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LNP023

CLNP023X2202 / NCT03832114

An open-label, non-randomized study on efficacy, pharmacokinetics, pharmacodynamics, safety and tolerability of LNP023 in two patient populations with C3 glomerulopathy

Statistical Analysis Plan (SAP)

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1 Introduction

1.1 Scope of document

The Review and Analysis Plan (RAP) documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial **"*CLNP023X2202"***.

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

1.2 Study reference documentation

Study protocol (v03) is available at the time of finalization of the SAP.

1.3 Study objectives

1.3.1. Primary objective(s)

Primary objective(s)	*Endpoint(s) related to primary objective(s)*
• **Cohort A:** To evaluate the efficacy of LNP023 in reducing proteinuria at Week 12	• Ratio to baseline of Urine Protein to Creatinine concentration Ratio (UPCR) derived from 24h urine collection.
• **Cohort B:** To assess histopathological changes in kidney biopsies at Week 12	• Change from baseline in C3 Deposit Score (based on immunofluorescence microscopy).

1.3.2. Secondary objective(s)

Secondary objective(s)	*Endpoint(s) related to secondary objective(s)*
• **All Cohorts:** To assess the relationship between LNP023 dose and pharmacodynamic biomarkers	• Biomarker levels of blood Bb
• **All Cohorts:** To assess the relationship between LNP023 dose and proteinuria	• 24h urine UPCR and UACR.
• **All Cohorts:** To assess the effect of LNP023 on renal function	• (i) change in and (ii) evolution of: urinary albumin (UA), urinary protein (UP) excretion; urine albumin to creatinine ratio (UACR) urine protein to creatinine ratio (UPCR), serum creatinine, estimated glomerular filtration rate (eGFR, using

	CKD-EPI formula), creatinine clearance, hematuria
• **All Cohorts:** To assess the effect of LNP023 on alternative complement pathway hyperactivity	• Blood level of C3.
• **All Cohorts:** To assess the safety and tolerability of LNP023	• ECG parameters, vital signs, safety laboratory assessments Commercially Confidential Information, AEs and SAEs.
• **All Cohorts:** To assess the plasma and urine pharmacokinetics of LNP023 in patients with C3G	• Plasma: Non-compartmental parameter analysis related to total drug, including but not limited to Cmax, Tmax, AUClast, AUCtau and Ctrough (Cmin) after the first dose on Day 7, Day 14, Day 21 and Day 28, as well as Cmin on Days 92 and 99 or 176 and 183. • Urine: Non-compartmental parameters, including but not limited to total cumulative urinary excretion (Ue) and renal plasma clearance (CLr).
• **Cohort B:** To evaluate the efficacy of LNP023 in reducing proteinuria at Week 12	• Ratio to baseline of UPCR and UACR derived from 24h urine collection.

1.3.1. Exploratory objective(s)

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1.4 Study design and treatment

The study is a non-confirmatory, open-label, two cohort single arm, non-randomized study evaluating the efficacy, safety, tolerability, pharmacokinetics, pharmacodynamics and dose/biomarker relation of LNP023 in two subject populations:

- Cohort A: enrolls non-transplanted C3G subjects with reduced C3 serum levels
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- Cohort B: enrolls subjects who have undergone kidney transplantation and have C3G recurrence.

Cohort B will start in parallel to Cohort A.

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In general, the subjects who will be enrolled into Cohort A and Cohort B, will be treated for up to 14 weeks Commercially Confidential Information with LNP023 as per the following doses and weeks:

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Subjects will be offered the possibility to continue LNP023 treatment for a long period by enrolling in an extension study. In this case subjects may roll-over directly into the extension study at the end of treatment period without study drug administration interruption.

Cohort A

Approximately 15 C3G subjects with native kidneys and with reduced serum C3 levels (male or female) will be enrolled in Cohort A to ensure that at least 12 subjects complete the study in this cohort.

Figure 1-1 depicts the study design of Cohort A, which consists of a screening period that lasts up to 60 days (made up by a screening visit and a run-in period), a baseline period of about 30 days (made up by two visits), a 12-week treatment period CCI , a safety follow-up period Commercially Confidential Information 12 weeks of safety follow up), and the end-of-study (EOS) visit scheduled on Day 175.

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Follow-up period: Commercially Confidential Information 12 weeks of safety follow-up without treatment. At the end of Treatment period CCI , if the Investigator does not deem it to be clinically beneficial for the subject to continue treatment, or if a subject does not want to continue treatment, the subject will enter the follow-up period.

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- A safety follow-up period of 12 weeks, without treatment, will follow. There will be 3 outpatient visits on Days 113, 127 and 155 Commercially Confidential Information

An end-of-study (EOS) visit is scheduled on Day 183Commercially Confidential Information

Efficacy in terms of proteinuria and individual clinical response to various pharmacodynamic markers as well as pharmacokinetics will be assessed over the 12-week treatment period.

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In this context, proteinuria will be assessed by collecting 24-h urine and first morning void urine to assess the change in and evolution of: UA and UP excretion, UACR and UPCR, creatinine clearance and hematuria.

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Cohort B

Approximately 12 C3G kidney transplanted subjects (male or female) with C3G recurrence subjects will be enrolled in Cohort B to ensure that at least 10 subjects complete the study in this Cohort.

Figure 1-3 depicts the study design of Cohort B, which consists of a screening period that lasts up to 60 days (made up by a screening visit and a run-in period), a baseline period of about 30 days (made up by two visits), a 12-week treatment period CCI , a safety follow-up period (Commercially Confidential Information 12 weeks of safety follow up) and the end-of-study (EOS) visit scheduled on Day 175.

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Follow-up period: A two-week down-taper of study medication and 12 weeks of safety follow-up without treatment. At the end of Treatment period 1 or 2, if the Investigator does not deem it to be clinically beneficial for the subject to continue treatment, or if a subject does not want to continue treatment, the subject will enter the follow-up period (refer to Figure 1-2).

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- A safety follow-up period up to 12 weeks with 3 outpatient visits on Days 113, 127 and 155 Commercially Confidential Information

An end of study visit scheduled on Day183 Commercially Confidential Information

Efficacy in terms of reversal of renal histopathologic changes will be assessed after the 12-week treatment period. Proteinuria and individual clinical response to various pharmacodynamic markers as well as pharmacokinetics will be assessed over the 12-week treatment period.

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In this context, proteinuria will be assessed by collecting 24-h urine and first morning void urine to assess the change in and evolution of: UA and UP excretion, UACR and UPCR, creatinine clearance and hematuria.

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2 First interpretable results (FIR)

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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 for Cohort A and B.

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

The PK analysis set will include all subjects with available PK data and no protocol deviations with relevant impact on PK data.

The PD analysis set 1 will include all subjects with available PD data and no protocol deviations with relevant impact on PD data, as well as no serious adverse event

The PD analysis set 2 will include all subjects with available PD data and no protocol deviations with relevant impact on PD data.

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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:		Exclude subject from PK analysis set
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD 1 and PD2 analysis sets
COMD02	Prohibited concomitant medication-4	Yes
Subjects are excluded from PK and PD analysis in case of these PDs:		Exclude subject from PK and PD analysis sets

5 Statistical methods for Pharmacokinetic (PK) parameters

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

5.1 Variables

The following pharmacokinetic parameters of LNP023 will be determined using the actual recorded sampling times and non-compartmental analysis method(s) with Phoenix WinNonlin (Version 8 or higher):

- Plasma: Cmax, Tmax, AUClast, AUCtau and Ctrough (Cmin) after the first dose on Day 7, Day 14, Day 21 and Day 28 as well as Cmin on Days 92 and 99 (Week 13 and 14) Commercially Confidential Information
- Urine: Non-compartmental parameters, including but not limited to total cumulative urinary excretion (Ue) and renal plasma clearance (CLr).

Other pharmacokinetic parameters may be calculated as appropriate. All parameters determined are considered at steady state.

5.2 Descriptive analyses

The following analyses will be implemented for each Cohort separately.

Individual LNP023 plasma and urine concentration data will be listed by treatment, subject, and visit/sampling time point, and plotted over time by subject. Descriptive summary statistics will be provided by treatment and visit/sampling time point,
Commercially Confidential Information . Pharmacokinetics parameters and will be listed by treatment and subject.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented. Commercially Confidential Information A geometric mean will not be reported if the dataset includes zero values.

All individual plasma concentration-time profiles for LNP023 concentration with median will be displayed graphically by treatment on semi-log view. In addition, the arithmetic mean (+/- SD) and geometric mean plasma concentration-time profiles for LNP023 by treatment over time will be displayed graphically on the linear and semi-log view.

Descriptive summary statistics of pharmacokinetic parameters will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented.

6 Statistical methods for Pharmacodynamic (PD) parameters

All subjects within the PD analysis set 1 will be included in the PD data analyses of primary and secondary objectives.

All subjects within the PD analysis set 2 will be included in the PD data analyses of exploratory objectives.

6.1 Primary objective

The primary objectives of this study are:

Cohort A: To evaluate the efficacy of LNP023 in reducing proteinuria at week 12, as assessed by ratio to baseline of Urine Protein to Creatinine concentration Ratio (UPCR) derived from 24-h urine collection in C3G subjects who have not received a kidney transplantation and have reduced C3 blood levels.

Cohort B: To assess histopathological changes in kidney biopsies at Week 12, as assessed by change from baseline in C3 Deposit Score (based on immunofluorescence microscopy) in C3G subjects who have received a kidney transplantation.

6.1.1 Variables

The primary endpoints of this study are:

Cohort A: Ratio to baseline in UPCR derived from 24-h urine collection at Week 12.

Baseline is defined to be the 24-h urine collection on Day -1 to Day 1.

Cohort B: Change from baseline in C3 Deposit Score (based on immunofluorescence microscopy) at Week 12.

The C3 Deposit score varies from 0 to 3 graded intensity values for C3 deposition for the mesangial and capillary location. The score for each location (mesangial and capillary) will be multiplied with a factor of 1 for segmental and a factor of 2 for global extend. The total score range will therefore range from 0 to 12. Renal biopsy data includes C3 data.

The C3 Deposit score was chosen as the primary end-point in this the Phase 2 study due to close target relationship as the target of LNP023, Factor B, is required to cleave C3 during AP activation. Improvement is expected following a three-month treatment period. C3 deposition is C3G-defining; hence baseline C3G scores of subject included in this study will be elevated.

Baseline is defined to be the histopathological data obtained from a renal biopsy taken during run-in phase if the most recent renal biopsy is older than 3 months. If the renal biopsy is not older than 3 months, the baseline data will be provided by the site.

6.1.2 Descriptive analyses

Cohort A: UPCR from 24-h urine measurements will be listed by treatment, subject and visit/time and descriptive statistics of the raw and ratio to baseline will be provided by treatment and visit/time. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum as appropriate.

Graphical methods will be employed to show group and individual summary plots over time by treatment level.

Cohort B: The change from baseline in C3 Deposit score will be listed by treatment, subject and visit/time and descriptive statistics will be provided by treatment and visit/time. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum as appropriate.

Graphical methods and pictures will be employed to show group and individual summary plots over time by treatment.

All Cohorts: Overlaying individual time profiles (spaghetti plots) to visualize trends in raw UPCR 24h by time and treatment group will be created.

6.1.3 Statistical model, assumptions and hypotheses

Cohort A: The log ratio to baseline in UPCR, will be analyzed using a mixed model repeated measures (MMRM), the analysis will include all data up to and including Week 12. This model will have the log ratio to baseline in UPCR as the dependent variable, baseline log transformed UPCR and time point (as study day relative to the start of study treatment, Day 28/29 and Day 84/85) as fixed effects. An unstructured covariance matrix will be used.

Model estimated means will be obtained at each timepoint, with Week 12 being of primary interest, along with the two-sided 80% confidence interval and p-value. Results will be back transformed to provide the geometric mean and their 80% CIs on the original scale.

Model estimated means will be obtained at each timepoint, with Week 12 being of primary interest, along with the two-sided 80% confidence interval and p-value. Results will be back transformed to provide the geometric mean and their 80% CIs on the original scale.

Cohort B: The Wilcoxon signed rank test will be used for C3 Deposit Score data at Week 12 timepoint to compare the median difference of change from baseline between periods. The Hodges-Lehmann estimate and two-sided 80% confidence interval for the median difference will be provided.

6.1.3.1 Model checking procedures

Model checking will not be performed in this exploratory study.

6.1.3.2 Graphical presentation of results

For Cohort A, model estimated means of the treatment at each timepoint will be provided along with their 80% CI.

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For Cohort B, individual summary plots by treatment for each group of C3 deposit score (activity, chronicity and mesangial) as well as for the total C3 Deposit Score will be provided.

6.1.3.3 Sensitivity analyses

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6.2 Secondary objectives

6.2.1 Variables

The secondary variables supporting the secondary objectives are provided below for all cohorts:

- Renal parameters:
  - Raw and ratio to baseline in UA, UACR, UP and UPCR (all from 24h urine collection)
  - Raw and ratio to baseline in creatinine clearance (from 24h urine collection)
  - Raw and change from baseline in serum creatinine and eGFR
  - Hematuria (from 24-h urine collection)

  - Using the DuBois and DuBois equation, the creatinine clearance is defined as follows:

$$CrCl = \frac{U_{Cr} \times U_{Vol}}{P_{Cr} \times T_{min}} \quad in\ mL/min$$

where,

- U_{Cr} is urine creatinine in mg/dL from Q2
- U_{Vol} is urine volume of the 24h urine in mL (from eCRF) and Q2
- P_{Cr} is plasma creatinine in mg/dL from Q2
- T_{min} is the time of collection in minutes, so for example, 1440 min for 24

➢ Using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, the eGFR is calculated as follows:

$$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018[\text{if female}] \times 1.159[\text{if black}]$$

where, S_{cr} is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of S_{cr}/κ or 1, and max indicates the maximum of S_{cr}/κ or 1. The equation does not require weight because the results are reported normalized to 1.73 m2 body surface area, which is an accepted average adult surface area.

- Ratio to baseline of UPCR and UACR derived from 24-h urine collection (only for Cohort B)
- Raw plasma levels of Bb from BMD and serum C3 from central lab, and their ratio to baseline.

Baseline for:

- all 24-h urine collection parameters, is defined to be the 24-h urine collection on Day -1 to Day 1.
- serum creatinine and eGFR, is defined to be the last available assessment prior to the first dose of study drug.
- plasma levels of Bb from BMD and serum C3 from central lab is defined to be the baseline visit assessment.

6.2.2 Descriptive analyses

The following descriptive analyses will be implemented for each cohort separately and pooled cohorts.

The secondary variables, except hematuria, will be listed by treatment, subject and visit/time. Summary statistics will be provided by treatment and visit/time for raw, change from baseline and ratio to baseline as deemed relevant. Summary statistics will include mean (arithmetic and geometric), SD, CV, median, minimum, maximum. For parameters that will be analyzed as change from baseline, geometric means and CV will not be provided in the summaries.

Graphical methods will be employed to show group and individual summary plots over time by treatment. Individual plots for raw and change from baseline to week 12, will be plotted with median overlaid by treatment as well as arithmetic mean (SE) change from baseline to week 12

will be also plotted by Cohort for UPCR, UACR, eGFR, plasma Bb, serum C3 blood levels and C3 Deposit score.

A shift table of changes from baseline in hematuria levels will be provided, considering the following three levels: <9rbc/hpf, ≥ 9 rbc/hpf to ≤ 50 rbc/hpf and >50 rbc/hpf (where >50 rbc/hpf cateogry includes also the too numerous to count (TNTC) values).

All Cohorts: Overlaying individual time profiles (spaghetti plots) to visualize trends in raw C3 deposit score by time and treatment group will be created.

6.2.3 Statistical model, assumptions and hypotheses

The following statistical analyses will be implemented for each cohort separately and pooled cohorts. For subjects who stopped the study drug intake due to Covid-19 and restarted drug intake after tested negative to Covid-19 (i.e. OTHER-5 and with PD identifier OTH36), their assessments after treatment discontinuation will not be consider.

For each secondary variable (apart from hematuria, Bb and C3 biomarker) a similar statistical model will be used as described for the primary variable in Section 6.1.3.

Additionally, for Cohort B only, the log ratio to baseline in UPCR and UACR derived from 24-h urine collection will also be analyzed with the same MMRM model as in Section 6.1.3.

6.2.3.1 Sensitivity analyses

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6.3 Exploratory objectives

6.3.1 Variables

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6.3.2 Descriptive analyses

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7 Statistical methods for safety and tolerability data

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

7.1 Variables

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

7.2 Descriptive analyses

Subject demographics and other baseline characteristics

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

Relevant medical histories and current medical conditions at baseline will be summarized (separately) by system organ class and preferred term, for all subjects.

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

Treatment

Data for study drug administration and concomitant therapies will be listed by treatment group and subject.

Data for study drug administration will be summarized by treatment group and will include number of subjects who took all the planned doses of LNP023.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by preferred term and cohort group for all subjects.

In addition, the above two summary tables will be produces for the medications of interest listed below:

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Concomitant medication is defined as any medication started on or after LNP023 treatment and ended/ongoing by Day 84. Prior medications are defined as any treatment started and ended before the first dose of LNP023 on Day 1.

Vital signs

All vital signs data will be listed by treatment, subject, and visit/time and if ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

ECG evaluations

All ECG data will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time and the number of subjects with values above key threshold values will be displayed.

The mean of replicates of ECG evaluations will be calculated and presented in the analyses.

Clinical laboratory evaluations

All laboratory data will be listed by treatment, subject, and visit/time 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 treatment and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Adverse events

All information obtained on adverse events will be displayed by run-in period, treatment period (i.e. dose-escalation phase, LNP023 200mg b.i.d., tapering down phase) and subject.

The number and percentage of subjects with adverse events will be tabulated by body system organ class (SOC) and preferred term (PT) with a breakdown by run-in and treatment period. A subject with multiple adverse events within a body system is only counted once towards the total of this body system and treatment period (including run-in period).

Summaries of SAEs will be provided in a similar manner.

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Further displays of AEs may be produced in order to appropriately describe the outcomes seen in this trial.

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 a same subject, 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.

7.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) will be created.

8 Statistical methods for Pharmacokinetic/Pharmacodynamic interactions

Graphical methods, such as scatterplots, will be used for efficacy biomarkers analyzed during this study against individual PK parameters such as Cmax or AUC as well as against as administered dose to establish the exposure/response relationship and to determine the (lowest) efficacious dose or exposure.

9 Statistical methods for biomarker data

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10 References

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Bomback, A. S., Santoriello, D., Avasare, R. S., Regunathan-Shenk, R., Canetta, P. A., Ahn, W., & Markowitz, G. S. (2018). C3 glomerulonephritis and dense deposit disease share a similar disease course in a large United States cohort of subjects with C3 glomerulopathy. Kidney international, 93(4), 977-985.

11 Appendix

11.1 Adverse events of Special Interest

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11.2 Histologic scoring of renal biopsies from C3G subjects

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