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Biostatistics & Statistical Programming /
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LNP023

Clinical Trial Protocol CLNP023X2201 / NCT03439839

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

Statistical Analysis Plan (SAP)

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report for trial ***"CLNP023X2201".***

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

Final study protocol v05 is available at the time of finalization of the Statistical Analysis Plan for CSR.

1.3 Study objectives

1.3.1 Primary objective(s)

Primary objective(s)	***Endpoints related to primary objective(s)***
• To assess the effect of LNP023 on the reduction of chronic hemolysis in PNH patients when administered in addition to SoC (monoclonal antibody with anti C5 activity)	• LDH level at study week 13

1.3.2 Secondary objective(s)

Secondary objective(s)	***Endpoints related to secondary objective(s)***
• To assess the safety and tolerability of LNP023 in patients with PNH when administered in addition to SoC (monoclonal antibody with anti C5 activity)	• All safety parameters including: blood chemistry, hematology, urinalysis, ECG evaluation, vital signs, adverse events, transfusions, PROs, patient diary
• To assess the effect of LNP023 on markers of intra and extravascular hemolysis when administered in addition to SoC (monoclonal antibody with anti C5 activity)	• Total and free hemoglobin, reticulocytes, LDH, C3 fragment deposition, PNH-type red blood cells, haptoglobin, bilirubin, red blood cell count, freedom from transfusion
• To assess the plasma PK of LNP023 in PNH patients	• Non-compartmental PK parameters of LNP023 in plasma, including but not limited to Cmax, Tmax and AUC and Ctrough.

1.3.3 Exploratory objective(s)

Exploratory objective(s)	*Endpoints related to exploratory objective(s)*
• To explore mechanism of action and PK-PD relationship of LNP023 in PNH patients when administered in addition to SoC (monoclonal antibody with anti C5 activity)	• Biomarker assessments may include but are not limited to Wieslab assay, CH50, Bb, sC5b-9 • Population PK and PD model parameters. Correlation analysis and/or PK-PD modelling of biomarkers using total and/or unbound drug levels, as determined by means of ex-vivo dialysis, may also be explored
• To evaluate if co-treatment with LNP023 results in sustainable increases in hemoglobin	• Change in total hemoglobin level from baseline
• To assess LNP023-induced changes in quality of life	• Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue
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• To assess the effect of LNP023 on markers associated with risk of thrombosis in PNH patients	• Assessments may include but are not limited to prothrombin time, partial prothrombin time, D-dimer

1.4 Study design and treatment

This is a non-confirmatory, open label, multiple dose study in patients with PNH. Two cohorts will be included in the study.

For Cohort 1 (approximately 10 patients) this study includes:

- a screening period of up to 68 days,
- a baseline visit,
- Treatment Part 1: 13 weeks of treatment with 200 mg LNP023 b.i.d. administered orally in addition to SoC,
- Treatment Part 2: treatment extension for approximately 2 to 3 year with the same treatment regimen as used in Part 1 in patients who benefited from the LNP023 treatment in Part 1. The same treatment regimen will be used as in Part 1, Note that patients can complete Part 2 any time after a minimal total duration of LNP023 treatment of 2 years (i.e., after V130) without being considered early discontinuations, for example, to transition to the roll-over extension program (REP),
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- an End of Study (EoS) visit 2 weeks after last LNP023 administration for patients not joining the REP; for patients joining the REP, the last treatment visit will become the EoS visit.
- a safety follow-up call conducted 30 days after last LNP023 administration on CLNP023X2201 study (applicable only for patients not joining the REP).

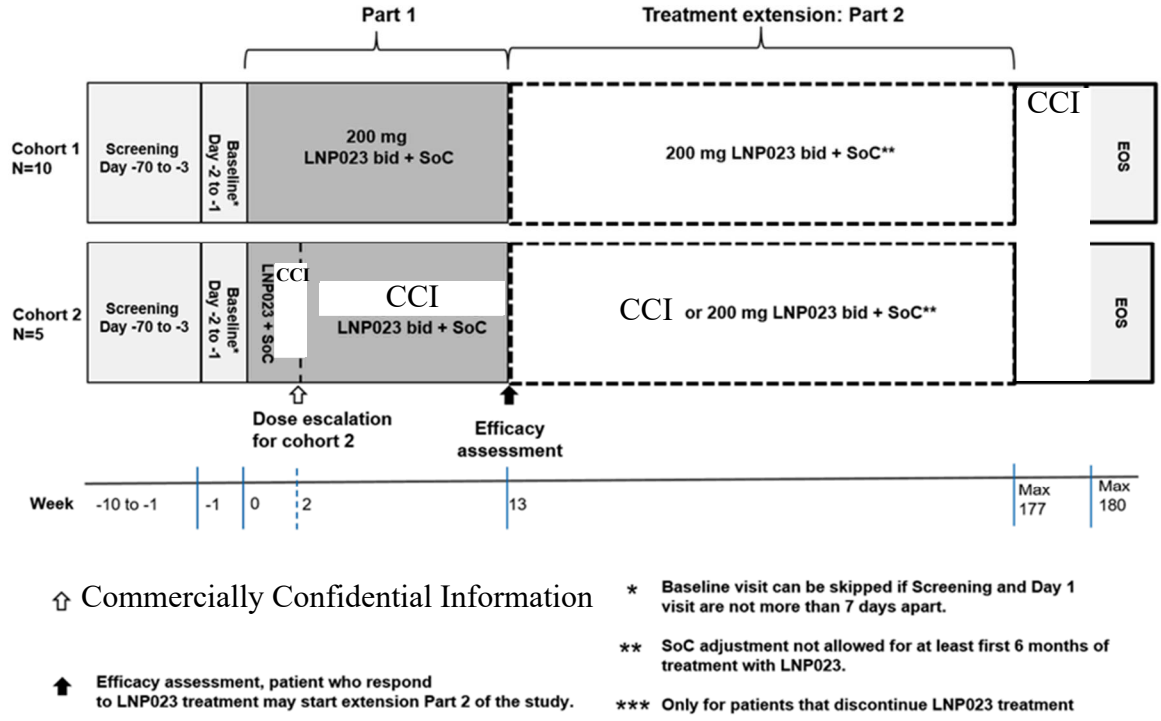
For Cohort 2 (approximately 5 patients) this study includes:

- a screening period of up to 68 days,
- a baseline visit,
- Treatment Part 1: Minimum of 2 weeks of treatment with CCI LNP023 CCI administered orally in addition to SoC. Commercially Confidential Information
- Treatment Part 2: Treatment extension for approximately 2 to 3 year with the same treatment regimen as used in Part 1 in patients who benefit from the LNP023 treatment in Part 1. For patients receiving CCI the dose might be escalated as described in Part 1. For patients receiving CCI the dose may be escalated as described for Part 1. Note that patients can complete Part 2 any time after a minimal total duration of LNP023 treatment of 2 years (i.e., after V130) without being considered early discontinuations, for example, to transition to the roll-over extension program (REP),
- Commercially Confidential Information
- and an End of Study (EoS) visit 2 weeks after last LNP023 administration for patients not joining the REP; for patients joining the REP, the last treatment visit will become the EoS visit.
- a safety follow-up call conducted 30 days after last administration of study treatment (applicable only for patients not joining the REP).

For all patients:

- The baseline visit can be skipped if Screening and Day 1 visit are not more than 7 days apart (Figure 2-1). If possible also other study visits, should be aligned with SoC administration. On Day 1 and any other visits when both SoC and LNP023 are administered, LNP023 is administered prior to SoC. Adjustment of the SoC dose or regimen are not allowed for the first 6 months of the treatment with LNP023.
- The expected study duration is between approximately 2.5 and 3.5 years.

Figure 1-1 Study design



2 First interpretable results (FIR)

No FIR will be produced for the final analysis.

3 Interim analyses

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4 Statistical methods: Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The safety analysis set will include all subjects that received any study drug.

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

The PD analysis set will include all subjects with any available PD data, who received any study drug and experienced no protocol deviations with relevant impact on PD data.

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from PK analysis in case of these PDs: INCL01		Exclude subject from PK analysis set
Subjects are excluded from PD analysis in case of these PDs: INCL01		Exclude subject from PD analysis set
Subjects are excluded from PK and PD analysis in case of these PDs: INCL01		Exclude subject from PK and PD analysis sets

5 Statistical methods: Group presentations

For summary statistics, subjects will be summarized as follows, depending on which study Part is being assessed, unless stated otherwise:

Part 1:

- All patients together, for the assessment of Part 1

Parts 1 and 2:

- Patients entering Part 2 alone for the whole duration of the study. So there will be assessments repeated for Part 1 which only include those patients who went onto Part 2.

In the event that no patients are lost from Part 1 into Part 2 the above grouping becomes unnecessary.

Individual (spaghetti) plots over time will be performed and will include the whole duration of the study.

6 Statistical methods for Pharmacokinetic (PK) parameters

All subjects in the PK analysis set will be included in the PK data analysis.

6.1 Variables

The following pharmacokinetic parameters of total LNP023 will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 8.3 or higher):

- Plasma: Cmax, Tmax, AUCtau, and Cmin (*i.e.*, Ctrough) at Day 1, 29 and 169 and 337. Other pharmacokinetic parameters as appropriate.
- Trough Plasma concentrations

6.2 Descriptive analyses

Concentration data will be listed by cohort, dose, patient, and visit/sampling time point (including Part). Descriptive summary statistics will be provided by cohort, dose, visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Commercially Confidential Information

Graphical methods will be employed to show mean and individual concentration-time profiles.

Pharmacokinetic parameters will be listed by cohort, dose, patient and Part, and summarized with descriptive statistics as listed above. For Tmax, only median, minimum, and maximum will be reported.

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All individual concentration-time profiles will be displayed graphically by cohort visit/sampling time point on linear and semi-log view based on nominal time. In addition, the arithmetic mean (+/-SD) concentration-time profiles by cohort, dose and visit over time will be displayed graphically on the linear and semi-log view based on nominal time.

7 Statistical methods for Pharmacodynamic (PD) parameters

All subjects in the PD analysis set will be included in the PD data analysis.

7.1 Primary objective

The primary objective of this study is to assess the effect of LNP023 on the reduction of chronic hemolysis, as assessed by LDH over time, in PNH patients when LNP023 is administered in addition to SoC (monoclonal antibody with anti C5 activity)

7.1.1 Variables

The primary variable is LDH level and it is measured over time, with week 13 (end of Part 1) considered the primary timepoint.

Baseline is defined as the mean of the last 3 measurements prior to study drug administration.

7.1.2 Descriptive analyses

The primary variable will be listed by cohort, patient and visit/time including Part, and descriptive statistics will be provided, by cohort, visit/time and study Part. Summary statistics

will include mean (arithmetic), SD, CV (arithmetic), median, minimum, maximum. Summary tables may include a combination of individual subject assessments and summary statistics.

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Given the severe nature of the indication and the need for close monitoring it is expected that there will be very little truly missing data.

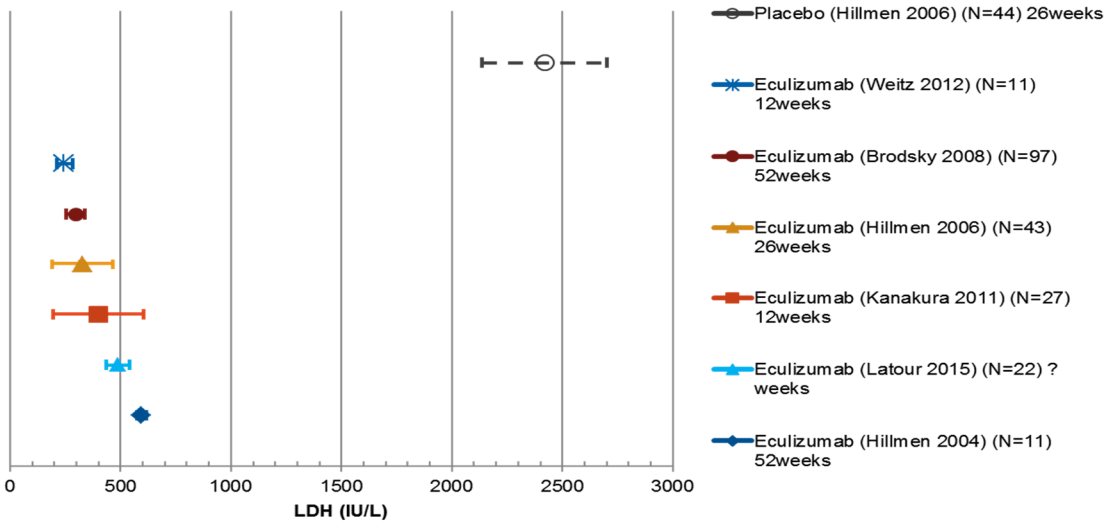
7.1.3 Statistical model, hypothesis, and method of analysis

The primary variable for assessing the effect of LNP023 (in addition to SoC) is the LDH value which is measured at multiple times during the study in both Parts.

A mixed model repeated measures (MMRM) analysis of variance model will be fitted to LDH levels over time in Part 1. The model will include timepoint (as study day relative to start of study treatment) as a fixed effect, and baseline LDH as a fixed covariate. An unstructured variance-covariance matrix will be used, if an unstructured covariance cannot be used simpler structures will be investigated such as autoregressive and toeplitz, decision on the optimal structure will be done based on information criteria.

Results from this modelling will be presented as the estimated mean value of LDH at week 13 together with the 95% confidence interval. These results will also be presented graphically in a forest plot also showing published data from trials of eculizumab, as shown below in Figure 7-1. Two of the comparative studies are known to be at the same time point but all comparisons to this study's estimate will be useful given their similarity.

Figure 7-1 Forest plot of LDH final mean estimates at from 6 studies of various lengths



7.1.4 Handling of missing values/censoring/discontinuations

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7.1.5 Sensitivity analyses

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There is no other obvious sensitivity analysis because with so few subjects, differences in results between different analyses are unlikely to be detected. However the effect of different ways of handling baseline LDH values, different variance-covariance structures and different fixed effect models could be examined to ensure robustness of results.

Patients who took prohibited concomitant medication during the study will be excluded from the primary endpoint analysis and the analysis related to IVH & EVH markers as part of a sensitivity analysis. Both descriptive and inferential analysis will be repeated with these patients excluded.

7.2 Secondary objectives

The secondary objective of the study are,

- To assess the safety and tolerability of LNP023 in patients with PNH when administered in addition to SoC (monoclonal antibody with anti C5 activity)
- To assess the effect of LNP023 on markers of intra and extravascular hemolysis when administered in addition to SoC (monoclonal antibody with anti C5 activity)
- To assess the plasma PK of total LNP023 in PNH patients

Please refer to Section 8 for analysis related to safety and tolerability and Section 6 for PK analysis.

7.2.1 Variables

The secondary variables are markers of disease activity and include: Total and free hemoglobin, reticulocytes, C3 fragment deposition, PNH-type red blood cells, PNH clone size, haptoglobin, bilirubin, red blood cell count, and freedom from transfusion.

7.2.2 Descriptive analyses

The secondary variables will be listed by cohort, dose, patient and visit/time including Part, and descriptive statistics will be provided, by cohort, dose, visit/time and study Part. Summary statistics will include mean (arithmetic, geometric), SD, CV (arithmetic, geometric), median,

minimum, maximum. Summary tables may include a combination of individual subject assessments and summary statistics.

Graphical methods will be employed to show individual overlaid profile plots over time by cohort. Summary plots may be provided or overlaid on the individual plots. Percentage change from baseline plots may also be provided.

The number and timing of transfusions will be listed and each one shown on plots where relevant and relevant descriptive summaries will be formed.

7.3 Exploratory objectives

The exploratory objectives of the study are:

- To explore mechanism of action and PK-PD relationship of LNP023 in PNH patients when administered in addition to SoC (monoclonal antibody with anti C5 activity)
- To evaluate if co-treatment with LNP023 results in sustainable increases in hemoglobin
- To assess LNP023-induced changes in quality of life

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- To assess the effect of LNP023 on markers associated with risk of thrombosis in PNH patients

7.3.1 Variables

Mechanism of action and PK-PD relationship:

- Biomarkers (See Section 9) including but are not limited to Wieslab assay, CH50, Bb, and sC5b-9. and possibly, depending on assay availability Factor B and Eculizumab concentrations
- Population PK and PD model parameters. Correlation analysis and/or PK-PD modelling of biomarkers using total and/or unbound drug levels, as determined by means of ex-vivo dialysis, may also be explored

Co-treatment effect in Hemoglobin:

- Hemoglobin level: Change in total hemoglobin level from baseline. Baseline is defined as the mean of all measurements prior to randomization.

Genetic research:

- Due to the exploratory nature of this objective endpoints are not predefined

Quality of life:

- Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue total score.

Risk of thrombosis markers:

- Risk of thrombosis parameters: Assessments may include but are not limited to prothrombin time, partial prothrombin time, D-dimer

7.3.2 Descriptive analyses

The exploratory variables will be listed by cohort, patient and visit/time including Part, and descriptive statistics will be provided, by cohort, visit/time and study Part. Summary statistics

of raw and change from baseline, where relevant, will include mean (arithmetic), SD, CV (arithmetic), median, minimum, maximum. Summary tables may include a combination of individual subject assessments and summary statistics.

Graphical methods will be employed to show individual overlaid profile plots over the time course of the whole study by cohort. Summary plots may be provided or overlaid on the individual plots. Percentage change from baseline plots may also be provided.

8 Statistical methods for safety and tolerability data

All subjects within the Safety analysis set will be included in the safety data analysis.

Safety summaries (tables, figures) will include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g., when change from baseline is used). In particular, summary tables for adverse events (AE) will summarize only on-treatment events.

The on-treatment period lasts from the date of first administration of study treatment to 7 days after the date of the last actual administration of any study treatment.

8.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, as well as subject demographics, baseline characteristics, exposure and treatment information.

8.2 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by subject and cohort. Summary statistics will be provided.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by cohort and subject.

Medical treatment

Data for study drug administration (rescue medication) and concomitant therapies will be listed by cohort, subject and study Part.

Number and percentage of subjects who received the vaccination during Screening period will be summarized.

Vital signs

All vital signs data will be listed by cohort, subject, and visit/time including Part and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by cohort, visit/time and study Part.

Individual and mean values over time will be plotted by cohort, visit/time, and study part.

ECG evaluations

All ECG data will be listed by cohort, subject and visit/time including Part, abnormalities will be flagged. Summary statistics will be provided by cohort, visit/time and study Part.

Clinical laboratory evaluations

All laboratory data will be listed by cohort, subject, and visit/time including Part and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a subject with any abnormal values. Summary statistics will be provided by cohort, visit/time and study Part.

Individual and mean values over time will be plotted by cohort, visit/time and study part.

Adverse events

All information obtained on adverse events will be displayed by subject.

The number and percentage of subjects with treatment-emergent adverse events will be tabulated by cohort, Part and overall, body system and preferred term. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

Adverse event reporting for Clinical Trial Safety Disclosure (CTSD)

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for the same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

Adverse events are considered treatment-emergent if they occur between the date of first administration of study treatment and up to 7 days after the date of the last actual administration of any study treatment.

Adverse events of special interest (AESI) definitions are found in the compound electronic Case Retrieval Strategy (eCRS). Treatment-emergent AESIs (based on the latest eCRS at the time of

DBL) will be summarized by frequency and percentage of patients by risk name, MedDRA preferred term and by cohort. A listing of the case retrieval strategy will be presented.

Exposure

Duration of exposure will be presented graphically, using a horizontal bar chart with subjects as the y-axis and the number of days exposed to LNP023 as the x-axis. Exposure data will be summarized (for SoC, for combination and LNP023 as a monotherapy) and listed by cohort, subject and visit/time including Part.

8.3 Graphical presentation

To visualize trends in longitudinal safety data (vitals, ECG, lab parameter), individual overlaid profile plots over time will be created by cohort.

9 Statistical methods for biomarker data

The following biomarkers will be analyzed in this trial and fully reported in the CSR, if the data is available.

Table 9-1 List of Biomarkers

Biomarker	Unit	Description	Read out*
Wieslab Assay	%	Alternative complement pathway activity	Wieslab
Bb	ng/ml	Circulating fragment Bb of Factor B	Bb
sC5b-9	ng/ml	Soluble C5b-9	SC5B-9
CH50	iu**	Classical complement pathway activity	CH50
C3-fragment deposition on PNH Type-I red blood cells (RBC)	%	Relative percentage (%) of C3d positive PNH Type-I RBC out of total PNH Type-I RBC	C3d+Type-I RBC
C3-fragment deposition on PNH Type-II RBC	%	Relative percentage (%) of C3d positive PNH Type-II RBC out of total PNH Type-II RBC	C3d+Type-II RBC
C3-fragment deposition on PNH Type-III RBC	%	Relative percentage (%) of C3d positive PNH Type-III RBC out of total PNH Type-III RBC	C3d+Type-III RBC
PNH Type-I RBC	%	Relative percentage (%) of PNH Type-I RBC out of total RBC	Type-I RBC
PNH Type-II RBC	%	Relative percentage (%) of PNH Type-II RBC out of total RBC	Type-II RBC
PNH Type-III RBC	%	Relative percentage (%) of PNH Type-III RBC out of total RBC	Type-III RBC
C3-fragment deposition on PNH RBC	%	Relative percentage (%) of C3d positive PNH RBC out of total PNH RBC	C3d+PNH RBC
PNH clone size	%	Relative percentage (%) of PNH Type-II and Type-III RBC out of total RBC	PNH clone size
Complement Factor B	Ug/mL	Circulating levels of complement factor B	Complement Factor B
GlyA+ RBC	iu*	Relative percentage (%) of GlyA-positive red blood cells out of total RBC	GlyA+RBC
RBC	Iu*	Relative percentage (%) of red blood cells out of acquired cells	RBC

* Biomarker name exactly as it will appear in the dataset
**For CH50, 1 iu corresponds to 1 CH50 KU Eq/L.
**1iu corresponds to 1%.

PNH clone size should be calculated as the sum of Type-II RBC and Type-III RBC.

These biomarker data will be listed by cohort, patient, and visit/time including Part. Summary statistics will be provided by cohort, visit/time and study Part. They will also be plotted as for other variables over time and by cohort.