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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Iptacopan (LNP023)

Trial Indication(s)

Idiopathic membranous nephropathy

Protocol Number

CLNP023D12201

Protocol Title

A randomized, open-label, two arm, parallel group, proof-of-concept clinical trial to investigate the efficacy and safety of LNP023 compared with rituximab in the treatment of subjects with idiopathic membranous nephropathy

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: November 23, 2019 (Actual)
Primary Completion Date: January 20, 2023 (Actual)
Study Completion Date: January 20, 2023 (Actual)

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Reason for Termination (If applicable)

Sponsor decision

Study Design/Methodology

This was a randomized, open-label, two arm, parallel group, proof-of-concept, nonconfirmatory study evaluating the efficacy and safety of LNP023 compared with rituximab in subjects with Idiopathic (primary) membranous nephropathy (iMN) who are at high risk of disease progression defined on the basis of anti- Phospholipase A2 Receptor (PLA2R) antibody titer ≥ 60 RU/mL and proteinuria with urine protein (UP) ≥ 3.5 g/24h

The overall study was planned for a total of 65 weeks and included a screening visit, a run-in period of up to 12 weeks including a baseline visit, Day 1 (day of first investigational drug administration), a treatment period of 24 weeks from Day 1 to Day 169, a follow-up period of 29 weeks without treatment, and an end-of-study (EOS) visit. As per protocol amendment v01, subjects were randomized 1:1 to LNP023 (investigational drug) or rituximab (comparator) and followed the below dosing schedule: - LNP023 50 mg orally b.i.d. for 4 weeks (last dose on morning of Day 29); dose was increased to 200 mg orally b.i.d. at Day 29 visit and taken for 20 weeks starting on Day 29 evening dose. - Rituximab 1g i.v. infusion on Day 1 and Day 15.

Initially, per protocol v00 subjects were planned to be randomized in a 1:1:1 ratio to 3 treatment arms:
- LNP023 low dose: LNP023 10 mg orally b.i.d. for 4 weeks followed by 50 mg orally b.i.d. for 20 weeks.
- LNP023 high dose: LNP023 25 mg orally b.i.d. for 4 weeks followed by 200 mg orally b.i.d. for 20 weeks.
- Rituximab 1g i.v. infusion on Day 1 and Day 15.

Following decision to discontinue the low-dose arm of LNP023 and implementation of protocol amendment 1 (v01) , ongoing subjects were switched to LNP023 200 mg b.i.d. dose after completion of their initial 4 weeks of treatment or any subsequent visit where drug dispensing was planned. Subjects enrolled after implementation of protocol v01 followed a high-dose regimen with LNP023 50 mg orally b.i.d. for the initial 4 weeks and LNP023 200 mg orally b.i.d. thereafter.

2 subjects were enrolled and had already completed treatment as per protocol amendment v00, i.e., LNP023 10 mg orally b.i.d. for 4 weeks followed by 50 mg orally b.i.d. for 20 weeks by the time protocol amendment v01 was implemented. 1

subject was switched from 50 mg b.i.d. to 200 mg b.i.d. at D141 visit and until D169/EOT visitEfficacy data from these 3 participants under protocol V00 low-dose LNP023 were not included in the study results as the low number of subjects would not have allowed for a meaningful analysis and interpretation of data.

The main reason for amendment 1 was to align with the clinical study results obtained from interim analysis of ongoing Phase 2 trials (at that time) with LNP023 in PNH (CLNP023X2201 and CLNP023X2204), IgAN (CLNP023X2203) and C3G (CLNP023X2202) which had shown a dose dependent inhibition of the complement alternative pathway and supported best efficacy results with LNP023 at dose levels of 200 mg b.i.d.

Despite the promising results from the above mentioned LNP023 trials in other indications, the CLNP023D12201 trial in idiopathic membranous nephropathy was early terminated following an Interim Analysis which revealed that LNP023 did not meet efficacy expectations as compared to rituximab, but did not show any unexpected or new safety findings.

Centers

18 centers in 9 countries: India(2), Argentina(3), United Kingdom(3), Germany(4), Spain(2), Czech Republic(1), Netherlands(1), Taiwan(1), China(1)

Objectives:

Primary objective: To assess the efficacy of LNP023 compared with rituximab.
Secondary objective: To assess the safety and tolerability of LNP023, to assess the relationship between LNP023 systemic drug exposure and pharmacodynamics, mode-of-action markers and clinical efficacy, to assess the effect of LNP023 compared with rituximab on proteinuria remission and renal function and to assess the pharmacokinetics of LNP023.

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

- LNP023 10 mg orally b.i.d. for 4 weeks followed by 50 mg orally b.i.d. for 20 weeks
- LNP023 25 or 50 mg orally b.i.d. for 4 weeks followed by 200 mg orally b.i.d. for 20 weeks
- Rituximab 1g i.v. infusion on Day 1 and Day 15

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Statistical Methods

The safety analysis set included all subjects who received any study drug.

The PK analysis set included all subjects with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received any LNP023 and experienced no protocol deviations with relevant impact on PK data. The

All subjects within the PD analysis set except for subjects randomized to the former LNP023 low dose arm (10/50 b.i.d.) were included in the PD data analysis.

The primary endpoint of this study was the ratio between baseline UPCR and UPCR at 24 weeks of treatment measured in 24h urine. The least squares means (LMS) of each treatment group and the differences between LNP023 200 mg and rituximab in change from baseline in log-transformed UPCR was estimated from the model at each timepoint along with the corresponding 95% confidence intervals. In secondary endpoint, the log-transformed ratio to baseline in UPCR measured in morning void were analyzed using a Mixed Model for Repeated Measures (MMRM). Summary statistics for the change from baseline to 24 weeks in eGFR (applying the CKD-EPI equation) was provided by treatment.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

• Female or male adult (≥18 years) subjects at screening visit with a diagnosis of idiopathic (primary) MN confirmed by renal biopsy within 36 months prior to screening. A renal biopsy may be taken at any time during the run-in period to confirm the diagnosis of MN and facilitate subject eligibility, if the most recent biopsy was performed greater than 36 months prior to the screening visit.
• Anti-PLA2R antibody titer of ≥ 60 RU/mL at screening visit. If sites opt to use a local laboratory, with prior agreement with sponsor, an anti-PLA2R titer performed within 4 weeks prior to screening visit can be used.
• Urine protein ≥ 3.5 g/24h at screening and baseline visits
• ≤50% reduction in both anti-PLA2R level and 24h urine protein between screening and baseline
• Estimated GFR (using the CKD-EPI formula) ≥ 30 mL/min per 1.73 m2 at screening
• Receiving stable dose at the maximum recommended dose according to local guidelines or maximum tolerated dose of ACEi and/or ARB and/or statins and/or diuretics for at least 8 weeks prior to Day 1
• Vaccination against Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenzae (in accordance with local

guidelines) at least 28 days prior to Day 1 and no longer than 5 years prior to Day 1.

Exclusion Criteria:
• Secondary causes of MN, e.g. systemic autoimmune diseases, solid or haematological malignancies, infections or chronic intake of drugs (e.g. gold salts, NSAIDs, penicillamines)
• Diagnostic renal biopsy showing evidence of crescent formation in glomeruli, suggestive of an alternative or additional diagnosis to primary idiopathic MN.
• Previous treatment with B-cell depleting or B-cell modifying agents such as, but not limited to rituximab, belimumab, daratumomab or bortezomib.
• Previous treatment with immunosuppressive agents such as cyclophosphamide, chlorambucil, mycophenolate mofetil (or equivalent), cyclosporine, tacrolimus or azathioprine within 90 days prior to Day 1. Low dose systemic corticosteroid therapy is permitted, though the subject should have been on stable dose equivalent to ≤10 mg prednisolone for at least 90 days prior to Day 1.
• Previous treatment with gemfibrozil or strong CYP2C8 inhibitors such as clopidogrel within 7 days prior to Day 1
• Presence or suspicion (based on judgment of the investigator) of active infection within 30 days prior to Day 1, or history of severe recurrent bacterial infections
• Known contra-indications for the use of rituximab, including hypersensitivity to the active substance or to murine proteins, or to any of the excipients (sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid, water for injections). Other contra-indications for the use of rituximab, including active, severe infection, patients in a severely immunocompromised state, severe heart failure (NYHA Class IV) or severe, uncontrolled cardiac disease.

Participant Flow Table

Overall Study

	LNP023 10/50 mg b.i.d.	LNP023 200 mg b.i.d.	Rituximab	Total
Arm/Group Description	As per protocol V00, participants took LNP023 10 mg orally b.i.d. for 4 weeks followed by LNP023 50 mg orally b.i.d. for 20 weeks	Combination of the LNP023 25/200 mg b.i.d. and 50/200 mg b.i.d. groups. Under protocol V00, participants took LNP023 25 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks. Under protocol v01, participants took LNP023 50 mg orally b.i.d.	Rituximab 1 g i.v. at Day 1 and Day 15	

		for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks.		
Started	3	19	15	37
Completed	3	9	14	26
Not Completed	0	10	1	11
Adverse Event	0	1	0	1
Patient Requires Other Treatment	0	1	0	1
Study Terminated By Sponsor	0	6	1	7
Subject Decision	0	1	0	1
Suspected Lack Of Efficacy	0	1	0	1

Baseline Characteristics

	LNP023 10/50 mg b.i.d.	**LNP023 200 mg b.i.d.**	**Rituximab**	**Total**
Arm/Group Description	As per protocol V00, participants took LNP023 10 mg orally b.i.d. for 4 weeks followed by LNP023 50 mg orally b.i.d. for 20 weeks	Combination of the LNP023 25/200 mg b.i.d. and 50/200 mg b.i.d. groups. Under protocol V00, participants took LNP023 25 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks. Under protocol v01, participants took LNP023 50 mg orally	Rituximab 1 g i.v. at Day 1 and Day 15	

		b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks.		
Number of Participants [units: participants]	3	19	15	37
Baseline Analysis Population Description				
Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation				
	55.0±18.52	48.9±8.84	46.7±15.33	48.5±12.43
Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
Female	1	4	1	6
Male	2	15	14	31
Race/Ethnicity, Customized (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
Asian	1	5	4	10
Black Or African American	0	0	1	1
Unknown	0	0	1	1
White	2	14	9	25

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Primary Outcome Result(s)

Ratio between baseline Urine Protein Creatinine Ratio (UPCR) and Urine Protein Creatinine Ratio at 24 weeks of treatment (from 24h urine collection)

Description	The primary endpoint of this study is the ratio between UPCR at 24 weeks of treatment measured in 24h urine and baseline UPCR . To assess the primary objective, the log-transformed ratio to baseline in UPCR was analyzed using a mixed model for repeated measures (MMRM). The results were back transformed and presented on the original scale. Efficacy data from these 3 participants under protocol V00 low-dose LNP023 (LNP023 10/50 mg b.i.d.) were not included in the study results as the low number of subjects would not have allowed for a meaningful analysis and interpretation of data.
Time Frame	Baseline, Day 113, Day 169
Analysis Population Description	PD set: PD (pharmacodynamics) analysis set included all participants who received any study drug and experienced no protocol deviations with relevant impact on PD/efficacy data. Participants randomized to the former LNP023 low dose arm (10/50 b.i.d.) were not included in the PD data analysis. Only participants with a value for UPCR at both Baseline and Day 113 or Day 169 were included in the analysis.

	LNP023 200 mg b.i.d.	**Rituximab**
Arm/Group Description	Combination of the LNP023 25/200 mg b.i.d. and 50/200 mg b.i.d. groups. Under protocol V00, participants took LNP023 25 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks. Under protocol v01, participants took LNP023 50 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks.	Rituximab 1 g i.v. at Day 1 and Day 15
Number of Participants Analyzed [units: participants]	10	13
Ratio between baseline Urine Protein Creatinine Ratio (UPCR) and Urine Protein Creatinine Ratio at 24 weeks of treatment (from 24h urine collection) (units: ratio to baseline)	**Geometric Mean (95% Confidence Interval)**	**Geometric Mean (95% Confidence Interval)**
Day 113	0.94 (0.74 to 1.20)	0.89 (0.71 to 1.10)
Day 169	0.88 (0.65 to 1.19)	0.64 (0.48 to 0.86)

Statistical Analysis

Groups	LNP023 200 mg b.i.d., Rituximab	
Type of Statistical Test	Superiority	
Non-Inferiority/Equivalence Test	Comparison of adjusted geometric mean ratios on Day 169	
P Value	0.2670	Calculated at one-sided 10% level from a lower-tailed test
Method	Mixed Models Analysis	
Other Adjusted geometric mean ratio	1.37	
95 % Confidence Interval 2-Sided	0.90 to 2.08	

Secondary Outcome Result(s)

Change from baseline in plasma levels of circulating fragment of factor B (Bb)

Description	The drug (LNP023) is expected to block the complement alternative pathway dysregulation and thereby should normalize complement biomarker levels in serum. Bb is a biomarker that accurately reflects the level of complement Alternative Pathway activation. Baseline is defined as the last non-missing measurement prior to randomization. Measurements for LNP023 group were done pre-dose. Efficacy data from these 3 participants under protocol V00 low-dose LNP023 (LNP023 10/50 mg b.i.d.) were not included in the study results as the low number of subjects would not have allowed for a meaningful analysis and interpretation of data.
Time Frame	Baseline, Day 15, Day 29, Day 57, Day 113 and Day 169
Analysis Population Description	PD set: PD (pharmacodynamics) analysis set included all participants who received any study drug and experienced no protocol deviations with relevant impact on PD/efficacy data. Participants randomized to the former LNP023 low dose arm (10/50 b.i.d.) were not included in the PD data analysis. Only participants with values of plasma levels of circulating fragment of factor B at both Baseline and the different time points were included in the analysis.

	LNP023 200 mg b.i.d.	Rituximab
Arm/Group Description	Combination of the LNP023 25/200 mg b.i.d. and 50/200 mg b.i.d. groups. Under protocol V00, participants took LNP023 25 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks. Under protocol v01, participants took LNP023 50 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks.	Rituximab 1 g i.v. at Day 1 and Day 15
Number of Participants Analyzed [units: participants]	17	13
Change from baseline in plasma levels of circulating fragment of factor B (Bb) (units: ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Day 15	1520.59 ± 9370.086	-417.69 ± 701.667
Day 29	-732.00 ± 1412.633	-318.46 ± 604.440
Day 57	-545.00 ± 1379.201	-75.38 ± 787.545
Day 113	-877.27 ± 1562.716	-219.17 ± 703.568
Day 169	-984.00 ± 1794.419	-570.00 ± 611.167

Change from baseline in plasma levels of sC5b-9

Description	Soluble C5b-9 (sC5b-9) is a biomarker of the complement pathway activity that correlate with disease progression. Baseline is defined as the last non-missing measurement prior to randomization. Measurements for LNP023 group were done pre-dose. Efficacy data from these 3 participants under protocol V00 low-dose LNP023 (LNP023 10/50 mg b.i.d.) were not included in the study results as the low number of subjects would not have allowed for a meaningful analysis and interpretation of data.
Time Frame	Baseline, Day 15, Day 29, Day 57, Day 113, Day 169
Analysis Population Description	PD set: PD (pharmacodynamics) analysis set included all participants who received any study drug and experienced no protocol deviations with relevant impact on PD/efficacy data. Participants randomized to the former LNP023 low dose arm (10/50 b.i.d.) were not included in the PD data analysis. Only participants with a value of plasma levels of sC5b-9 at both Baseline and the different time points were included in the analysis.

	LNP023 200 mg b.i.d.	Rituximab
Arm/Group Description	Combination of the LNP023 25/200 mg b.i.d. and 50/200 mg b.i.d. groups. Under protocol V00, participants took LNP023 25 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks. Under protocol v01, participants took LNP023 50 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks.	Rituximab 1 g i.v. at Day 1 and Day 15
Number of Participants Analyzed [units: participants]	17	13
Change from baseline in plasma levels of sC5b-9 (units: ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Day 15	-80.40 ± 98.229	-38.49 ± 52.258
Day 29	-82.80 ± 118.338	-24.51 ± 94.826
Day 57	-90.62 ± 108.483	-14.02 ± 107.651
Day 113	-113.32 ± 108.118	-24.95 ± 128.721
Day 169	-84.07 ± 96.045	-21.76 ± 122.654

Ratio to baseline of urine protein creatinine ratio (UPCR) measured in first morning void

Description	Adjusted geometric mean ratio to baseline of Urine Protein Creatinine Ratio (UPCR) measured in first morning void. First morning void urine sample was collected in the morning of the day before the visit and kept in the fridge. Efficacy data from these 3 participants under protocol V00 low-dose LNP023 (LNP023 10/50 mg b.i.d.) were not included in the study results as the low number of subjects would not have allowed for a meaningful analysis and interpretation of data.
Time Frame	Baseline, Day 15, Day 29, Day 57, Day 85, Day 113, Day 141, Day 169, Day 266 and Day 378
Analysis Population Description	PD set: PD (pharmacodynamics) analysis set included all participants who received any study drug and experienced no protocol deviations with relevant impact on PD/efficacy data. Participants randomized to the former LNP023 low dose arm (10/50 b.i.d.) were not included in the PD data analysis. Only participants with a value of UPCR measured in first morning void at the different time points were included in the analysis.

	LNP023 200 mg b.i.d.	Rituximab
Arm/Group Description	Combination of the LNP023 25/200 mg b.i.d. and 50/200 mg b.i.d. groups. Under protocol V00, participants took LNP023 25 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks. Under protocol v01, participants took LNP023 50 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks.	Rituximab 1 g i.v. at Day 1 and Day 15
Number of Participants Analyzed [units: participants]	18	13
Ratio to baseline of urine protein creatinine ratio (UPCR) measured in first morning void (units: ratio to baseline)	**Geometric Mean (95% Confidence Interval)**	**Geometric Mean (95% Confidence Interval)**
Day 15	0.94 (0.65 to 1.34)	1.15 (0.75 to 1.76)
Day 29	0.98 (0.70 to 1.36)	0.90 (0.60 to 1.35)
Day 57	1.02 (0.71 to 1.48)	0.77 (0.51 to 1.16)
Day 85	1.03 (0.68 to 1.56)	0.75 (0.50 to 1.13)
Day 113	1.05 (0.68 to 1.63)	0.92 (0.60 to 1.41)
Day 141	0.75 (0.48 to 1.19)	0.77 (0.48 to 1.23)
Day 169	0.72 (0.44 to 1.16)	0.55 (0.34 to 0.89)
Day 266	0.57 (0.33 to 0.99)	0.34 (0.20 to 0.57)
Day 378 (End Of Study)	0.37 (0.22 to 0.63)	0.46 (0.27 to 0.76)

Statistical Analysis

Groups	LNP023 200 mg b.i.d., Rituximab	Day 15
Type of Statistical Test	Superiority	
P Value	0.4598	Calculated from a two-sided test at the 0.05 significance level
Method	Other Mixed Model for Repeated Measures	
Other Adjusted geometric mean ratios	0.81	Comparison of adjusted geometric mean ratios: Test vs Ref.
95 % Confidence Interval 2-Sided	0.47 to 1.42	

Statistical Analysis

Groups	LNP023 200 mg b.i.d., Rituximab	Day 169
Type of Statistical Test	Superiority	
P Value	0.4528	Calculated from a two-sided test at the 0.05 significance level
Method	Other Mixed Model for Repeated Measures	
Other Geometric mean ratios	1.30	Comparison of adjusted geometric mean ratios: Test vs Ref.
95 % Confidence Interval 2-Sided	0.65 to 2.61	

Number of participants by treatment response at 24 weeks of treatment

Description Participants were considered complete responders if at 24 weeks of treatment, they showed complete remission of proteinuria (i.e., Urine Protein (UP) ≤ 0.3 g/24h), partial responders if they showed partial remission (i.e., UP > 0.3g/24h and ≤ 3.5 g/24h and a reduction of UP by >50% from baseline), and non-responders if UP >3.5g/24h and/or reduction of UP from baseline <50%. Efficacy data from these 3

	participants under protocol V00 low-dose LNP023 (LNP023 10/50 mg b.i.d.) were not included in the study results as the low number of subjects would not have allowed for a meaningful analysis and interpretation of data.
Time Frame	Baseline, Day 169
Analysis Population Description	PD set: PD (pharmacodynamics) analysis set included all participants who received any study drug and experienced no protocol deviations with relevant impact on PD/efficacy data. Participants randomized to the former LNP023 low dose arm (10/50 b.i.d.) were not included in the PD data analysis. Only participants with UP values at both baseline and Day 169 were included in the analysis.

	LNP023 200 mg b.i.d.	**Rituximab**
Arm/Group Description	Combination of the LNP023 25/200 mg b.i.d. and 50/200 mg b.i.d. groups. Under protocol V00, participants took LNP023 25 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks. Under protocol v01, participants took LNP023 50 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks.	Rituximab 1 g i.v. at Day 1 and Day 15
Number of Participants Analyzed [units: participants]	9	9
Number of participants by treatment response at 24 weeks of treatment (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
Day 169 : Complete	0 (%)	0 (%)
Day 169 : Partial	2 (22.22%)	2 (22.22%)
Day 169 : No response	7 (77.78%)	7 (77.78%)

Change from baseline in (eGFR) estimated Glomerular Filtration Rate over time

Description	Changes in renal function were assessed via estimated glomerular filtration rate (eGFR). Change in eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Efficacy data from these 3 participants under protocol V00 low-dose

	LNP023 (LNP023 10/50 mg b.i.d.) were not included in the study results as the low number of subjects would not have allowed for a meaningful analysis and interpretation of data.
Time Frame	Baseline, Day 15, Day 29, Day 57, Day 85, Day 113, Day 141, Day 169
Analysis Population Description	PD set: PD (pharmacodynamics) analysis set included all participants who received any study drug and experienced no protocol deviations with relevant impact on PD/efficacy data. Participants randomized to the former LNP023 low dose arm (10/50 b.i.d.) were not included in the PD data analysis. Only participants with a value at both Baseline and the different time points were included in the analysis.

	LNP023 200 mg b.i.d.	**Rituximab**
Arm/Group Description	Combination of the LNP023 25/200 mg b.i.d. and 50/200 mg b.i.d. groups. Under protocol V00, participants took LNP023 25 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks. Under protocol v01, participants took LNP023 50 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks.	Rituximab 1 g i.v. at Day 1 and Day 15
Number of Participants Analyzed [units: participants]	19	13
Change from baseline in (eGFR) estimated Glomerular Filtration Rate over time (units: mL/min/1.73 m^2)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Day 15	2.3 ± 12.07	0.3 ± 8.33
Day 29	-0.5 ± 8.53	6.1 ± 10.44
Day 57	2.0 ± 11.10	9.2 ± 21.05
Day 85	-1.6 ± 11.53	10.2 ± 16.40
Day 113	1.2 ± 8.64	10.8 ± 15.41
Day 141	-1.8 ± 9.10	7.1 ± 9.29
Day 169	-1.3 ± 7.36	3.1 ± 13.21

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Pharmacokinetic parameter Tmax in plasma

Description	Pharmacokinetics of LNP023 : Tmax is the time to reach maximum (peak) plasma drug concentration after dose administration (time). Actual sampling time points were considered for the calculation of PK parameters.
Time Frame	Day 29 and Day 113 (pre-dose and 0.25 hours, 0.5 hours, 1 hour 2 hours, 4 hours and 6 hours post dose)
Analysis Population Description	PK set: PK (pharmacokinetic) analysis set included all participants with at least one available valid PK concentration measurement, who received any LNP023 and experienced no protocol deviations with relevant impact on PK data. Only participants with PK values at the different time points were included in the analysis.

	LNP023 10 mg b.i.d.	**LNP023 25 mg b.i.d.**	**LNP023 50 mg b.i.d. (4-week administration)**	**LNP023 50 mg b.i.d. (20-week administration)**	**LNP023 200 mg b.i.d.**
Arm/Group Description	Low dose of LNP023 under Protocol V00, LNP023 10mg taken orally b.i.d. during the first 4 weeks of treatment	High dose of LNP023 under Protocol V00, LNP023 25mg taken orally b.i.d. during the first 4 weeks of treatment	Under Protocol V01, LNP023 50mg taken orally b.i.d. during the first 4 weeks of treatment	Under Protocol V00, LNP023 50mg taken orally b.i.d. during the last 20 weeks of treatment	Under protocol V00, participants took LNP023 25 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks. Under protocol v01, participants took LNP023 50 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks.
Number of Participants Analyzed [units: participants]	2	3	10	2	7
Pharmacokinetic parameter Tmax in plasma (units: hours)	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**
Day 29	2.04 (2.00 to 2.08)	2.00 (1.00 to 4.00)	2.03 (1.00 to 4.38)		

Day 113	2.05 (2.00 to 2.10)	1.00 (0.250 to 6.00)

Pharmacokinetic parameter Cmax in plasma

Description	Pharmacokinetics of LNP023: Cmax is the maximum (peak) observed plasma drug concentration after dose administration (mass x volume-1)
Time Frame	Day 29 and Day 113 (pre-dose and 0.25 hours, 0.5 hours, 1 hour 2 hours, 4 hours and 6 hours post dose)
Analysis Population Description	PK set: PK (pharmacokinetic) analysis set included all participants with at least one available valid PK concentration measurement, who received any LNP023 and experienced no protocol deviations with relevant impact on PK data. Only participants with PK values at the different time points were included in the analysis.

	LNP023 10 mg b.i.d.	**LNP023 25 mg b.i.d.**	**LNP023 50 mg b.i.d. (4-week administration)**	**LNP023 50 mg b.i.d. (20-week administration)**	**LNP023 200 mg b.i.d.**
Arm/Group Description	Low dose of LNP023 under Protocol V00, LNP023 10mg taken orally b.i.d. during the first 4 weeks of treatment.	High dose of LNP023 under Protocol V00, LNP023 25mg taken orally b.i.d. during the first 4 weeks of treatment	Under Protocol V01, LNP023 50mg taken orally b.i.d. during the first 4 weeks of treatment	Under Protocol V00, LNP023 50mg taken orally b.i.d. during the last 20 weeks of treatment	Under protocol V00, participants took LNP023 25 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks. Under protocol v01, participants took LNP023 50 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks.
Number of Participants Analyzed [units: participants]	2	3	10	2	7
Pharmacokinetic parameter Cmax in plasma (units: ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**

Day 29	1200 ± 799	2070 ± 938	2140 ± 917		
Day 113				1220 ± 304	4810 ± 2850

Pharmacokinetic parameter AUClast in plasma

Description	Pharmacokinetics of LNP023: AUClast is the AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
Time Frame	Day 29 and Day 113 (pre-dose and 0.25 hours, 0.5 hours, 1 hour 2 hours, 4 hours and 6 hours post dose)
Analysis Population Description	PK set: PK (pharmacokinetic) analysis set included all participants with at least one available valid PK concentration measurement, who received any LNP023 and experienced no protocol deviations with relevant impact on PK data. Only participants with PK values at the different time points were included in the analysis.

	LNP023 10 mg b.i.d.	**LNP023 25 mg b.i.d.**	**LNP023 50 mg b.i.d. (4-week administration)**	**LNP023 50 mg b.i.d. (20-week administration)**	**LNP023 200 mg b.i.d.**
Arm/Group Description	Low dose of LNP023 under Protocol V00, LNP023 10mg taken orally b.i.d. during the first 4 weeks of treatment.	High dose of LNP023 under Protocol V00, LNP023 25mg taken orally b.i.d. during the first 4 weeks of treatment.	Under Protocol V01, LNP023 50mg taken orally b.i.d. during the first 4 weeks of treatment	Under Protocol V00, LNP023 50mg taken orally b.i.d. during the last 20 weeks of treatment	Under protocol V00, participants took LNP023 25 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks. Under protocol v01, participants took LNP023 50 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks.
Number of Participants Analyzed [units: participants]	2	3	10	2	7

Pharmacokinetic parameter AUClast in plasma (units: hr*ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Day 29	5970 ± 4150	8140 ± 3080	9920 ± 3960		
Day 113				5940 ± 989	22200 ± 15600

Pharmacokinetic parameter AUCtau in plasma

Description	Pharmacokinetics of LNP023 : AUCtau is the AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)
Time Frame	Day 29 and Day 113 (pre-dose and 0.25 hours, 0.5 hours, 1 hour 2 hours, 4 hours and 6 hours post dose)
Analysis Population Description	PK set: PK (pharmacokinetic) analysis set included all participants with at least one available valid PK concentration measurement, who received any LNP023 and experienced no protocol deviations with relevant impact on PK data. Only participants with PK values at the different time points were included in the analysis.

	LNP023 10 mg b.i.d.	**LNP023 25 mg b.i.d.**	**LNP023 50 mg b.i.d. (4-week administration)**	**LNP023 50 mg b.i.d. (20-week administration)**	**LNP023 200 mg b.i.d.**
Arm/Group Description	Low dose of LNP023 under Protocol V00, LNP023 10mg taken orally b.i.d. during the first 4 weeks of treatment.	High dose of LNP023 under Protocol V00, LNP023 25mg taken orally b.i.d. during the first 4 weeks of treatment	Under Protocol V01, LNP023 50mg taken orally b.i.d. during the first 4 weeks of treatment	Under Protocol V00, LNP023 50mg taken orally b.i.d. during the last 20 weeks of treatment	Under protocol V00, participants took LNP023 25 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks. Under protocol v01, participants took LNP023 50 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks.

Number of Participants Analyzed [units: participants]	2	3	10	2	7
Pharmacokinetic parameter AUCtau in plasma (units: hr*ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Day 29	9850 ± 5790	12800 ± 3490	16500 ± 5920		
Day 113				10700 ± 1640	36800 ± 26100

Pharmacokinetics in urine: renal plasma clearance derived from 24 hour urine sample

Description	Pharmacokinetics of LNP023 in urine: Renal plasma clearance derived from 24 hour urine sample
Time Frame	Day 113
Analysis Population Description	PK set: PK (pharmacokinetic) analysis set included all participants with at least one available valid PK concentration measurement, who received any LNP023 and experienced no protocol deviations with relevant impact on PK data. Only participants with PK values at Day 113 were included in the analysis.

	LNP023 50 mg b.i.d. (20-week administration)	**LNP023 200 mg b.i.d.**
Arm/Group Description	Under Protocol V00, LNP023 50mg taken orally b.i.d. during the last 20 weeks of treatment	Under protocol V00, participants took LNP023 25 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks. Under protocol v01, participants took LNP023 50 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks.
Number of Participants Analyzed [units: participants]	1	7
Pharmacokinetics in urine: renal plasma clearance derived from 24 hour urine sample (units: L/hr)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Day 113	0.602	1.19 ± 0.668

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

Safety Results

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment plus 29 weeks post treatment, up to maximum duration of 53 weeks.
Additional description	The LNP023 200mg group is the sum of subjects from v00 (25/200mg, n=4) and v01 (50/200mg, n=15). A separation by subgroup was not justified as Part A doses were similar (25 vs 50mg), short-termed (4 weeks) and below levels expected to be efficacious, while the Part B dose of 200 mg was the same for all for up to 20 weeks. Moreover, if separated, the difference in subject numbers may have carried a risk of under- or over-interpretation of findings
Source Vocabulary for Table Default	MedDRA (25.1)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	LNP023 10/50 mg b.i.d. N = 3	LNP023 200 mg b.i.d. (combination of 25/200 mg, 50/200 mg) N = 19	Pooled N = 22	Rituximab 1 g i.v. N = 15	Total N = 37

Arm/Group Description	As per protocol V00, participants took LNP023 10 mg orally b.i.d. for 4 weeks followed by LNP023 50 mg orally b.i.d. for 20 weeks	Combination of the LNP023 25/200 mg b.i.d. and 50/200 mg b.i.d. groups. Under protocol V00, participants took LNP023 25 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks. Under protocol v01, participants took LNP023 50 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks.	Combination of the LNP023 10/50 mg b.i.d., 25/200 mg b.i.d. and 50/200 mg b.i.d. groups.	Rituximab 1 g i.v. at Day 1 and Day 15.	Total
Total Number Affected	0	0	0	0	0
Total Number At Risk	3	19	22	15	37

Serious Adverse Events

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment plus 29 weeks post treatment, up to maximum duration of 53 weeks.
Additional description	The LNP023 200mg group is the sum of subjects from v00 (25/200mg, n=4) and v01 (50/200mg, n=15). A separation by subgroup was not justified as Part A doses were similar (25 vs 50mg), short-termed (4 weeks) and below levels expected to be efficacious, while the Part B dose of 200 mg was the same for all for up to 20 weeks. Moreover, if separated, the difference in subject numbers may have carried a risk of under- or over-interpretation of findings
Source Vocabulary for Table Default	MedDRA (25.1)
Collection Approach for Table Default	Systematic Assessment

	LNP023 10/50 mg b.i.d. N = 3	LNP023 200 mg b.i.d. (combination of 25/200 mg, 50/200 mg) N = 19	Pooled N = 22	Rituximab 1 g i.v. N = 15	Total N = 37
Arm/Group Description	As per protocol V00, participants took LNP023 10 mg orally b.i.d. for 4 weeks followed by LNP023 50 mg orally b.i.d. for 20 weeks	Combination of the LNP023 25/200 mg b.i.d. and 50/200 mg b.i.d. groups. Under protocol V00, participants took LNP023 25 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks. Under protocol v01, participants took LNP023 50 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks.	Combination of the LNP023 10/50 mg b.i.d., 25/200 mg b.i.d. and 50/200 mg b.i.d. groups.	Rituximab 1 g i.v. at Day 1 and Day 15	Total
Total # Affected by any Serious Adverse Event	0	3	3	4	7
Total # at Risk by any Serious Adverse Event	3	19	22	15	37
Infections and infestations					
COVID-19 pneumonia	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Lower respiratory tract infection	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Renal and urinary disorders					

Acute kidney injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (2.70%)
Respiratory, thoracic and mediastinal disorders					
Pulmonary embolism	0 (0.00%)	1 (5.26%)	1 (4.55%)	2 (13.33%)	3 (8.11%)
Skin and subcutaneous tissue disorders					
Erythema	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (2.70%)

Other (Not Including Serious) Adverse Events

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment plus 29 weeks post treatment, up to maximum duration of 53 weeks.
Additional description	The LNP023 200mg group is the sum of subjects from v00 (25/200mg, n=4) and v01 (50/200mg, n=15). A separation by subgroup was not justified as Part A doses were similar (25 vs 50mg), short-termed (4 weeks) and below levels expected to be efficacious, while the Part B dose of 200 mg was the same for all for up to 20 weeks. Moreover, if separated, the difference in subject numbers may have carried a risk of under- or over-interpretation of findings
Source Vocabulary for Table Default	MedDRA (25.1)
Collection Approach for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	LNP023 10/50 mg b.i.d. N = 3	LNP023 200 mg b.i.d. (combination of 25/200 mg, 50/200 mg) N = 19	Pooled N = 22	Rituximab 1 g i.v. N = 15	Total N = 37
Arm/Group Description	As per protocol V00, participants took LNP023 10 mg orally b.i.d. for 4 weeks followed by LNP023 50 mg orally b.i.d. for 20 weeks	Combination of the LNP023 25/200 mg b.i.d. and 50/200 mg b.i.d. groups. Under protocol V00, participants took LNP023 25 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks. Under protocol v01, participants took LNP023 50 mg orally b.i.d. for 4 weeks followed by LNP023 200 mg orally b.i.d. for 20 weeks.	Combination of the LNP023 10/50 mg b.i.d., 25/200 mg b.i.d. and 50/200 mg b.i.d. groups.	Rituximab 1 g i.v. at Day 1 and Day 15	Total
Total # Affected by any Other Adverse Event	2	13	15	7	22
Total # at Risk by any Other Adverse Event	3	19	22	15	37
Blood and lymphatic system disorders					
Lymphopenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (2.70%)
Endocrine disorders					
Hypothyroidism	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Gastrointestinal disorders					
Abdominal pain lower	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)

Diarrhoea	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Dyspepsia	1 (33.33%)	0 (0.00%)	1 (4.55%)	1 (6.67%)	2 (5.41%)
Epigastric discomfort	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Inguinal hernia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (2.70%)
General disorders and administration site conditions					
Chest pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (2.70%)
Fatigue	0 (0.00%)	2 (10.53%)	2 (9.09%)	0 (0.00%)	2 (5.41%)
Influenza like illness	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Oedema	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Oedema peripheral	0 (0.00%)	2 (10.53%)	2 (9.09%)	0 (0.00%)	2 (5.41%)
Pyrexia	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Infections and infestations					
Coronavirus infection	0 (0.00%)	1 (5.26%)	1 (4.55%)	1 (6.67%)	2 (5.41%)
COVID-19	0 (0.00%)	3 (15.79%)	3 (13.64%)	1 (6.67%)	4 (10.81%)
Ear infection	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Influenza	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Lower respiratory tract infection	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Nasopharyngitis	0 (0.00%)	1 (5.26%)	1 (4.55%)	2 (13.33%)	3 (8.11%)
Pneumonia	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Respiratory tract infection viral	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Injury, poisoning and procedural complications					
Fall	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (2.70%)
Head injury	1 (33.33%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Infusion related reaction	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (2.70%)

Limb injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (2.70%)
Post-traumatic pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (2.70%)
Investigations					
Alanine aminotransferase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (2.70%)
Aspartate aminotransferase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (2.70%)
Liver function test increased	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Metabolism and nutrition disorders					
Gout	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (13.33%)	2 (5.41%)
Hypertriglyceridaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (2.70%)
Hyperuricaemia	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Hypokalaemia	0 (0.00%)	2 (10.53%)	2 (9.09%)	1 (6.67%)	3 (8.11%)
Vitamin B12 deficiency	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Musculoskeletal and connective tissue disorders					
Arthralgia	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Back pain	0 (0.00%)	2 (10.53%)	2 (9.09%)	0 (0.00%)	2 (5.41%)
Bone hypertrophy	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Muscle spasms	1 (33.33%)	1 (5.26%)	2 (9.09%)	1 (6.67%)	3 (8.11%)
Nervous system disorders					
Dizziness	0 (0.00%)	2 (10.53%)	2 (9.09%)	0 (0.00%)	2 (5.41%)
Headache	0 (0.00%)	3 (15.79%)	3 (13.64%)	0 (0.00%)	3 (8.11%)
Hypersomnia	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Syncope	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Psychiatric disorders					

Sleep disorder	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Renal and urinary disorders					
Nephrotic syndrome	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (2.70%)
Reproductive system and breast disorders					
Epididymal cyst	1 (33.33%)	0 (0.00%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Respiratory, thoracic and mediastinal disorders					
Dysphonia	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Dyspnoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (2.70%)
Epistaxis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (2.70%)
Skin and subcutaneous tissue disorders					
Pruritus	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (2.70%)
Rash maculo-papular	0 (0.00%)	1 (5.26%)	1 (4.55%)	0 (0.00%)	1 (2.70%)
Vascular disorders					
Hypertension	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (2.70%)

Other Relevant Findings

Not applicable

Conclusion:

In conclusion, the treatment with LNP023 at a dose level of 200 mg b.i.d in subjects with idiopathic membranous nephropathy was well tolerated. Sponsor decided to terminate the study after interim analysis of 12 LNP023 and 14 rituximab subjects because it could already be predicted at that point that the primary goal of superiority of LNP023 vs rituximab in the reduction of UPCR at 24 weeks was not possible to achieve if the study continued to completion.

Date of Clinical Trial Report

29 November 2023