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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Iptacopan

Trial Indication(s)

Paroxysmal nocturnal hemoglobinuria with signs of active hemolysis

Protocol Number

CLNP023X2201

Protocol Title

An open label, single arm, multiple dose study to assess efficacy, safety, pharmacokinetics and pharmacodynamics of LNP023 when administered in addition to Standard of Care (SoC) in patients with paroxysmal nocturnal hemoglobinuria (PNH) with signs of active hemolysis

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: April 09, 2018 (Actual)
Primary Completion Date: April 22, 2020 (Actual)
Study Completion Date: February 28, 2022 (Actual)

Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

This was a Phase 2, open label, single arm, multiple dose study to assess efficacy, safety, pharmacokinetics and pharmacodynamics of iptacopan when administered in addition to Standard of Care (SoC) in patients with paroxysmal nocturnal hemoglobinuria (PNH) with signs of active hemolysis. The study consisted of a screening period of up to 68 days, a baseline visit, and Treatment periods Part 1 and Part 2. The planned duration of Treatment Part 1 was 13 weeks; the planned duration of Treatment Part 2 (treatment extension) was between approximately 2 to 3 years.

In addition to SoC (anti-C5 antibody eculizumab), patients were administered iptacopan as follows: Cohort 1: Orally administered iptacopan 200 mg b.i.d. (Bis In Die -Twice daily) in Part 1 and Part 2. Cohort 2: Orally administered iptacopan 50 mg b.i.d. for a minimum of 2 weeks in addition to SoC; this could be increased to iptacopan 200 mg b.i.d. at study day 15 or at any time later in the study if lactate dehydrogenase (LDH) was not within limit of normal or reduced by at least 60% as compared to baseline values. Adjustment of the SoC dose or regimen is not allowed during the first 6 months of study Part 1. However, for stable patients without signs of active hemolysis who are at least for 6 months in the trial and having received continued concomitant treatment with iptacopan and eculizumab at a dose level of at least 900 mg intravenous (IV) q2w (once every 2 weeks), the dose of eculizumab might be adjusted as per the investigator's discretion.

Centers

3 centers in 3 countries: Germany(1), Italy(1), France(1)

Publication

Citation: Risitano AM, Röth A, Soret J, Frieri C, de Fontbrune FS, Marano L, Alashkar F, Benajiba L, Marotta S, Rozenberg I, Milojevic J, End P, Nidamarthy PK, Junge G, Peffault de Latour R. Addition of iptacopan, an oral factor B inhibitor, to eculizumab in patients with paroxysmal nocturnal haemoglobinuria and active haemolysis: an open-label, single-arm, phase 2, proof-of-concept trial. PMID:33765419

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Pubmed ID: 33765419

Objectives:

Primary objective:
To assess the effect of iptacopan on the reduction of chronic hemolysis in PNH patients when administered in addition to SoC (monoclonal antibody with anti C5 activity)

Secondary objectives:

- To assess the safety and tolerability of iptacopan in patients with PNH when administered in addition to SoC (monoclonal antibody with anti C5 activity)
- To assess the effect of iptacopan on markers of intra and extravascular hemolysis when administered in addition to SoC (monoclonal antibody with anti C5 activity)
- To assess the plasma pharmacokinetic(s) (PK) of iptacopan in PNH patients

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

Oral iptacopan hard gelatin capsule 50 or 200 mg b.i.d

Statistical Methods

Primary endpoint: The primary variable for assessing the effect of iptacopan (in addition to SoC) was LDH level, which was measured over time with Day 92/Week 13 (end of Part 1) considered the primary time point.

Secondary endpoints: The variables for assessing the effect of iptacopan on markers of intra and extravascular hemolysis when administered in addition to SoC were total and free hemoglobin; reticulocytes; C3 fragment deposition;; PNH clone size; haptoglobin; bilirubin; RBC cell count; and freedom from transfusion.

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Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Male and female patients between the age of 18-80 (inclusive) at Baseline with a diagnosis of PNH based on documented clone size of ≥10% by RBCs and/or granulocytes, measured by glycosylphosphatidylinositol (GPI)-deficiency on flow cytometry (screening or medical history data acceptable).
2. For Cohort 1 only: LDH values ≥1.5 × Upper limit of normal (ULN) range for at least 3 pre-SoC dosing measurements taken in relation to 3 different SoC dosing dates over a maximum of 10 weeks prior to Day 1 (Screening, Baseline, or medical history data acceptable). All other Screening pre-SoC LDH values must be >1 × ULN range (for pre-SoC samples collected at the same day as SoC administration).
3. For Cohort 2 only: LDH values ≥1.25 × ULN range for at least 3 pre-SoC dosing measurements taken in relation to 3 different SoC dosing dates over a maximum of
10 weeks prior to Day 1 (Screening, Baseline, or medical history data acceptable). All other Screening pre-SoC LDH values must be >1 × ULN range (for pre-SoC samples
collected at the same day as SoC administration).
4. For Cohort 2 only: Hemoglobin level <10.5 g/dL at Baseline.
5. PNH patients on stable regimen of SoC complement blockade (monoclonal antibody with anti C5 activity) for at least 3 months prior to first treatment with iptacopan.
6. Previous vaccination against N. meningitidis types A, C, Y and W-135 is required at least 4 weeks prior to first dosing with iptacopan. Vaccination against N. meningitidis type B should be conducted if available and acceptable by local regulations, at least 4 weeks prior to first dosing with iptacopan. If iptacopan treatment must start earlier than 4 weeks post vaccination, prophylactic antibiotic treatment must be initiated.
7. Previous vaccination for the prevention of S. pneumoniae and H. influenzae at least 4 weeks prior to first dosing with iptacopan. If iptacopan treatment must start earlier than 4 weeks post vaccination, prophylactic antibiotic treatment must be initiated.

Exclusion Criteria:

1. Known or suspected hereditary complement deficiency at Screening.
2. History of hematopoietic stem cell transplantation as verified both at Screening and at Baseline (unless baseline was skipped).
3. Patients with laboratory evidence of bone marrow failure.
4. A positive Human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C test result at Screening.
5. Presence or suspicion (based on judgment of the Investigator) of active infection within 2 weeks prior to first dose of iptacopan, or history of severe recurrent bacterial infections.
6. History of recurrent meningitis, history of meningococcal infections despite vaccination as verified both at Screening and at Baseline (unless Baseline was skipped).
7. Patients on immunosuppressive agents such as (but not limited to) cyclosporine, mycophenolate mofetil, tacrolimus,

cyclophosphamide, methotrexate less than 8 weeks
prior to first treatment with iptacopan unless on a stable regimen for at least 3 months prior to first iptacopan dose.
8. Systemic corticosteroids administered at the dose of ≥10 mg per day prednisone equivalent within less than 4 weeks prior to first treatment with iptacopan.
9. Severe concurrent co-morbidities; e.g., patients with severe kidney disease (dialysis), advanced cardiac disease (New York Heart disease Association (NYHA) class IV), severe pulmonary arterial hypertension (World Health Organization (WHO) class IV), unstable thrombotic event not amenable to active treatment as judged by
the Investigator both at Screening and at Baseline (unless Baseline was skipped).

Participant Flow Table

Overall Study

	Cohort 1: LNP023 200mg bid + SoC	Cohort 2: LNP023 50mg/200mg bid + SoC	Total
Arm/Group Description	Orally administered iptacopan 200 mg b.i.d. in Part 1 and Part 2 in addition to SoC.	Orally administered iptacopan 50 mg b.i.d. for a minimum of 2 weeks in addition to SoC; this could be increased to iptacopan 200 mg b.i.d. at study day 15 or at any time later in the study if LDH was not within limit of normal or reduced by at least 60% as compared to baseline values.	
Started	10	6	16
Completed	7	6	13
Not Completed	3	0	3
Death	3	0	3

Baseline Characteristics

	Cohort 1: LNP023 200mg bid + SoC	Cohort 2: LNP023 50mg/200mg bid + SoC	Total

Arm/Group Description	Orally administered iptacopan 200 mg b.i.d. in Part 1 and Part 2 in addition to SoC.	Orally administered iptacopan 50 mg b.i.d. for a minimum of 2 weeks in addition to SoC; this could be increased to iptacopan 200 mg b.i.d. at study day 15 or at any time later in the study if LDH was not within limit of normal or reduced by at least 60% as compared to baseline values.	
Number of Participants [units: participants]	10	6	16
Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation			
	44.4±15.57	51.7±9.83	47.1±13.82
Age Categorical (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
<=18 years	0	0	0
Between 18 and 65 years	9	6	15
>=65 years	1	0	1
Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Female	3	3	6
Male	7	3	10
Race/Ethnicity, Customized (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Unknown	0	1	1

White	10	5	15

Summary of Efficacy

Primary Outcome Result(s)

Percent change from baseline in lactate dehydrogenase (LDH) level at Day 92

Description	Serum LDH was used as an intravascular hemolysis marker to assess the effect of iptacopan on the reduction of chronic hemolysis in paroxysmal nocturnal hemoglobinuria (PNH) patients when administered in addition to SoC (monoclonal antibody with anti C5 activity) Baseline is defined as the mean of the last 3 measurements prior to dose administration.
Time Frame	Baseline and Day 92

	Cohort 1: LNP023 200mg bid + SoC	Cohort 2: LNP023 50mg/200mg bid + SoC	Total
Arm/Group Description	Orally administered iptacopan 200 mg b.i.d. in Part 1 and Part 2 in addition to SoC.	Orally administered iptacopan 50 mg b.i.d. for a minimum of 2 weeks in addition to SoC; this could be increased to iptacopan 200 mg b.i.d. at study day 15 or at any time later in the study if LDH was not within limit of normal or reduced by at least 60% as compared to baseline values.	Participants from Cohort 1 and Cohort 2

Number of Participants Analyzed [units: participants]	9	5	14
Percent change from baseline in lactate dehydrogenase (LDH) level at Day 92 (units: Percent change from Baseline)	**Mean (90% Confidence Interval)**	**Mean (90% Confidence Interval)**	**Mean (90% Confidence Interval)**
Day 92	-53.59 (-61.38 to -45.79)	-25.56 (-46.92 to -4.20)	-43.58 (-53.57 to -33.58)

Secondary Outcome Result(s)

Absolute change from baseline in Lactate dehydrogenase (LDH) level

Description: Serum LDH was used as an intravascular hemolysis marker to assess the effect of iptacopan on the reduction of chronic hemolysis in paroxysmal nocturnal hemoglobinuria (PNH) patients when administered in addition to SoC (monoclonal antibody with anti C5 activity) Baseline is defined as the mean of the last 3 measurements prior to dose administration.

Time Frame: Baseline, day 8, 15, 29, 57 and 92

	Cohort 1: LNP023 200mg bid + SoC	**Cohort 2: LNP023 50mg/200mg bid + SoC**	**Total**
Arm/Group Description	Orally administered iptacopan 200 mg b.i.d. in Part 1 and Part 2 in addition to SoC.	Orally administered iptacopan 50 mg b.i.d. for a minimum of 2 weeks in addition to SoC; this could be increased to iptacopan 200 mg b.i.d. at study day 15 or at any time later in the study if LDH was not within limit of normal or reduced by at least 60% as compared to baseline values.	Participants from Cohort 1 and Cohort 2
Number of Participants Analyzed [units: participants]	10	6	16

Absolute change from baseline in Lactate dehydrogenase (LDH) level (units: U/L)	**Mean (90% Confidence Interval)**	**Mean (90% Confidence Interval)**	**Mean (90% Confidence Interval)**
Day 8	-272.57 (-349.07 to -196.07)	-145.22 (-196.30 to -94.15)	-224.81 (-279.88 to -169.74)
Day 15	-353.97 (-486.36 to -221.57)	-175.07 (-247.55 to -102.59)	-294.33 (-388.42 to -200.24)
Day 29	-368.17 (-510.15 to -226.18)	-191.22 (-258.88 to -123.56)	-301.81 (-395.89 to -207.73)
Day 57	-317.07 (-459.11 to -175.03)	-135.89 (-212.28 to -59.50)	-249.13 (-344.24 to -154.01)
Day 92	-330.52 (-488.02 to -173.01)	-109.07 (-196.69 to -21.45)	-251.43 (-361.88 to -140.98)

Absolute change from baseline in hemoglobin

Description: Hemoglobin was used as a marker of intra and extravascular hemolysis when administered in addition to SoC (monoclonal antibody with anti C5 activity) to assess the effect of iptacopan. Baseline is defined as the mean of all pre-dose measurements.

Time Frame: Baseline; day 1, 2, 8, 15, 22, 29, 36, 43, 57, 71, 85, 92, 113, 127, 141, 155, 169, 197, 225, 253, 281, 309, 337, 393, 449, 505, 561, 617, 673, 729, 785, 841, 897, 953, 1009, 1065, 1121, 1177, 1233

	Cohort 1: LNP023 200mg bid + SoC	**Cohort 2: LNP023 50mg/200mg bid + SoC**
Arm/Group Description	Orally administered iptacopan 200 mg b.i.d. in Part 1 and Part 2 in addition to SoC.	Orally administered iptacopan 50 mg b.i.d. for a minimum of 2 weeks in addition to SoC; this could be increased to iptacopan 200 mg b.i.d. at study day 15 or at any time later in the study if LDH was not within limit of normal or reduced by at least 60% as compared to baseline values.
Number of Participants Analyzed [units: participants]	10	6

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Absolute change from baseline in hemoglobin (units: g/L)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Day 1	-4.05 ± 8.750	-6.67 ± 7.218
Day 2	-3.65 ± 7.638	-8.06 ± 6.830
Day 8	12.85 ± 9.228	20.11 ± 13.475
Day 15	20.25 ± 10.122	26.44 ± 10.047
Day 22	24.15 ± 11.898	35.11 ± 11.065
Day 29	28.25 ± 13.131	35.11 ± 10.141
Day 36	29.55 ± 12.166	33.94 ± 10.062
Day 43	26.15 ± 12.571	31.11 ± 7.428
Day 57	27.05 ± 10.855	35.94 ± 10.804
Day 71	24.53 ± 12.259	28.54 ± 8.080
Day 85	28.65 ± 15.722	30.72 ± 15.008
Day 92	31.85 ± 14.543	32.43 ± 14.584
Day 113	30.14 ± 14.831	32.43 ± 11.092
Day 127	33.92 ± 16.882	38.92 ± 13.519
Day 141	28.05 ± 17.088	37.23 ± 15.802
Day 155	28.28 ± 17.370	37.83 ± 12.287
Day 169	27.05 ± 17.253	39.43 ± 11.174
Day 197	28.95 ± 15.429	31.89 ± 16.385
Day 225	28.65 ± 17.258	28.67 ± 7.147
Day 253	26.95 ± 18.015	28.17 ± 12.039
Day 281	29.91 ± 18.351	45.54 ± 16.168
Day 309	27.17 ± 15.152	36.29 ± 9.866
Day 337	26.28 ± 16.733	32.50 ± 10.700
Day 393	28.47 ± 18.801	39.79 ± 12.930

Day 449	31.22 ± 18.573	37.93 ± 10.547
Day 505	24.89 ± 13.435	44.28 ± 18.271
Day 561	29.25 ± 18.665	40.13 ± 11.653
Day 617	32.23 ± 18.335	42.78 ± 17.771
Day 673	38.42 ± 13.407	38.13 ± 15.418
Day 729	31.28 ± 15.366	34.92 ± 11.357
Day 785	11.63 ± 22.691	40.04 ± 26.752
Day 841	24.27 ± 18.109	38.54 ± 23.649
Day 897	31.85 ± 17.303	56.83 ± 20.035
Day 953	23.93 ± 14.964	
Day 1009	23.99 ± 19.396	
Day 1065	29.07 ± 17.334	
Day 1121	27.27 ± 14.536	
Day 1177	32.28 ± 11.180	
Day 1233	33.08 ± 10.196	

Absolute change from baseline in free hemoglobin

Description	Free hemoglobin was used as a marker of intra and extravascular hemolysis when administered in addition to SoC (monoclonal antibody with anti C5 activity) to assess the effect of iptacopan. Baseline is defined as the mean of all pre-dose measurements.
Time Frame	Baseline; day 1, 2, 8, 15, 22, 29, 36, 43, 57, 71, 85, 92, 113, 127, 141, 155, 169, 197, 225, 253, 281, 309, 337, 393, 449, 505, 561, 617, 673, 729, 785, 841, 897, 953, 1009, 1065, 1121, 1177, 1233

	Cohort 1: LNP023 200mg bid + SoC	**Cohort 2: LNP023 50mg/200mg bid + SoC**

Arm/Group Description	Orally administered iptacopan 200 mg b.i.d. in Part 1 and Part 2 in addition to SoC.	Orally administered iptacopan 50 mg b.i.d. for a minimum of 2 weeks in addition to SoC; this could be increased to iptacopan 200 mg b.i.d. at study day 15 or at any time later in the study if LDH was not within limit of normal or reduced by at least 60% as compared to baseline values.
Number of Participants Analyzed [units: participants]	10	6
Absolute change from baseline in free hemoglobin (units: mg/dL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Day 1	15.26 ± 36.879	9.16 ± 15.310
Day 2	-26.73 ± 40.706	-3.94 ± 6.785
Day 8	-24.03 ± 43.102	-2.04 ± 6.725
Day 15	-23.16 ± 41.190	14.21 ± 43.762
Day 22	-22.90 ± 39.726	-0.66 ± 6.960
Day 29	-20.03 ± 42.349	-1.21 ± 8.108
Day 36	-12.42 ± 47.495	-2.56 ± 6.914
Day 43	-13.63 ± 24.961	-0.54 ± 6.546
Day 57	1.71 ± 14.138	-1.84 ± 6.662
Day 71	-17.92 ± 34.378	0.18 ± 1.466
Day 85	-16.80 ± 47.407	1.90 ± 2.338
Day 92	-25.12 ± 42.237	-3.31 ± 6.295
Day 113	-24.00 ± 41.084	16.09 ± 42.454
Day 127	-18.07 ± 52.791	1.42 ± 2.945
Day 141	-24.03 ± 40.625	-1.52 ± 8.137
Day 155	-20.58 ± 43.690	-2.43 ± 8.741
Day 169	-1.00 ± 91.222	10.24 ± 19.275
Day 197	14.93 ± 105.958	3.19 ± 5.185

Day 225	10.64 ± 101.866	15.89 ± 32.159
Day 253	-21.97 ± 40.320	34.84 ± 61.838
Day 281	-24.19 ± 39.910	-1.36 ± 7.326
Day 309	-21.57 ± 42.638	-2.26 ± 9.656
Day 337	-20.69 ± 42.592	31.39 ± 55.947
Day 393	-17.29 ± 42.263	-2.11 ± 8.297
Day 449	-28.60 ± 44.210	-3.93 ± 7.781
Day 505	-33.24 ± 41.787	-1.69 ± 6.335
Day 561	-34.25 ± 43.692	1.59 ± 2.372
Day 617	-34.68 ± 44.127	-0.22 ± 6.960
Day 673	-37.43 ± 54.005	2.39 ± 15.832
Day 729	-28.88 ± 38.550	-3.99 ± 7.294
Day 785	-2.55 ± 4.388	-0.67 ± 3.206
Day 841	-33.12 ± 43.462	1.60 ± 4.485
Day 897	-12.98 ± 22.233	4.77 ± 5.468
Day 953	-34.41 ± 46.196	
Day 1009	8.39 ± 135.082	
Day 1065	-34.10 ± 44.867	
Day 1121	-33.45 ± 43.628	
Day 1177	-16.30 ± 23.441	
Day 1233	-12.27 ± 20.734	

Absolute change from baseline in reticulocytes count

Description Reticulocytes count was used as a marker of intra and extravascular hemolysis when administered in addition to SoC (monoclonal antibody with anti C5 activity) to assess the effect of iptacopan. Baseline is defined as the mean of all pre-dose measurements.

Time Frame Baseline; day 1, 2, 8, 15, 22, 29, 36, 43, 57, 71, 85, 92, 113, 127, 141, 155, 169, 197, 225, 253, 281, 309, 337, 393, 449, 505, 561, 617, 673, 729, 785, 841, 897, 953, 1009, 1065, 1121, 1177, 1233

	Cohort 1: LNP023 200mg bid + SoC	**Cohort 2: LNP023 50mg/200mg bid + SoC**
Arm/Group Description	Orally administered iptacopan 200 mg b.i.d. in Part 1 and Part 2 in addition to SoC.	Orally administered iptacopan 50 mg b.i.d. for a minimum of 2 weeks in addition to SoC; this could be increased to iptacopan 200 mg b.i.d. at study day 15 or at any time later in the study if LDH was not within limit of normal or reduced by at least 60% as compared to baseline values.
Number of Participants Analyzed [units: participants]	10	6
Absolute change from baseline in reticulocytes count (units: 10^9/L)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Day 1	4.44 ± 33.269	1.62 ± 22.790
Day 2	8.61 ± 52.306	4.39 ± 31.658
Day 8	-96.94 ± 69.179	-104.55 ± 88.085
Day 15	-130.15 ± 80.335	-130.40 ± 107.295
Day 22	-139.26 ± 78.206	-147.70 ± 99.438
Day 29	-132.28 ± 76.822	-169.68 ± 129.743
Day 36	-130.73 ± 72.017	-167.51 ± 137.214
Day 43	-129.02 ± 64.301	-160.05 ± 132.859
Day 57	-117.69 ± 65.394	-149.53 ± 116.803
Day 71	-106.83 ± 62.973	-146.87 ± 129.217
Day 85	-113.96 ± 65.278	-167.16 ± 156.013
Day 92	-110.54 ± 62.638	-150.02 ± 105.893
Day 113	-96.78 ± 66.366	-147.06 ± 129.118

Day 127	-107.84 ± 57.904	-149.92 ± 115.401
Day 141	-115.17 ± 70.942	-108.39 ± 54.412
Day 155	-99.90 ± 62.273	-98.67 ± 65.700
Day 169	-109.39 ± 63.159	-84.57 ± 64.082
Day 197	-98.87 ± 85.280	-152.09 ± 137.856
Day 225	-104.11 ± 72.206	-143.68 ± 149.716
Day 253	-104.30 ± 64.401	-139.05 ± 127.212
Day 281	-111.11 ± 60.896	-121.06 ± 66.564
Day 309	-116.88 ± 51.145	-114.06 ± 77.982
Day 337	-113.31 ± 61.144	-170.89 ± 142.577
Day 393	-58.54 ± 152.003	-183.20 ± 122.298
Day 449	-89.44 ± 77.782	-152.66 ± 124.244
Day 505	-100.68 ± 64.132	-135.80 ± 117.488
Day 561	-101.63 ± 67.525	-163.34 ± 121.860
Day 617	-101.73 ± 54.916	-132.40 ± 122.940
Day 673	-137.05 ± 63.373	-150.14 ± 130.898
Day 729	-101.16 ± 63.442	-179.15 ± 131.007
Day 785	-56.22 ± 26.739	-134.60 ± 141.947
Day 841	-103.96 ± 60.469	-145.80 ± 140.363
Day 897	-111.41 ± 58.641	-81.27 ± 36.298
Day 953	-91.00 ± 52.203	
Day 1009	-110.33 ± 61.354	
Day 1065	-127.35 ± 61.501	
Day 1121	-115.96 ± 55.981	
Day 1177	-140.14 ± 73.898	

Day 1233	-123.40 ± 70.558

Absolute change from baseline in C3 fragment deposition on PNH RBC

Description	C3 fragment deposition on PNH Red blood cell (RBC) was used as a marker of intra and extravascular hemolysis when administered in addition to SoC (monoclonal antibody with anti C5 activity) to assess the effect of iptacopan. Baseline is defined as Day 1 pre-dose measurement.
Time Frame	Day 1 pre dose, day 8, 22, 29, 57, 92, 113, 141, 169, 253, 337, 505, 673, 785, 953, 1121, 1233

	Cohort 1: LNP023 200mg bid + SoC	**Cohort 2: LNP023 50mg/200mg bid + SoC**
Arm/Group Description	Orally administered iptacopan 200 mg b.i.d. in Part 1 and Part 2 in addition to SoC.	Orally administered iptacopan 50 mg b.i.d. for a minimum of 2 weeks in addition to SoC; this could be increased to iptacopan 200 mg b.i.d. at study day 15 or at any time later in the study if LDH was not within limit of normal or reduced by at least 60% as compared to baseline values.
Number of Participants Analyzed [units: participants]	10	5
Absolute change from baseline in C3 fragment deposition on PNH RBC (units: % C3 fragment deposition on PNH RBC)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Day 8	-5.59 ± 6.541	-1.24 ± 4.510
Day 22	-8.02 ± 8.198	-2.35 ± 5.620
Day 29	-11.64 ± 7.990	-4.36 ± 2.662
Day 57	-8.90 ± 5.778	-5.35 ± 2.357
Day 92	-8.70 ± 6.310	-6.21 ± 0.866
Day 113	-13.65 ± 9.927	-5.10 ± 2.478
Day 141	-13.18 ± 11.489	-6.19 ± 4.818
Day 169	-11.06 ± 5.874	-4.66 ± 3.175

Day 253	-10.08 ± 6.259	-4.36 ± 1.538
Day 337	-11.21 ± 6.118	-4.08 ± 3.340
Day 505	-16.04 ± 2.732	-6.76 ± 2.650
Day 673	-15.19 ± 2.805	
Day 785	-1.00	
Day 953	-15.28 ± 3.528	
Day 1121	-0.94	
Day 1233	-12.74	

Mean PNH clone size

Description: Mean PNH clone size on Red Blood Cells (RBC) was used as a marker of intra and extravascular hemolysis when administered in addition to SoC (monoclonal antibody with anti C5 activity) to assess the effect of iptacopan. Baseline is defined as the mean of all pre-dose measurements.

Time Frame: Day 1 pre dose, day 8, 22, 29, 57, 92, 113, 141, 169, 253, 337, 505, 673, 785, 953, 1121, 1233

	Cohort 1: LNP023 200mg bid + SoC	**Cohort 2: LNP023 50mg/200mg bid + SoC**
Arm/Group Description	Orally administered iptacopan 200 mg b.i.d. in Part 1 and Part 2 in addition to SoC.	Orally administered iptacopan 50 mg b.i.d. for a minimum of 2 weeks in addition to SoC; this could be increased to iptacopan 200 mg b.i.d. at study day 15 or at any time later in the study if LDH was not within limit of normal or reduced by at least 60% as compared to baseline values.
Number of Participants Analyzed [units: participants]	10	6
Mean PNH clone size (units: PNH Red Blood Cells)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Day 1 pre dose	54.75 ± 32.536	46.10 ± 31.436

Day 8	66.32 ± 29.570	64.45 ± 27.711
Day 22	75.23 ± 23.458	79.37 ± 20.270
Day 29	75.34 ± 20.837	78.87 ± 17.642
Day 57	85.87 ± 15.660	86.45 ± 12.576
Day 92	89.20 ± 16.861	85.38 ± 12.939
Day 113	89.28 ± 18.936	86.02 ± 9.626
Day 141	93.91 ± 6.105	80.25 ± 6.638
Day 169	87.60 ± 19.644	83.69 ± 11.187
Day 253	90.30 ± 18.176	82.28 ± 12.649
Day 337	88.69 ± 20.381	91.68 ± 11.905
Day 505	98.33 ± 1.738	88.45 ± 10.419
Day 673	97.45 ± 2.370	92.48 ± 6.626
Day 785	83.61 ± 9.327	
Day 953	96.08 ± 3.825	
Day 1121	93.74 ± 7.410	
Day 1233	69.83 ± 43.045	

Mean Haptoglobin levels

Description	Haptoglobin level was used as a marker of intra and extravascular hemolysis when administered in addition to SoC (monoclonal antibody with anti C5 activity) to assess the effect of iptacopan. Baseline is defined as the mean of all pre-dose measurements.
Time Frame	Day 2, 8, 15, 22, 29, 36, 43, 57, 71, 85, 92, 113, 127, 141, 155, 169, 197, 225, 253, 281, 309, 337, 393, 449, 505, 561, 617, 673, 729, 785, 841, 897, 953, 1009, 1065, 1121, 1177, 1233

	Cohort 1: LNP023 200mg bid + SoC	**Cohort 2: LNP023 50mg/200mg bid + SoC**

Arm/Group Description	Orally administered iptacopan 200 mg b.i.d. in Part 1 and Part 2 in addition to SoC.	Orally administered iptacopan 50 mg b.i.d. for a minimum of 2 weeks in addition to SoC; this could be increased to iptacopan 200 mg b.i.d. at study day 15 or at any time later in the study if LDH was not within limit of normal or reduced by at least 60% as compared to baseline values.
Number of Participants Analyzed [units: participants]	9	4
Mean Haptoglobin levels (units: g/L)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Day 2	0.55 ± 0.071	0.30 ± 0.141
Day 8	0.70 ± 0.548	0.77 ± 0.306
Day 15	0.93 ± 0.960	0.60 ± 0.141
Day 22	1.18 ± 1.387	0.70 ± 0.483
Day 29	0.94 ± 0.896	0.83 ± 0.586
Day 36	1.08 ± 0.779	0.97 ± 0.503
Day 43	1.26 ± 1.401	0.70 ± 0.520
Day 57	0.63 ± 0.416	1.20
Day 71	0.75 ± 0.473	0.80
Day 85	0.87 ± 0.611	
Day 92	0.95 ± 0.495	0.80
Day 113	0.63 ± 0.493	0.50
Day 127	0.47 ± 0.208	
Day 141	0.57 ± 0.306	0.70
Day 155	0.50	0.80
Day 169	0.63 ± 0.577	0.50
Day 197	0.80 ± 0.700	

Day 225	0.65 ± 0.705	
Day 253	0.63 ± 0.519	
Day 281	0.50 ± 0.283	0.30
Day 309	0.75 ± 0.071	0.50
Day 337	0.40	
Day 393	0.60 ± 0.283	
Day 449	0.20	0.60
Day 505	0.60 ± 0.141	0.60
Day 561	0.60	0.70
Day 617	0.30 ± 0.141	1.90 ± 1.838
Day 673	0.30	0.70
Day 729	0.35 ± 0.071	0.50
Day 785	1.00	1.25 ± 0.919
Day 841	0.47 ± 0.153	0.85 ± 0.212
Day 897	0.33 ± 0.058	
Day 953	0.50 ± 0.141	
Day 1009	0.45 ± 0.071	
Day 1065	2.05 ± 1.768	
Day 1121	1.00 ± 0.935	
Day 1177	0.40 ± 0.000	
Day 1233	0.95 ± 0.636	

Absolute change from baseline in total bilirubin

Description: Bilirubin was used as a marker of intra and extravascular hemolysis when administered in addition to SoC (monoclonal antibody with anti C5 activity) to assess the effect of iptacopan. Baseline is defined as the mean of all pre-dose measurements.

Time Frame: Baseline; day 1, 2, 8, 15, 22, 29, 36, 43, 57, 71, 85, 92, 113, 127, 141, 155, 169, 197, 225, 253, 281, 309, 337, 393, 449, 505, 561, 617, 673, 729, 785, 841, 897, 953, 1009, 1065, 1121, 1177, 1233

	Cohort 1: LNP023 200mg bid + SoC	**Cohort 2: LNP023 50mg/200mg bid + SoC**
Arm/Group Description	Orally administered iptacopan 200 mg b.i.d. in Part 1 and Part 2 in addition to SoC.	Orally administered iptacopan 50 mg b.i.d. for a minimum of 2 weeks in addition to SoC; this could be increased to iptacopan 200 mg b.i.d. at study day 15 or at any time later in the study if LDH was not within limit of normal or reduced by at least 60% as compared to baseline values.
Number of Participants Analyzed [units: participants]	10	6
Absolute change from baseline in total bilirubin (units: umol/L)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Day 1	2.94 ± 13.038	1.36 ± 4.978
Day 2	-21.06 ± 15.647	-25.47 ± 21.598
Day 8	-23.66 ± 16.081	-25.97 ± 24.380
Day 15	-23.86 ± 16.538	-26.97 ± 24.043
Day 22	-25.36 ± 15.403	-25.14 ± 23.541
Day 29	-24.66 ± 15.026	-26.14 ± 22.345
Day 36	-23.96 ± 15.945	-25.31 ± 27.658
Day 43	-24.66 ± 14.552	-25.14 ± 23.727
Day 57	-24.16 ± 13.946	-22.81 ± 21.233
Day 71	-23.16 ± 15.154	-27.92 ± 24.924

Day 85	-23.66 ± 14.595	-28.42 ± 26.075
Day 92	-21.66 ± 13.985	-27.87 ± 25.234
Day 113	-21.06 ± 15.026	-26.87 ± 23.200
Day 127	-22.18 ± 13.357	-27.79 ± 26.965
Day 141	-22.46 ± 14.404	-18.23 ± 9.473
Day 155	-19.73 ± 12.376	-16.23 ± 9.565
Day 169	-21.66 ± 13.383	-14.83 ± 10.281
Day 197	-24.21 ± 13.678	-23.71 ± 28.849
Day 225	-23.06 ± 12.410	-30.06 ± 36.183
Day 253	-21.36 ± 12.192	-24.21 ± 30.342
Day 281	-23.46 ± 12.150	-16.54 ± 8.694
Day 309	-22.86 ± 12.078	-11.21 ± 10.635
Day 337	-22.76 ± 13.248	-28.71 ± 29.338
Day 393	-19.73 ± 15.644	-28.00 ± 27.769
Day 449	-24.64 ± 13.021	-23.50 ± 25.603
Day 505	-27.30 ± 12.450	-25.81 ± 24.978
Day 561	-21.98 ± 14.718	-21.10 ± 30.888
Day 617	-28.85 ± 11.516	-23.47 ± 21.451
Day 673	-27.58 ± 13.453	-24.50 ± 25.562
Day 729	-23.64 ± 12.971	-32.13 ± 28.799
Day 785	-11.54 ± 5.370	-26.67 ± 33.656
Day 841	-20.49 ± 12.006	-29.42 ± 32.316
Day 897	-24.49 ± 13.627	-16.00 ± 7.542
Day 953	-23.92 ± 14.707	
Day 1009	-23.92 ± 14.204	

Day 1065	-25.65 ± 13.844
Day 1121	-23.35 ± 14.363
Day 1177	-29.78 ± 11.559
Day 1233	-28.78 ± 12.328

Number of participants with on study transfusions from packed RBC units

Description Number of participants with on study transfusions from packed RBC units was collected.

Time Frame Up to 46 months

	Cohort 1: LNP023 200mg bid + SoC	Cohort 2: LNP023 50mg/200mg bid + SoC
Arm/Group Description	Orally administered iptacopan 200 mg b.i.d. in Part 1 and Part 2 in addition to SoC.	Orally administered iptacopan 50 mg b.i.d. for a minimum of 2 weeks in addition to SoC; this could be increased to iptacopan 200 mg b.i.d. at study day 15 or at any time later in the study if LDH was not within limit of normal or reduced by at least 60% as compared to baseline values.
Number of Participants Analyzed [units: participants]	10	6
Number of participants with on study transfusions from packed RBC units (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	2 (20%)	2 (33.33%)

Pharmacokinetics profile: Maximum plasma concentration (Cmax)

Description Cmax is the maximum (peak) observed plasma drug concentration after single dose administration (mass x volume-1). PK assessment parameters were determined using the actual recorded sampling times and non-compartmental methods. In Cohort 2, patients were supposed to be orally administered iptacopan 50 mg b.i.d. in addition to SoC; this was increased to iptacopan 200 mg b.i.d. at study day 15 or

at any time later in the study if LDH was not within limit of normal or reduced by at least 60% as compared to baseline values. One patient in Cohort 2 was orally administered iptacopan 25 mg at day 1 due to a dosing error.

Time Frame Day 1, 29, 169, 337

	Cohort 1: LNP023 200mg bid + SoC	Cohort 2: LNP023 25mg bid + SoC	Cohort 2: LNP023 50mg bid + SoC	Cohort 2: LNP023 200mg bid + SoC
Arm/Group Description	Orally administered iptacopan 200 mg b.i.d. in Part 1 and Part 2 in addition to SoC.	Orally administered iptacopan 25 mg b.i.d. at the respective visit due to dosing error	Orally administered iptacopan 50 mg b.i.d. at the respective visit	Orally administered iptacopan 200 mg b.i.d. at the respective visit
Number of Participants Analyzed [units: participants]	10	1	6	3
Pharmacokinetics profile: Maximum plasma concentration (Cmax) (units: ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Day 1	3400 ± 1060	1610	1570 ± 366	
Day 29	3500 ± 1340		1770 ± 469	
Day 169	3530 ± 853		1180	3130 ± 824
Day 337	4030 ± 1140		2470	4370 ± 1790

Pharmacokinetics profile: Area Under the Curve (AUC) tau

Description The AUCtau is the area under the plasma concentration-time curve calculated to the end of a dosing interval (tau) at steady-state. PK assessment parameters were determined using the actual recorded sampling times and non-compartmental methods. In Cohort 2, patients were supposed to be orally administered iptacopan 50 mg b.i.d. in addition to SoC; this was increased to iptacopan 200 mg b.i.d. at study day 15 or at any time later in the study if LDH was not within limit of normal or reduced by at least 60% as compared to baseline values. One patient in Cohort 2 was orally administered iptacopan 25 mg at day 1 due to a dosing error.

Time Frame day 1, 29, 169, 337

	Cohort 1: LNP023 200mg bid + SoC	Cohort 2: LNP023 25mg bid + SoC	Cohort 2: LNP023 50mg bid + SoC	Cohort 2: LNP023 200mg bid + SoC
Arm/Group Description	Orally administered iptacopan 200 mg b.i.d. in Part 1 and Part 2 in addition to SoC.	Orally administered iptacopan 25 mg b.i.d. at the respective visit due to dosing error	Orally administered iptacopan 50 mg b.i.d. at the respective visit	Orally administered iptacopan 200 mg b.i.d. at the respective visit
Number of Participants Analyzed [units: participants]	10	1	6	3
Pharmacokinetics profile: Area Under the Curve (AUC) tau (units: h*ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Day 1	18200 ± 6700	9470	8620 ± 1310	
Day 29	24400 ± 8720		14800 ± 4100	
Day 169	25600 ± 7570		10700	23900 ± 5920
Day 337	26900 ± 7640		16900	37800 ± 15500

Pharmacokinetics profile: Time to reach maximum plasma concentration (Tmax)

Description: Tmax is the time to reach maximum (peak) plasma drug concentration after single dose administration (time). PK assessment parameters were determined using the actual recorded sampling times and non-compartmental methods. In Cohort 2, patients were supposed to be orally administered iptacopan 50 mg b.i.d. in addition to SoC; this was increased to iptacopan 200 mg b.i.d. at study day 15 or at any time later in the study if LDH was not within limit of normal or reduced by at least 60% as compared to baseline values. One patient in Cohort 2 was orally administered iptacopan 25 mg at day 1 due to a dosing error.

Time Frame: Day 1, 29, 169, 337

	Cohort 1: LNP023 200mg bid + SoC	Cohort 2: LNP023 25mg bid + SoC	Cohort 2: LNP023 50mg bid + SoC	Cohort 2: LNP023 200mg bid + SoC
Arm/Group Description	Orally administered iptacopan 200 mg b.i.d. in Part 1 and Part 2 in addition to SoC.	Orally administered iptacopan 25 mg b.i.d. at the respective visit due to dosing error	Orally administered iptacopan 50 mg b.i.d. at the respective visit	Orally administered iptacopan 200 mg b.i.d. at the respective visit

Number of Participants Analyzed [units: participants]	10	1	6	3
Pharmacokinetics profile: Time to reach maximum plasma concentration (Tmax) (units: hours)	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**
Day 1	1.50 (1.00 to 6.00)	2.00 (2.00 to 2.00)	2.00 (2.00 to 2.00)	
Day 29	2.00 (1.00 to 2.00)		2.04 (2.00 to 4.00)	
Day 169	2.00 (1.00 to 4.00)		4.00 (4.00 to 4.00)	2.00 (1.83 to 2.00)
Day 337	2.00 (1.00 to 2.00)		2.03 (2.03 to 2.03)	2.00 (1.05 to 5.00)

Red Blood Cell Count: Mean erythrocytes levels

Description	Erythrocytes levels were used as a marker of intra and extravascular hemolysis when administered in addition to SoC (monoclonal antibody with anti C5 activity) to assess the effect of iptacopan.
Time Frame	Screening, Baseline, Day 2,8,15,22,29,36,43,57,71,85,92,113,127,141,155,169,197,225,253,281,309,337,393,449,505,561,617,673,729,729,785,841,897,953,1009,1065,1121,1177,1233

	Cohort 1: LNP023 200mg bid + SoC	**Cohort 2: LNP023 50mg/200mg bid + SoC**
Arm/Group Description	Orally administered iptacopan 200 mg b.i.d. in Part 1 and Part 2 in addition to SoC.	Orally administered iptacopan 50 mg b.i.d. for a minimum of 2 weeks in addition to SoC; this could be increased to iptacopan 200 mg b.i.d. at study day 15 or at any time later in the study if LDH was not within limit of normal or reduced by at least 60% as compared to baseline values.
Number of Participants Analyzed [units: participants]	10	6

Red Blood Cell Count: Mean erythrocytes levels (units: 10^12/L)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Screening	3.12 ± 0.887	2.42 ± 0.427
Baseline	2.73 ± 0.466	2.40 ± 0.442
Day 1	2.67 ± 0.615	2.16 ± 0.498
Day 2	2.70 ± 0.485	2.17 ± 0.520
Day 8	3.17 ± 0.585	3.00 ± 0.812
Day 15	3.43 ± 0.723	3.23 ± 0.794
Day 22	3.58 ± 0.835	3.57 ± 0.900
Day 29	3.72 ± 0.857	3.62 ± 0.870
Day 36	3.75 ± 0.753	3.62 ± 0.804
Day 43	3.67 ± 0.807	3.55 ± 0.758
Day 57	3.69 ± 0.852	3.72 ± 0.574
Day 71	3.50 ± 0.787	3.48 ± 0.591
Day 85	3.65 ± 0.841	3.60 ± 0.520
Day 92	3.76 ± 0.828	3.56 ± 0.483
Day 113	3.58 ± 0.807	3.58 ± 0.444
Day 127	3.69 ± 0.822	3.75 ± 0.265
Day 141	3.64 ± 0.799	3.44 ± 0.493
Day 155	3.53 ± 0.815	3.52 ± 0.432
Day 169	3.62 ± 0.826	3.54 ± 0.378
Day 197	3.68 ± 0.774	3.77 ± 0.577
Day 225	3.70 ± 0.894	3.43 ± 0.513
Day 253	3.62 ± 0.930	3.45 ± 0.412
Day 281	3.81 ± 0.875	3.73 ± 0.403
Day 309	3.50 ± 0.728	3.58 ± 0.427

Day 337	3.50 ± 0.714	3.75 ± 0.580
Day 393	3.63 ± 0.876	4.00 ± 0.356
Day 449	3.80 ± 0.920	3.94 ± 0.378
Day 505	3.63 ± 1.053	3.92 ± 0.360
Day 561	3.47 ± 0.937	3.92 ± 0.370
Day 617	3.80 ± 1.149	3.85 ± 0.389
Day 673	3.74 ± 0.716	3.86 ± 0.270
Day 729	3.74 ± 1.021	3.93 ± 0.150
Day 785	2.83 ± 0.618	3.78 ± 0.263
Day 841	3.64 ± 1.081	3.80 ± 0.294
Day 897	3.89 ± 1.123	3.95 ± 0.071
Day 953	3.62 ± 1.196	
Day 1009	3.61 ± 1.316	
Day 1065	3.87 ± 1.073	
Day 1121	3.69 ± 1.006	
Day 1177	4.06 ± 0.829	
Day 1233	4.14 ± 0.844	

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

Summary of Safety

Safety Results

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment plus 14 days post treatment, up to a maximum duration of 187 weeks. Serious adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 189 weeks.
Source Vocabulary for Table Default	MedDRA (24.1)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	Cohort 1: LNP023 200mg bid + SoC N = 10	**Cohort 2: LNP023 50mg bid + SoC N = 6**	**Cohort 2: LNP023 200mg bid + SoC N = 5**	**Total N = 16**
Arm/Group Description	Orally administered iptacopan 200 mg b.i.d. in Part 1 and Part 2 in addition to SoC.	Orally administered iptacopan 50 mg b.i.d. in Part 1 and iptacopan 50 mg b.i.d. or 200 mg b.i.d. in Part 2 in addition to SoC. This arm summarizes all events that started when treated with iptacopan 50 mg b.i.d. in Cophort 2	Orally administered iptacopan 50 mg b.i.d. in Part 1 and iptacopan 50 mg b.i.d. or 200 mg b.i.d. in Part 2 in addition to SoC. This arm summarizes all events that started when treated with iptacopan 200 mg b.i.d. in Cohort 2. Total number at risk only	Total

			includes patients who received LNP023 200mg bid.	
Total Number Affected	3	0	0	3
Total Number At Risk	10	6	5	16

Serious Adverse Events

	Cohort 1: LNP023 200mg bid + SoC N = 10	**Cohort 2: LNP023 50mg bid + SoC N = 6**	**Cohort 2: LNP023 200mg bid + SoC N = 5**	**Total N = 16**
Arm/Group Description	Orally administered iptacopan 200 mg b.i.d. in Part 1 and Part 2 in addition to SoC.	Orally administered iptacopan 50 mg b.i.d. in Part 1 and iptacopan 50 mg b.i.d. or 200 mg b.i.d. in Part 2 in addition to SoC. This arm summarizes all events that started when treated with iptacopan 50 mg b.i.d. in Cophort 2	Orally administered iptacopan 50 mg b.i.d. in Part 1 and iptacopan 50 mg b.i.d. or 200 mg b.i.d. in Part 2 in addition to SoC. This arm summarizes all events that started when treated with iptacopan 200 mg b.i.d. in Cohort 2. Total number at risk only includes patients who received LNP023 200mg bid.	Total
Total # Affected by any Serious Adverse Event	4	0	2	6
Total # at Risk by any Serious Adverse Event	10	6	5	16
Infections and infestations				
Escherichia bacteraemia	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Urinary tract infection	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (6.25%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Basal cell carcinoma	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Bladder transitional cell carcinoma	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (6.25%)
Lymphoproliferative disorder	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Squamous cell carcinoma of the oral cavity	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Squamous cell carcinoma of the tongue	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Nervous system disorders				
Haemorrhage intracranial	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Renal and urinary disorders				
Urinary bladder polyp	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (6.25%)
Vascular disorders				
Penetrating aortic ulcer	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)

Other (Not Including Serious) Adverse Events

	Cohort 1: LNP023 200mg bid + SoC N = 10	**Cohort 2: LNP023 50mg bid + SoC N = 6**	**Cohort 2: LNP023 200mg bid + SoC N = 5**	**Total N = 16**
Arm/Group Description	Orally administered iptacopan 200 mg b.i.d. in Part 1 and Part 2 in addition to SoC.	Orally administered iptacopan 50 mg b.i.d. in Part 1 and iptacopan 50 mg b.i.d. or 200 mg b.i.d.	Orally administered iptacopan 50 mg b.i.d. in Part 1 and iptacopan 50 mg b.i.d. or 200 mg b.i.d.	Total

		in Part 2 in addition to SoC. This arm summarizes all events that started when treated with iptacopan 50 mg b.i.d. in Cophort 2	in Part 2 in addition to SoC. This arm summarizes all events that started when treated with iptacopan 200 mg b.i.d. in Cohort 2. Total number at risk only includes patients who received LNP023 200mg bid.	
Total # Affected by any Other Adverse Event	10	4	5	16
Total # at Risk by any Other Adverse Event	10	6	5	16
Blood and lymphatic system disorders				
Anaemia	2 (20.00%)	0 (0.00%)	1 (20.00%)	3 (18.75%)
Thrombocytopenia	2 (20.00%)	0 (0.00%)	1 (20.00%)	3 (18.75%)
Cardiac disorders				
Palpitations	0 (0.00%)	1 (16.67%)	1 (20.00%)	1 (6.25%)
Ear and labyrinth disorders				
Vertigo	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (6.25%)
Endocrine disorders				
Hyperthyroidism	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (6.25%)
Gastrointestinal disorders				
Abdominal pain	1 (10.00%)	1 (16.67%)	0 (0.00%)	2 (12.50%)
Abdominal pain upper	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Aphthous ulcer	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Constipation	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (6.25%)

Diarrhoea	2 (20.00%)	0 (0.00%)	0 (0.00%)	2 (12.50%)
Dysphagia	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Nausea	1 (10.00%)	1 (16.67%)	0 (0.00%)	2 (12.50%)
Tongue ulceration	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Vomiting	1 (10.00%)	1 (16.67%)	0 (0.00%)	2 (12.50%)
General disorders and administration site conditions				
Asthenia	2 (20.00%)	2 (33.33%)	0 (0.00%)	4 (25.00%)
Chest pain	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Medical device site irritation	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Medical device site pain	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Non-cardiac chest pain	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Oedema peripheral	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Pyrexia	3 (30.00%)	1 (16.67%)	1 (20.00%)	5 (31.25%)
Hepatobiliary disorders				
Hepatic cytolysis	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Ocular icterus	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Infections and infestations				
Bronchitis	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (6.25%)
COVID-19	1 (10.00%)	1 (16.67%)	0 (0.00%)	2 (12.50%)
Ear infection	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Fungal skin infection	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Herpes zoster	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Influenza	1 (10.00%)	1 (16.67%)	0 (0.00%)	2 (12.50%)
Nasopharyngitis	2 (20.00%)	0 (0.00%)	0 (0.00%)	2 (12.50%)

Oral herpes	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Periodontitis	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Pharyngitis	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (6.25%)
Pyelonephritis	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Rhinitis	2 (20.00%)	0 (0.00%)	0 (0.00%)	2 (12.50%)
Upper respiratory tract infection	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (6.25%)
Vaginal infection	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Wound infection	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (6.25%)
Injury, poisoning and procedural complications				
Contusion	1 (10.00%)	1 (16.67%)	0 (0.00%)	2 (12.50%)
Foot fracture	2 (20.00%)	0 (0.00%)	0 (0.00%)	2 (12.50%)
Limb injury	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (6.25%)
Traumatic haematoma	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (6.25%)
Vaccination complication	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Investigations				
Blood creatine phosphokinase increased	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Gamma-glutamyltransferase increased	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (6.25%)
SARS-CoV-2 test negative	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (6.25%)
Weight decreased	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Metabolism and nutrition disorders				
Hypercholesterolaemia	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Hyperferritinaemia	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Hypertriglyceridaemia	2 (20.00%)	2 (33.33%)	0 (0.00%)	4 (25.00%)
Hyperuricaemia	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)

Vitamin B12 deficiency	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Musculoskeletal and connective tissue disorders				
Arthralgia	1 (10.00%)	1 (16.67%)	0 (0.00%)	2 (12.50%)
Back pain	2 (20.00%)	0 (0.00%)	0 (0.00%)	2 (12.50%)
Chondropathy	0 (0.00%)	0 (0.00%)	2 (40.00%)	2 (12.50%)
Joint swelling	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Musculoskeletal chest pain	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Osteopenia	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (6.25%)
Spinal pain	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Angiofibroma	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Nervous system disorders				
Ageusia	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (6.25%)
Anosmia	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (6.25%)
Cervical radiculopathy	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (6.25%)
Headache	2 (20.00%)	2 (33.33%)	1 (20.00%)	5 (31.25%)
Migraine	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Paraesthesia	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Sciatica	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (6.25%)
Psychiatric disorders				
Alcohol abuse	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (6.25%)
Insomnia	2 (20.00%)	1 (16.67%)	0 (0.00%)	3 (18.75%)
Nightmare	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)

Poor quality sleep	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Renal and urinary disorders				
Dysuria	2 (20.00%)	0 (0.00%)	1 (20.00%)	3 (18.75%)
Haematuria	0 (0.00%)	0 (0.00%)	2 (40.00%)	2 (12.50%)
Nocturia	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Pollakiuria	1 (10.00%)	0 (0.00%)	1 (20.00%)	2 (12.50%)
Urinary bladder polyp	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (6.25%)
Reproductive system and breast disorders				
Breast pain	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Dysmenorrhoea	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Genital discomfort	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Haematospermia	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Vulvovaginal dryness	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Respiratory, thoracic and mediastinal disorders				
Cough	1 (10.00%)	1 (16.67%)	0 (0.00%)	2 (12.50%)
Dyspnoea	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (6.25%)
Dyspnoea exertional	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Epistaxis	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (6.25%)
Rhinorrhoea	2 (20.00%)	1 (16.67%)	0 (0.00%)	3 (18.75%)
Upper respiratory tract congestion	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Skin and subcutaneous tissue disorders				
Actinic keratosis	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Alopecia	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Dermatitis acneiform	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)

Dry skin	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Ecchymosis	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Eczema	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Onycholysis	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Petechiae	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Pruritus	1 (10.00%)	0 (0.00%)	1 (20.00%)	2 (12.50%)
Psoriasis	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Social circumstances				
Andropause	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Vascular disorders				
Flushing	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Haematoma	1 (10.00%)	1 (16.67%)	0 (0.00%)	2 (12.50%)
Hot flush	1 (10.00%)	0 (0.00%)	0 (0.00%)	1 (6.25%)
Hypertension	0 (0.00%)	1 (16.67%)	1 (20.00%)	2 (12.50%)

Other Relevant Findings

Not applicable

Conclusion:

- Overall, results show that iptacopan as add-on treatment was able to inhibit chronic residual Intravascular hemolysis and Extravascular hemolysis contributing to residual anemia in these patients with a rapid onset of effect which was sustained over time. As a result, anemia improved in absence of red blood cell transfusions in the large majority of patients, demonstrating clear hematological benefits with iptacopan.

- Treatment with iptacopan 200 mg b.i.d. in addition to standard of care resulted in a clinically important reduction in lactate dehydrogenase levels at Day 92 (Week 13); marked improvement in markers of disease activity; and inhibition of both complement alternative pathway and complement classic pathway activity and thus control of Intravascular hemolysis and Extravascular hemolysis. Iptacopan at the dose of 200 mg b.i.d. led to a numerically better and more complete inhibition of Intravascular hemolysis and Extravascular hemolysis.
- Following discontinuation of standard of care after 6 months and continuation with iptacopan monotherapy, effects were fully maintained and durable up to 176 weeks.
- Treatment with iptacopan was well tolerated up to 176 weeks without relevant new safety findings at dose levels of 50 mg and 200 mg b.i.d. in patients with paroxysmal nocturnal hemoglobinuria with signs of active hemolysis. The majority of AEs were of mild or moderate severity; there was a low discontinuation rate due to AEs and no treatment-emergent deaths were suspected to be related to iptacopan.

Date of Clinical Trial Report

5 December 2022

Date of Initial Inclusion on Clinical Trial Results website

February 2023

Date of Latest Update

Not Applicable

Reason for Update

Not Applicable