 to =<50, at baseline=3	3	0	0

LNP023 100mg >50, baseline=3	2	1	0
LNP023 200mg <9, baseline=4	4	0	0
LNP023 200mg >=9 to =<50, baseline=2	2	0	0
LNP023 200mg >50, baseline=0	0	0	0
Placebo <9, baseline=4	4	0	0
Placebo >=9 to =<50, baseline=1	0	0	1
Placebo >50, baseline=0	0	0	0

Mixed Model of Repeated Measures (MMRM) of the change from baseline in protein level urine using the urine protein-creatinine ratio (UPCR) from 24 hour urine collection - Part 2 up to Day 180

(Time Frame: Baseline, Days 30, 90 and 180)

	LNP023 10 mg BID	LNP023 50 mg BID	LNP023 100 mg BID - Part 2	LNP023 200 mg BID	Placebo
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day	Placebo identical to LNP023 taken orally twice a day
Number of Participants Analyzed [units: participants]	9	10	19	11	11
Mixed Model of Repeated Measures (MMRM) of the change from baseline in protein level urine using the urine protein-creatinine ratio (UPCR) from 24 hour urine					

collection - Part 2 up to Day 180 (units: mg/d) Geometric Mean (80% Confidence Interval)					
Day 180	1.06 (0.803 to 1.394)	0.59 (0.452 to 0.779)	0.66 (0.540 to 0.798)	0.73 (0.568 to 0.940)	0.91 (0.705 to 1.185)

Statistical Analysis

Groups	LNP023 10 mg BID, Placebo
Other Geometric mean ratio	1.16
80 % Confidence Interval 2-Sided	0.792 to 1.692

Statistical Analysis

Groups	LNP023 50 mg BID, Placebo
Other Geometric mean ratio	0.65
80 % Confidence Interval 2-Sided	0.446 to 0.945

Statistical Analysis

Groups	LNP023 100 mg BID - Part 2, Placebo
Other Geometric mean ratio	0.72

80 % Confidence Interval 2-Sided	0.518 to 0.997

Statistical Analysis

Groups	LNP023 200 mg BID, Placebo
Other Geometric mean ratio	0.80
80 % Confidence Interval 2-Sided	0.558 to 1.146

Mixed Model of Repeated Measures (MMRM) of the ratio to baseline in 24 hour urine albumin to creatinine (UACR) - Part 2 up to Day 180

(Time Frame: Baseline, Days 30, 90 and 180)

	LNP023 10 mg BID	**LNP023 50 mg BID**	**LNP023 100 mg BID - Part 2**	**LNP023 200 mg BID**	**Placebo**
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken orally twice a day	200 mg taken twice a day	Placebo identical to LNP023 taken orally twice a day
Number of Participants Analyzed [units: participants]	9	10	19	11	11
Mixed Model of Repeated Measures (MMRM) of the ratio to baseline in 24 hour urine albumin to creatinine (UACR) - Part 2 up to Day 180 (units: Ratio to baseline) Geometric Mean (80% Confidence Interval)					

Day 180	1.04 (0.779 to 1.392)	0.61 (0.454 to 0.808)	0.65 (0.526 to 0.792)	0.69 (0.533 to 0.902)	0.91 (0.696 to 1.200)

Statistical Analysis

Groups	LNP023 10 mg BID, Placebo
Other Ratio to placebo (of ratio to baseline)	1.14
80 % Confidence Interval 2-Sided	0.765 to 1.699

Statistical Analysis

Groups	LNP023 50 mg BID, Placebo
Other Ratio to placebo (of ratio to baseline)	0.66
80 % Confidence Interval 2-Sided	0.446 to 0.984

Statistical Analysis

Groups	LNP023 100 mg BID - Part 2, Placebo
Other Ratio to placebo (of ratio to baseline)	0.71
80 % Confidence Interval 2-Sided	0.501 to 0.995

Statistical Analysis

Groups	LNP023 200 mg BID, Placebo
Other Ratio to placebo (of ratio to baseline)	0.76
80 % Confidence Interval 2-Sided	0.520 to 1.107

Safety Results

All-Cause Mortality

	LNP023 10 mg BID N = 20	LNP023 50 mg BID N = 19	LNP023 100 mg BID N = 22	LNP023 200 mg BID N = 26	Placebo N = 25
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken twice a day	200 mg taken twice a day	Placebo identical to LNP023 taken twice a day
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment plus 7 days post treatment, up to a maximum duration of 197 days.
Source Vocabulary for Table Default	MedDRA (24.0)

Assessment Type for Table Default	Systematic Assessment

	LNP023 10 mg BID N = 20	LNP023 50 mg BID N = 19	LNP023 100 mg BID N = 22	LNP023 200 mg BID N = 26	Placebo N = 25
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken twice a day	200 mg taken twice a day	Placebo identical to LNP023 taken twice a day
Total participants affected	0 (0.00%)	1 (5.26%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Infections and infestations					
COVID-19*	0 (0.00%)	1 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders					
Aspiration*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)

* Non-systematic Assessment

Other Adverse Events by System Organ Class

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment plus 7 days post treatment, up to a maximum duration of 197 days.
Source Vocabulary for Table Default	MedDRA (24.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	1.8%

	LNP023 10 mg BID N = 20	LNP023 50 mg BID N = 19	LNP023 100 mg BID N = 22	LNP023 200 mg BID N = 26	Placebo N = 25
Arm/Group Description	10 mg taken twice a day	50 mg taken twice a day	100 mg taken twice a day	200 mg taken twice a day	Placebo identical to LNP023 taken twice a day
Total participants affected	14 (70.00%)	16 (84.21%)	15 (68.18%)	14 (53.85%)	17 (68.00%)
Blood and lymphatic system disorders					
Anaemia*	0 (0.00%)	1 (5.26%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Cardiac disorders					
Bundle branch block right*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Palpitations*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
Sinus bradycardia*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
Supraventricular extrasystoles*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
Tachycardia*	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	0 (0.00%)
Wolff-Parkinson-White syndrome*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
Ear and labyrinth disorders					
Vertigo*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Eye disorders					
Asthenopia*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal disorders					

Abdominal discomfort*	0 (0.00%)	3 (15.79%)	2 (9.09%)	0 (0.00%)	0 (0.00%)
Abdominal pain*	1 (5.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
Abdominal pain lower*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Abdominal pain upper*	2 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Aphthous ulcer*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diarrhoea*	0 (0.00%)	2 (10.53%)	1 (4.55%)	1 (3.85%)	3 (12.00%)
Dyspepsia*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Epigastric discomfort*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Food poisoning*	0 (0.00%)	1 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrooesophageal reflux disease*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Mouth haemorrhage*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Mouth ulceration*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
Nausea*	3 (15.00%)	1 (5.26%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Toothache*	0 (0.00%)	0 (0.00%)	1 (4.55%)	1 (3.85%)	0 (0.00%)
Vomiting*	3 (15.00%)	2 (10.53%)	0 (0.00%)	1 (3.85%)	1 (4.00%)
General disorders and administration site conditions					
Asthenia*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Chest pain*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
Face oedema*	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	0 (0.00%)
Fatigue*	0 (0.00%)	2 (10.53%)	1 (4.55%)	0 (0.00%)	3 (12.00%)
Feeling hot*	0 (0.00%)	1 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Influenza like illness*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Oedema*	1 (5.00%)	1 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oedema peripheral*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)

Pain*	2 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pyrexia*	0 (0.00%)	2 (10.53%)	1 (4.55%)	1 (3.85%)	0 (0.00%)
Infections and infestations					
Asymptomatic bacteriuria*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	1 (4.00%)
Bronchitis*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Conjunctivitis*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
COVID-19*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Gastroenteritis*	0 (0.00%)	0 (0.00%)	2 (9.09%)	0 (0.00%)	1 (4.00%)
Gingivitis*	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	1 (4.00%)
Hordeolum*	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	0 (0.00%)
Influenza*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
Nasopharyngitis*	2 (10.00%)	2 (10.53%)	0 (0.00%)	1 (3.85%)	2 (8.00%)
Norovirus infection*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Onychomycosis*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
Oral herpes*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Otitis externa*	0 (0.00%)	1 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Otitis media*	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	0 (0.00%)
Pharyngitis*	0 (0.00%)	1 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Respiratory tract infection*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Tonsillitis*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
Tooth abscess*	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	0 (0.00%)
Tracheobronchitis*	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	0 (0.00%)
Upper respiratory tract infection*	1 (5.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	0 (0.00%)

Urinary tract infection*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Viral infection*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications					
Overdose*	0 (0.00%)	1 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin abrasion*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Investigations					
Activated partial thromboplastin time prolonged*	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	0 (0.00%)
Amylase increased*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Blood creatinine increased*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Blood potassium increased*	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	0 (0.00%)
Blood pressure increased*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Blood testosterone decreased*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blood triglycerides increased*	0 (0.00%)	1 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Coagulation test abnormal*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	1 (4.00%)
Cystatin C increased*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
Lipase increased*	1 (5.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	1 (4.00%)
Pancreatic enzymes increased*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
SARS-CoV-2 test negative*	1 (5.00%)	1 (5.26%)	2 (9.09%)	0 (0.00%)	0 (0.00%)

Weight increased*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Metabolism and nutrition disorders					
Decreased appetite*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
Diabetes mellitus*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
Gout*	0 (0.00%)	1 (5.26%)	0 (0.00%)	1 (3.85%)	0 (0.00%)
Hypercholesterolaemia*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hyperkalaemia*	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	1 (4.00%)
Hypermagnesaemia*	0 (0.00%)	1 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hyperuricaemia*	0 (0.00%)	1 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hyponatraemia*	0 (0.00%)	1 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypophosphataemia*	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	0 (0.00%)
Iron deficiency*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Metabolic acidosis*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
Vitamin B12 deficiency*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Musculoskeletal and connective tissue disorders					
Arthralgia*	2 (10.00%)	0 (0.00%)	2 (9.09%)	0 (0.00%)	0 (0.00%)
Back pain*	1 (5.00%)	0 (0.00%)	3 (13.64%)	1 (3.85%)	3 (12.00%)
Bursitis*	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	0 (0.00%)
Flank pain*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
Joint swelling*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Muscle spasms*	0 (0.00%)	0 (0.00%)	2 (9.09%)	0 (0.00%)	1 (4.00%)
Musculoskeletal stiffness*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Pain in extremity*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)

Plantar fasciitis*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Polyarthritis*	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Essential thrombocythaemia*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Polycythaemia vera*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Nervous system disorders					
Disturbance in attention*	0 (0.00%)	0 (0.00%)	2 (9.09%)	0 (0.00%)	0 (0.00%)
Dizziness*	2 (10.00%)	3 (15.79%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
Dysaesthesia*	0 (0.00%)	1 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Epilepsy*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Head discomfort*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Headache*	2 (10.00%)	2 (10.53%)	2 (9.09%)	2 (7.69%)	6 (24.00%)
Migraine*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Syncope*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
Taste disorder*	0 (0.00%)	1 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tremor*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders					
Insomnia*	1 (5.00%)	0 (0.00%)	1 (4.55%)	1 (3.85%)	0 (0.00%)
Renal and urinary disorders					
Dysuria*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Haematuria*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)

Renal pain*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Renal vasculitis*	0 (0.00%)	1 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Reproductive system and breast disorders					
Dysmenorrhoea*	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	1 (4.00%)
Respiratory, thoracic and mediastinal disorders					
Cough*	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (4.00%)
Dyspnoea exertional*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
Epistaxis*	1 (5.00%)	0 (0.00%)	2 (9.09%)	0 (0.00%)	2 (8.00%)
Oropharyngeal pain*	0 (0.00%)	2 (10.53%)	0 (0.00%)	1 (3.85%)	0 (0.00%)
Rhinitis allergic*	0 (0.00%)	1 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Throat irritation*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders					
Acne*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
Alopecia*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Dermatosis*	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	0 (0.00%)
Dry skin*	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	0 (0.00%)
Eczema*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eczema nummular*	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.00%)
Erythema*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pruritus*	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.85%)	0 (0.00%)
Rash*	0 (0.00%)	1 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vasculitic rash*	0 (0.00%)	1 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vascular disorders					

Hot flush*	1 (5.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypertension*	1 (5.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (4.00%)
Hypotension*	3 (15.00%)	0 (0.00%)	0 (0.00%)	2 (7.69%)	0 (0.00%)

* Non-systematic Assessment

Other Relevant Findings

None

Conclusion:

- LNP023 b.i.d. ranging from 10 mg to 200 mg was safe and well tolerated. The LNP023 safety profile was similar to the placebo safety profile and there was no evident dose effect on the incidence of adverse events.
- This study met its primary objective by demonstrating a statistically significant dose response effect of LNP023 vs. placebo on the reduction in proteinuria (24h urine sample) after 90 days of treatment (one-sided multiplicity adjusted p-value=0.038).
- At Day 90, the highest reduction of 23% (80% CI: 8, 34) from baseline in urine protein to creatinine ratio as compared to placebo was estimated for the LNP023 dose of 200 mg b.i.d.
- In the subgroup of patients who received treatment for 180 days, urine protein to creatinine ratio continued to decrease between 90 and 180 days of treatment except in placebo and LNP023 10 mg b.i.d. group.

LNP023 b.i.d. induced a clear dose-dependent inhibition of the complement alternative pathway up to 90 days of treatment. In the subgroup of patients who received treatment for 180 days, only the LNP023 dose of 200 mg b.i.d. was able to sustain a strong inhibition with all the biomarkers tested up to Day 180.

The results of this study support the LNP023 dose of 200 mg b.i.d. for subsequent clinical development of LNP023 for IgAN as well as other indications.

Date of Clinical Trial Report

May 27, 2022