Otsuka Pharmaceutical
Development & Commercialization, Inc.

EU NON-INTERVENTIONAL POST-AUTHORISATION SAFETY STUDY (NI-PASS) PROTOCOL

Protocol Title	An observational post-authorisation safety study (PASS) in Europe to further characterise and quantify long-term safety profile with respect to neurotoxicity, chronic nephrotoxicity, and malignancy with use of voclosporin
Protocol No.	348-201-00021
Protocol Version Identifier:	2.0
Protocol Date:	08 Aug 2023
European Union (EU) Post-authorisation Study (PAS) Register Number:	Not registered yet
Active Substance:	Voclosporin
Medicinal Product:	Lupkynis™
Product Reference:	EMEA/H/C/005256
Procedure Number:	Not issued yet
Marketing Authorisation Holder(s):	Otsuka Pharmaceutical Netherlands B.V.
Joint Post-authorisation Safety Study (PASS):	No
Research Question and Objective(s):	This PASS will evaluate the long-term risks with use of voclosporin in lupus nephritis (LN) patients treated with voclosporin in the real-world setting in Europe, as per the approved Summary of Product Characteristics (SmPC), by assessing the incidence of the following safety events: neurotoxicity, chronic nephrotoxicity, and any malignancy.

Countries of Study:	The planned countries for study sites (patient recruitment) where voclosporin is available may include (but are not limited to): Germany, Italy, Spain, Sweden, Belgium, and the United Kingdom. Additional countries may be included to support patient recruitment where voclosporin is available.
Author:	PPD
European Union (EU) Qualified Person for Pharmacovigilance (QPPV):	PPD

Marketing Authorisation Holder

Marketing Authorisation Holder (MAH)	Otsuka Pharmaceutical Netherlands B.V. (OPNL) Herikerbergweg 292 1101 CT, Amsterdam Netherlands
MAH Contact Person	PPD

Signature Page

Declaration of Qualified Person Responsible for Pharmacovigilance (QPPV)
Title: An observational post-authorisation safety study (PASS) in Europe to further characterise and quantify long-term safety profile with respect to neurotoxicity, chronic nephrotoxicity, and malignancy with use of voclosporin.
This study protocol was subjected to critical review. The information it contains is consistent with the International Society for Pharmacoepidemiology Guidelines on Good Pharmacoepidemiology Practices.

_____ _____

PPD Date
Title: EU QPPV for Voclosporin study
Institution: Otsuka Pharmaceutical Netherlands B.V.

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List of In-text Tables

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2 List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ACE	Angiotensin-converting enzyme
ACR	American College of Rheumatology
AE	Adverse event
ALT	Alanine aminotransferase
Anti-dsDNA	Anti-double-stranded deoxyribonucleic acid
AST	Aspartate aminotransferase
AT	As-treated
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence interval
CNI	Calcineurin inhibitors
CRO	Contract research organisation
CsA	Cyclosporine A
CY	Cyclophosphamide
EC	Ethics committee
eCRFs	Electronic case report forms
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EULAR/ERA-EDTA	European League Against Rheumatism and European Renal Association–European, and Dialysis and Transplant Association
GPP	Good pharmacoepidemiology practices
HCQ	Hydroxychloroquine
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IR	Incidence rate
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
ITT	Intention-to-treat
LN	Lupus nephritis
MedDRA	Medical Dictionary for Regulatory Activities
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid
NI-PASS	Non-interventional post-authorisation safety study
OPC	Otsuka pharmaceutical co.
OPDC	Otsuka pharmaceutical development & commercialization, inc.
PASS	Post-authorisation safety study
PGA	Physician global assessment

PRES	Posterior Reversible Encephalopathy Syndrome
PYs	Person--years
Q	Quarter
RMP	Risk management plan
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SLE	Systemic lupus erythematosus
SLEDAI-2K	Systemic lupus erythematosus disease activity index 2000
SmPC	Summary of Product Characteristics
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UPCR	Urine protein creatinine ratio
US	United States or United States of America
WHO	World Health Organization

3 Responsible Parties

Table 3-1 Responsible Parties

	Contact Information
Otsuka Pharmaceutical Netherlands B.V. (OPNL)	Otsuka Pharmaceutical Netherlands B.V. (OPNL) Herikerbergweg 292 1101 CT, Amsterdam Netherlands
Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC)	Otsuka Pharmaceutical Development & Commercialization Inc. 2440 Research Blvd. Rockville, Maryland 20850 United States of America
Contract Research Organization (CRO)	To be confirmed

A list of all investigators will be provided in the study report or the publication.

4 Abstract

Protocol Title:	An observational post-authorisation safety study (PASS) in Europe to further characterise and quantify long-term safety profile with respect to neurotoxicity, chronic nephrotoxicity, and malignancy with use of voclosporin.
Study Type:	Non-interventional post-authorisation safety study (NI-PASS)
Indication:	Lupus Nephritis
Rationale and Background:	Lupus nephritis (LN) is a serious complication of systemic lupus erythematosus (SLE), a systemic autoimmune disease characterised by widespread deposition of immune complexes in affected tissues, including the kidney.[1] Around 10%-30% of those with LN will develop kidney failure requiring dialysis or kidney transplant, the presence of which has been associated with a 26-fold increase in mortality risk compared with a demographically matched general population.[2–6] The estimated prevalence of LN in Europe ranged from 0.44 to 1.4 per 10,000 persons.[7–9] The prevalence varies based on age, gender, and race, and such differences may drive the range observed in Europe. The current treatment approach for LN includes high dose of corticosteroids plus immunosuppressant such as mycophenolate mofetil (MMF), cyclophosphamide or azathioprine, and calcineurin inhibitors (CNIs) (in combination with MMF and corticosteroid) to achieve remission of LN. The recently published EULAR/ERA-EDTA guidelines (2019, joint guidelines of the European League Against Rheumatism and European Renal Association–European, and Dialysis and Transplant Association) refer to initial treatment with the above -mentioned regimen followed by maintenance therapy with less aggressive treatment regimen including MMF or azathioprine.[10] Since the disease is divided into different classes (I-VI), the treatment recommendations vary by LN class and biomarkers, leading to individualised, heterogeneous LN treatment patterns. Voclosporin is a novel CNI immunosuppressant. Calcineurin is a calcium/calmodulin-dependent phosphatase required for the induction of T-cell lymphokine production and proliferation. The immunosuppressant activity results in inhibition of lymphocyte proliferation, T-cell cytokine production, and expression of T-cell activation surface antigens.[11] Further, calcineurin inhibition stabilises podocytes and protects against proteinuria. Although, CNIs (including cyclosporine A [CsA], tacrolimus) other than voclosporin are not approved in the

	European Union (EU) and the United Kingdom for the treatment of LN, they are recommended in a subset of patients with LN, by the EULAR/ERA-EDTA guidelines.[10] In the EU, voclosporin is indicated in combination with MMF for the treatment of adult patients with active Class III, IV, or V (including mixed class III/V and IV/V) LN. The important potential risks of particular long-term safety interest according to the risk management plan (RMP) for voclosporin include malignancy, neurotoxicity, and nephrotoxicity (acute or chronic).[12] This EU PASS is part of a post-authorisation development plan aimed at monitoring the long-term safety of voclosporin (neurotoxicity, chronic nephrotoxicity and malignancy) in the European population within the framework of a comprehensive RMP. In addition to this study, the post-authorisation development plan includes a renal biopsy sub-study, which concluded there was no indication of CNI-induced nephrotoxicity occurring in subjects treated with voclosporin for approximately 18 months.[13]
Research Questions and Objective(s):	The study will evaluate the long-term risks with use of voclosporin in LN patients in the real-world setting when used in accordance with the approved EU Summary of Product Characteristics (SmPC),[a] by assessing the incidence of the following safety events: neurotoxicity, chronic nephrotoxicity, and any malignancy. Primary: • To describe the incidence rate (IR) of neurotoxicity in LN patients who initiated voclosporin treatment. • To describe the IR of chronic nephrotoxicity in LN patients who initiated voclosporin treatment. • To describe the IR of any malignancies in LN patients who initiated voclosporin treatment. Secondary: • To describe the incidence proportions of neurotoxicity, chronic nephrotoxicity, and any malignancies in LN patients who initiated voclosporin treatment.
Study Design:	This PASS is a multicentre, prospective, observational cohort study to assess the long-term safety of voclosporin in LN patients in Europe. The prospective study design with primary data collection enables collecting granular data on exposures, outcomes, and other variables, as available. The study is non-interventional, and all decisions on clinical management

[a] Voclosporin prescriptions in accordance with the EU SmPC as assessed by the physician.

of the patients are made by the physician as part of routine standard care and independent of participation in the study.

Adult patients with active LN, who initiated voclosporin in combination with MMF in accordance with the EU SmPC and are able to provide an informed consent will be included in the study. Initiation is defined as starting voclosporin in combination with newly or previously initiated MMF (may include other prescribed combinations concomitantly, e.g., corticosteroids) as the first LN drug, adding voclosporin to an existing LN therapy, or switching to voclosporin from an existing LN drug. Patients who initiated voclosporin within 120 days (4 months) of enrolment (new users) will be included in this PASS, while patients who were already treated with voclosporin (> 120 days) at the time of enrolment (prevalent users) are not included, meaning that the new-user design is applied in PASS.

The primary outcomes are neurotoxicity, chronic nephrotoxicity, and any malignancy. The study period is anticipated as 6-years which consists of an expected 4-year enrolment period, and a minimum of 2-year observation period for each patient enrolled. With the 2-year observation period, each patient has the possibility for at least 2 years of individual follow-up time, unless if they meet the censoring criteria earlier (withdrawal of consent by the patient, site withdrawal, lost to follow-up, death, enrolment in a clinical trial with an investigational drug, initiating another CNI, or initiating combination use deviating from the SmPC [eg, cyclophosphamide] during the follow-up, whichever occurs first).

The study period starts at the time of enrolment of the first patient into the study (first patient, first visit anticipated in second quarter [Q2] 2024) and ends when the observation period of the last enrolled patient is completed (last patient, last visit anticipated in Q2 2030). The index date (time zero, start of follow-up) will be the date of initiating voclosporin, which may occur within 120 days prior to enrolment. Patients will be followed during their individual follow-up time (Q2 2030), until withdrawal of consent by the patient, site withdrawal, lost to follow-up, death, enrolment in a clinical trial with an investigational drug, initiating another CNI, or initiating combination use deviating from the SmPC (eg, cyclophosphamide) during follow-up, whichever occurs first.

	The main analyses of the outcomes neurotoxicity, chronic nephrotoxicity, and any malignancies will be performed as as-treated (AT) analyses (where the patients are censored at the end of the risk window for the safety outcomes, defined as 30 days after the date of discontinuation of voclosporin treatment), and intention-to-treat (ITT) analyses approach (where patients will be followed regardless of voclosporin discontinuation). The IRs of the safety outcomes will be assessed during the patients' individual follow-up time. The outcomes neurotoxicity, chronic nephrotoxicity, and malignancy will be reported descriptively only, and no comparative analyses will be conducted. A progress report will be developed in Q4 2027 based on data received in Q2 2027 or earlier if 50% enrolment has been reached.
Population:	Adult LN patients with clinically active disease status who initiated voclosporin treatment in combination with MMF as per approved SmPC at the enrolment visit or within 120 days (4 months) before the enrolment visit, and who were able to provide an informed consent, will be included in the study. The MMF can be initiated prior to voclosporin, or at the same time with voclosporin initiation. Further, other prescribed combinations (eg, corticosteroids) are allowed concomitantly with voclosporin and MMF. Patients continue to be included in the study population even if the voclosporin treatment is discontinued or temporarily interrupted. For each patient, the index date (time zero; start of follow-up) will be the date of initiating voclosporin (indicated by date of prescription or date of treatment initiation as informed by patient, whichever is available), which may occur within 120 days (4 months) prior to enrolment. Patients will be recruited from sites (where voclosporin is available) in which LN patients are treated, including specialised secondary care and research centres specialised in treating LN patients. Prior to the inclusion of a patient in the study, a decision would be made by the patient and the treating physician to initiate treatment with commercially available voclosporin. <u>Inclusion criteria</u> • Male or female aged 18 years or older at the time of

	enrolment. • Clinically active LN at enrolment, as assessed by the physician. • Ability to understand and provide written informed consent at enrolment. • Initiation of voclosporin at the enrolment visit or within 120 days (4 months) before the enrolment visit, according to the approved EU SmPC in combination with newly or previously initiated MMF (may include other prescribed combinations concomitantly, eg, corticosteroids). Initiation is defined as starting voclosporin in combination with newly or previously initiated MMF (may include other prescribed combinations concomitantly, eg, corticosteroids) as the first LN drug, adding voclosporin to an existing LN therapy, or switching to voclosporin from an existing LN drug (including but not limited to mycophenolic acid [MPA], cyclophosphamide, azathioprine, CNIs [CsA, tacrolimus], hydroxychloroquine [HCQ], rituximab, and/or belimumab) Exclusion criteria • Participation in a clinical trial within 120 days (4 months) of enrolment. • Concurrent dosing with a medicinal product not currently approved in EU and the United Kingdom. • Concurrent dosing with any other CNIs (eg, tacrolimus, CsA). Patients who meet all of the inclusion and none of the exclusion criteria will form the study population.
Variables:	**Exposures:** Exposure to voclosporin will be assessed by the treating physician, at initiation of voclosporin at the enrolment visit or within 120 days (4 months) before the enrolment visit. Initiation is defined as starting voclosporin in combination with newly or previously initiated MMF (may include other prescribed combinations concomitantly, eg, corticosteroids) as the first LN drug, adding voclosporin to an existing LN therapy, or switching to voclosporin from an existing LN drug (including but not limited to MPA, cyclophosphamide, azathioprine, CNIs [CsA, tacrolimus], HCQ, rituximab, and/or belimumab). **Outcomes:** **Neurotoxicity**, defined as occurrence of neurological adverse events (AEs) that are related to voclosporin as reported by the

physician. The neurotoxicity events include, but are not limited to, headache, tremor, dizziness, neuralgia, migraine, paraesthesia, hypoesthesia, seizure, tension headache, disturbance in attention, and posterior reversible encephalopathy syndrome (PRES, characterised by headache, seizures, altered mental status, visual loss). Investigations, such as neuroimaging or neurophysiological examination, conducted for the management of an AE are obtained based on healthcare provider discretion. The findings pertaining to investigations can be part of AE reporting and are routinely considered when assessing causality between drug and AE.
Chronic nephrotoxicity should be assessed when there is a decline in estimated glomerular filtration rate (eGFR) from baseline to below 60 mL/min/1.73m^2 and the decline is > 10% per year, and sustained for more than 3 months. Clinical judgement will be used as applicable to ensure the differentiation between the presentation of acute and chronic nephrotoxicity. This includes an assessment of attribution of decline in kidney function to primary LN disease progression.
Any malignancy, encompassing all malignancies.

Other variables:
All the variables listed would be collected, as available, from the patient's medical records. Being a non-interventional study, there are no mandatory requirements or collection time-points for variables. The potential data elements include:

- **Demographic and medical characteristics**
  - Demographic characteristics
  - Lifestyle factors
  - Body weight, height, and body mass index (BMI)
  - All prior comorbidities (diagnoses)
  - Relevant procedures and surgeries
  - Pregnancy status
  - Physical examination and vital signs
  - History of the safety outcomes
- **SLE and LN characteristics**
  - Diagnosis date of SLE
  - LN disease onset
  - Date of onset of LN symptoms
  - Date of LN diagnosis
  - Recording of indication characteristics
  - Disease related signs and symptoms (American College of Rheumatology [ACR])[14]

- Disease activity indices (Systemic Lupus Erythematosus Disease Activity Index 2000 [SLEDAI-2K][15], Physician Global Assessment [PGA][16])

- **Medications**
  - History of all available previous LN treatments and any medications other than LN treatment. Medications before initiation of voclosporin will be included regardless of discontinuation at the start or during voclosporin use
  - Concomitant and new LN medications, this includes concomitant treatments with voclosporin, add on treatments during voclosporin treatment, and switching voclosporin treatment to another LN treatment
  - Any other concomitant and new medications other than LN treatments, including those for SLE
  - History of and concomitant vaccinations
- **Laboratory assessments**
  - Haematology, renal, liver assessments
  - Kidney biopsy
  - Inflammatory biomarkers
- **Adverse events**
  - AEs and serious adverse events (SAEs), including drug-drug interactions between voclosporin and vaccines, clinically significant laboratory values

Prior and concomitant medications will be coded for analysis using the latest version of the World Health Organization (WHO) Drug dictionary, the Anatomical Therapeutic Chemical (ATC) codes. Diagnoses/comorbidities will be coded for analysis using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA®).

Censoring variables:
Censoring criteria, include withdrawal of consent by patient, site withdrawal, lost to follow-up, death, enrolment in a clinical trial with an investigational drug during the follow-up, initiating another CNI, or initiating combination use deviating from the SmPC (eg, cyclophosphamide) during the follow-up.

In the analysis of each respective outcome, patients are also censored, during the follow-up, at the occurrence of the outcome of interest. The censoring will be outcome specific, eg, in the analysis of neurotoxicity, patients are censored when

	neurotoxicity is observed, while for the analysis of malignancy the follow-up continues. In the AT analyses patients are also to be censored at the end of the risk window for the safety outcomes.
Data Sources:	Data will be collected from sites (where voclosporin is available) in which LN patients are treated, including specialised secondary care and research centres specialised in treating LN patients. Site personnel will record all data for each study patient as described in this protocol, from the patient's medical records, through electronic case report forms (eCRFs) using an electronic data capture (EDC) system provided and approved by the Sponsor. Once written informed consent has been obtained, study site personnel will complete and enter the baseline data collection for each patient into the EDC system.
Data Collection Method (if applicable):	Using the eCRFs, site personnel will collect data from the patients' medical records. The collected data will be available in the patients' medical records as part of normal clinical practice, and all patient visits will be conducted according to the treating physician's normal clinical practice. Thus, this study does not include mandatory visits, tests, or assessments and if data is not available, it will not be solicited. Data will be collected at the time of each patient visit according to routine care, without specific data collection time points.
Study Size:	The planned number of patients to be included in this PASS is approximately 300 patients initiating voclosporin treatment.
Data Analysis:	The analyses to address the study objectives will be performed in the study population. All analyses will be descriptive. For the primary objectives, the IRs per 1000 person-years (PYs) (with 95% confidence intervals [CIs]) for the outcomes will be calculated. The main analyses for the outcomes neurotoxicity, chronic nephrotoxicity, and any malignancies will be performed as AT analyses (where patients are censored at the end of the risk window for the safety outcomes, defined as of 30 days after the date of discontinuation of voclosporin) and ITT analyses approach (where patients will be followed regardless of discontinuation of voclosporin).
Study Duration:	The study period is anticipated as 6 years, consisting of an expected 4-year enrolment period, and a minimum of 2-year observation period for each patient.
Study Sites	The planned countries for study sites (patient recruitment) where voclosporin is available may include (but are not limited to): Germany, Italy, Spain, Sweden, Belgium, and the United Kingdom. Additional countries may be included to support patient recruitment where voclosporin is available.
Milestones:	

	Milestone	Planned Date
	Registration in the EU PASS Register	Q1 2024
	Start of data collection	Q2 2024
	End of data collection for progress report	Q2 2027 or earlier if 50% enrolment has been reached
	Progress report	Q4 2027
	End of data collection	Q2 2030
	Final report of study results	Q4 2030

5 Amendments and Updates

Initial Protocol: 21 Mar 2023

Protocol Amendment 1: 08 Aug 2023

6 Milestones

Milestone	Planned Date
Registration in the EU PASS Register	Q1 2024
Start of data collection	Q2 2024
End of data collection for progress report	Q2 2027 or earlier if 50% enrolment has been reached
Progress report	Q4 2027
End of data collection	Q2 2030
Final report of study results	Q4 2030

Abbreviations: EU: European Union; PASS: post-authorisation safety study; Q: quarter

7 Rationale and Background

Lupus nephritis (LN) is a serious complication of systemic lupus erythematosus (SLE), a systemic autoimmune disease characterised by widespread deposition of immune complexes in affected tissues, including the kidney.[1] Around 10%-30% of those with LN will develop kidney failure requiring dialysis or kidney transplant, the presence of which has been associated with a 26-fold increase in mortality risk compared with a demographically matched general population.[2–6] The estimated prevalence of LN in Europe ranged from 0.44 to 1.4 per 10,000 persons.[7–9] The prevalence varies based on age, gender, and race, and such difference may drive the range observed in Europe. Proteinuria is the defining aspect of LN and indicates damage to the kidney; if not resolved, this damage becomes permanent. A rapid reduction in proteinuria has been well-correlated with improving long-term outcomes (progression to end stage renal disease [ESRD]/dialysis/transplant), therefore, an important goal of treatment in LN.[10]

Treatment of LN is based, in large part, on the classification of LN (classes I-VI). The proliferative classes (III and IV) require aggressive treatment with corticosteroids and immunosuppressive agents. First-line treatment of Class V (membranous LN) is similar to classes III/IV. The current treatment approach for LN includes high dose of corticosteroids plus immunosuppressant such as mycophenolate mofetil (MMF), cyclophosphamide or azathioprine, and calcineurin inhibitors (CNIs) (in combination with MMF and corticosteroid) to achieve remission of LN. The recently published EULAR/ERA-EDTA guidelines (2019, joint guidelines of the European League Against Rheumatism and European Renal Association–European, and Dialysis and Transplant Association) refer to initial treatment with the above-mentioned regimen followed by maintenance therapy with less aggressive treatment regimen including MMF or azathioprine.[10] Since the disease is divided into different classes (I-VI), the treatment recommendations vary by LN class and biomarkers, leading to individualised, heterogeneous LN treatment patterns.

Voclosporin is a novel CNI which is structurally similar to cyclosporine A, except for the modification of a functional group on amino acid-1 of the molecule.[17] This alteration enhances the binding of voclosporin to calcineurin and has been shown in both in vitro and in vivo animal studies to increase the potency by two- to five-fold compared to cyclosporine A (CsA).[17,18] Calcineurin is a calcium/calmodulin-dependent phosphatase required for the induction of T-cell lymphokine production and proliferation. The immunosuppressant activity results in inhibition of lymphocyte proliferation, T-cell cytokine production, and expression of T-cell activation surface antigens.[11] Further, the inhibition of calcineurin stabilises podocytes and reduces proteinuria via multiple

mechanisms. Although, CNIs (including CsA, tacrolimus) other than voclosporin are not approved in the European Union (EU) and the United Kingdom for the treatment of LN, they are recommended in a subset of patients with LN, by the EULAR/ERA-EDTA guidelines.[10]

In the EU, voclosporin is indicated in combination with MMF for the treatment of adult patients with active Class III, IV, or V (including mixed Class III/V and IV/V) LN. The important potential risks of particular long-term safety interest according to risk management plan (RMP) for voclosporin include malignancy, neurotoxicity, and nephrotoxicity (acute or chronic).[12] This EU post-authorisation safety study (PASS) is part of a post-authorisation development plan aimed at monitoring the long-term safety of voclosporin (especially neurotoxicity, chronic nephrotoxicity, and malignancy) in the European population within the framework of a comprehensive RMP. In addition to this study, the post-authorisation development plan includes a separate renal biopsy sub-study, which concluded there was no indication of CNI-induced nephrotoxicity occurring in subjects treated with voclosporin for approximately 18 months.[13]

8 Research Question and Objectives

This PASS will evaluate the long-term risks with use of voclosporin in LN patients in the real-world setting when used in accordance with the approved EU Summary of Product Characteristics (SmPC),[a] by assessing the incidence of the following safety events: neurotoxicity, chronic nephrotoxicity, and any malignancy.

8.1 Primary Objective

- To describe the incidence rate (IR) of neurotoxicity in LN patients who initiated voclosporin treatment.
- To describe the IR of chronic nephrotoxicity in LN patients who initiated voclosporin treatment.
- To describe the IR of any malignancies in LN patients who initiated voclosporin treatment.

8.2 Secondary Objective

- To describe the incidence proportions of neurotoxicity, chronic nephrotoxicity, and any malignancies in LN patients who initiated voclosporin treatment.

9 Research Methods

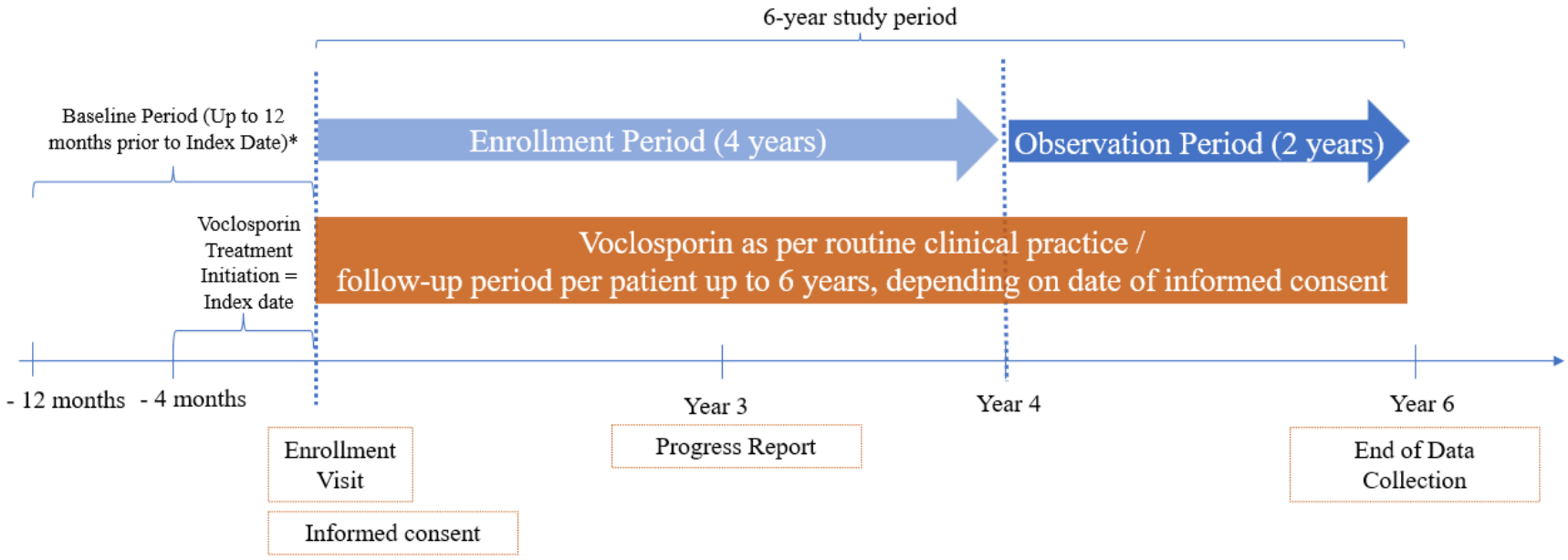
9.1 Study Design

This PASS is a multicentre, prospective, observational cohort study to assess the long-term safety of voclosporin in LN patients in Europe. The prospective study design with primary data collection enables collecting granular data on exposures, outcomes, and other variables, as available. The study is non-interventional, and all decisions on the clinical management of the patients are made by the physician as part of routine standard care and independent of participation in the study.

Adult patients with active LN, who initiated voclosporin in combination with MMF in accordance with the EU SmPC and are able to provide an informed consent will be included in the study. Patients who initiated voclosporin within 120 days (4 months) of enrolment (new users) will be included in this PASS, while patients who were already treated with voclosporin (> 120 days) at the time of enrolment (prevalent users) are not included, meaning that the new-user design is applied in PASS. Prevalent users are defined as patients who initiated voclosporin for more than 4 months (>120 days) at the time of enrolment.

The primary outcomes are neurotoxicity, chronic nephrotoxicity, and any malignancy. The study period is anticipated to be 6 years, which consists of an expected 4-year enrolment period, and a 2-year observation period (Figure 9.1.1-1). With the 2-year observation period, each patient has the possibility for at least 2 years of individual follow-up time, unless if they meet the censoring criteria earlier (withdrawal of consent by patient, site withdrawal, lost to follow-up, death, enrolment in a clinical trial with an investigational drug, initiating another CNI, or initiating combination use deviating from the SmPC (eg, cyclophosphamide) during the follow-up, whichever occurs first). In the main as-treated (AT) analyses, the follow-up of patients will be restricted to the end of the risk window for the safety outcomes, defined as 30 days after the date of discontinuation of voclosporin treatment. Additionally, all outcomes will be assessed using the intention-to-treat (ITT) approach, as main analyses.

The IRs of the safety outcomes will be assessed during the patients' individual follow-up time. The outcomes neurotoxicity, chronic nephrotoxicity, and malignancy will be reported descriptively only, and no comparative analyses will be conducted.



*The Baseline Period varies for different variables and is extended from 12 months for some *Other* variables, as detailed in Section 9.3.3

Figure 9.1.1-1 Summary of Study Periods, at Study-Level

9.1.1 Study Endpoints

9.1.1.1 Primary Endpoints

- IR of neurotoxicity in LN patients who initiated voclosporin treatment.
- IR of chronic nephrotoxicity in LN patients who initiated voclosporin treatment.
- IR of any malignancies in LN patients who initiated voclosporin treatment.

9.1.1.2 Secondary Endpoints

- Incidence proportions of neurotoxicity, chronic nephrotoxicity, and any malignancies in LN patients who initiated voclosporin treatment.

9.1.1.3 Exploratory Endpoint

No exploratory endpoints.

9.1.2 Rationale for the Study Design

The observational, non-interventional nature of this PASS enables investigating long--term safety outcomes in real-world settings. The prospective design utilising primary data collection offers the opportunity to collect a broad range of clinically relevant data on exposures, outcomes, and other variables and to define and utilise uniform data collection and validation methods across the participating sites. The new users design, including exclusively initiators of voclosporin, was chosen to mitigate bias associated with including prevalent users. Specifically, the healthy user bias ('depletion of susceptibles') can be avoided by including exclusively new users. Including prevalent users would lead to overseeing adverse events (AEs) in the beginning of voclosporin treatment, because prevalent users are survivors of earlier adverse outcomes and thereby later during their use have a decreased risk of the safety outcomes.[19]

This study focuses on voclosporin and is descriptive by design. As outlined in the approved RMP for Lupkynis (voclosporin), this EU PASS aims to further characterise and quantify the long-term risk of neurotoxicity, chronic nephrotoxicity, and malignancies among LN patients treated with Lupkynis in the post-marketing setting. Voclosporin demonstrated an acceptable benefit-risk profile during exposure over a 3-year treatment period in placebo-controlled clinical trials.[20] However, for CNIs, class effects have been described concerning the occurrence of neurotoxicity, chronic nephrotoxicity, and malignancies.[21–26] This observational PASS will add long-term safety data from an additional 300 participants to safety data from placebo-controlled trials that enrolled a total of 267 voclosporin-exposed participants.[20] The study protocol of this PASS is written enabling comprehensive collection of data on exposures, safety

outcomes, and other variables. The study design enables calculating IRs quantitatively, and additionally characterising risks (if any) qualitatively.

9.2 Setting

In this prospective study utilising primary data collection, patients will be recruited from sites in which LN patients are treated, including specialised secondary care and research centres specialised in treating LN patients. The planned countries for study sites (patient recruitment) where voclosporin is available may include (but are not limited to): Germany, Italy, Spain, Sweden, Belgium, and the United Kingdom. Additional countries maybe included to support patient recruitment where voclosporin is available.

9.2.1 Study Period

The study period starts at the time of enrolment of the first patient into the study (first patient, first visit anticipated in second quarter [Q2] 2024), and ends when the observation period of the last enrolled patient is completed (last patient, last visit anticipated in Q2 2030) (Figure 9.1.1-1). For each patient, the index date (time zero; start of follow-up) will be the date of initiating voclosporin (indicated by date of prescription or date of treatment initiation as informed by the patient, whichever is available), which may occur within 120 days (4 months) prior to enrolment. Patients will be followed during their individual follow-up time from the index date until end of the observation period (Q2 2030), until withdrawal of consent by the patient, site withdrawal, lost to follow-up, death, enrolment in a clinical trial with an investigational drug, initiating another CNI, or initiating combination use deviating from the SmPC (eg, cyclophosphamide) during the follow-up, whichever occurs first (Figure 9.2.1-1).

The safety outcomes neurotoxicity, chronic nephrotoxicity, and any malignancies will be collected during the individual follow-up.

Baseline data will be collected for varying periods (ie, demographic characteristics at index date, body weight, body mass index [BMI], lifestyle factors, laboratory assessments within 3 months prior to and at index date, prior comorbidities, disease severity within 12 months prior to and at index date, disease characteristics at any time available, etc.), as detailed in Figure 9.2.1-1 and further in Section 9.3.3.

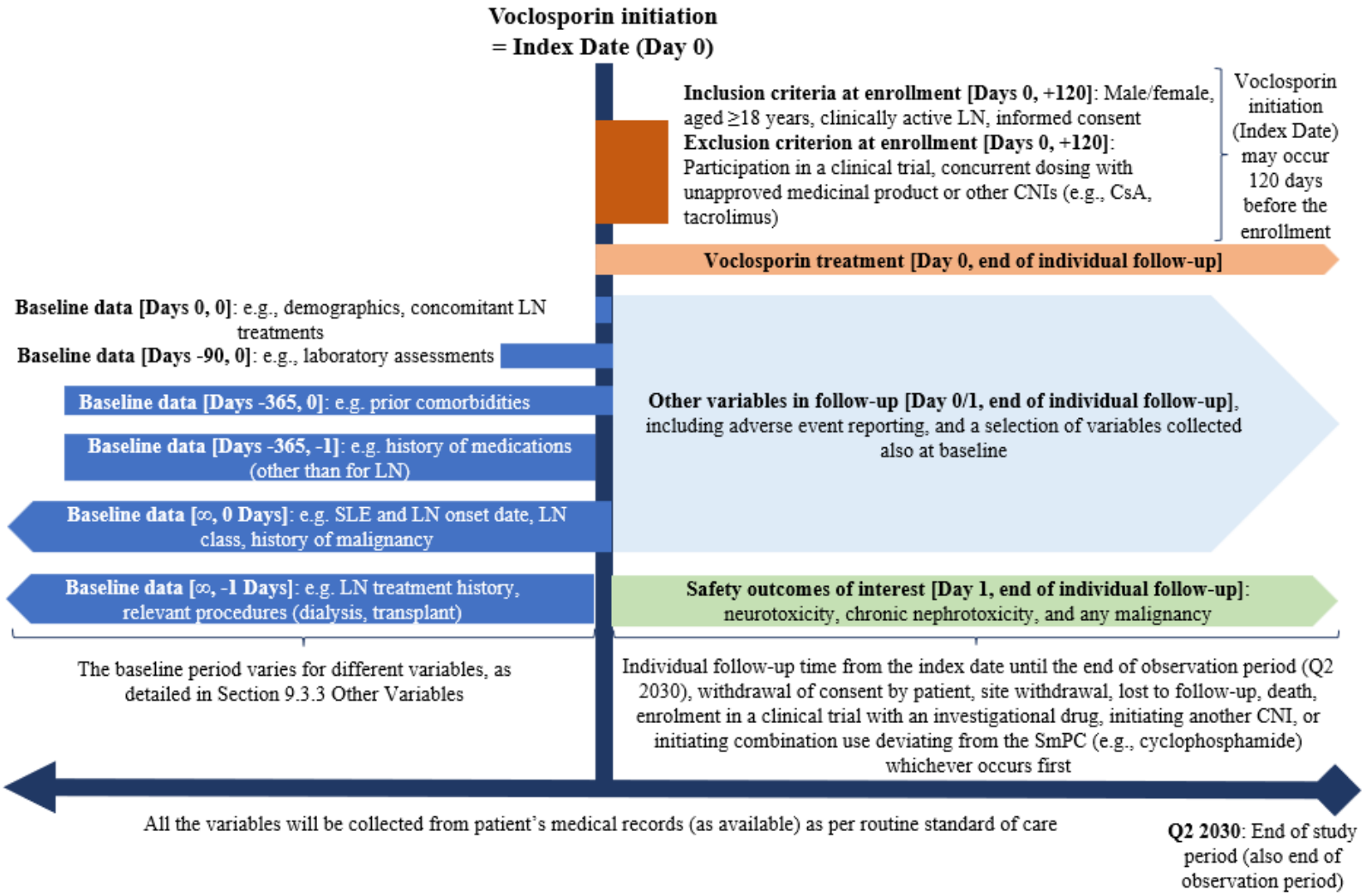


Figure 9.2.1-1 Detailed Study Periods, at Individual-Level

In the analysis of each respective outcome, patients are also censored at the occurrence of the outcome of interest. The censoring will be outcome specific, eg, in the analysis of neurotoxicity, patients are censored when neurotoxicity (any symptom included in the outcome definition) is observed, while for the analysis of malignancy the follow-up continues. The censoring is outcome specific, because after experiencing a specific outcome (eg, neurotoxicity) for the first time, the same patient is no longer at risk of developing the same outcome as an incident (new) event. However, after experiencing an incident neurotoxicity outcome, the same patient is still at risk of developing another incident outcome (eg, chronic nephrotoxicity or malignancy). In the AT analyses, patients are also to be censored at the end of the risk window for the safety outcomes, defined as 30 days after the date of discontinuation of voclosporin treatment.

Being an initiator (new-user) of voclosporin will be defined by the treating physician using all available patient history available for the physician, which was considered more robust than providing a specific time period when patients would not be allowed to have prior voclosporin (ie, washout window).

9.2.2 Study Population

The source population from which patients are included to this PASS are LN patients treated in the sites of the countries of interest (where voclosporin is available). The sites include specialised secondary care and research centres specialised in treating LN patients.

Prior to inclusion in the study, a decision would be made by the patient and the treating physician to initiate treatment with commercially available voclosporin. Adult LN patients with clinically active disease status who initiated voclosporin treatment in combination with MMF, as per approved SmPC at the enrolment visit or within 120 days (4 months) before the enrolment visit, and who were able to provide an informed consent, will be included in the study. The MMF can be initiated prior to voclosporin, or at the same time with voclosporin initiation. Further, other prescribed combinations (eg, corticosteroids) are allowed concomitantly with voclosporin and MMF. Patients continue to be included in the study population even if the voclosporin treatment is discontinued or temporarily interrupted (see definitions in Section 9.3.1). Patients are not allowed to re-enter the study population after meeting any of the following censoring criteria: withdrawal of consent by the patient, site withdrawal, lost to follow-up, enrolment in a clinical trial with an investigational drug during follow-up, initiating another CNI, or initiating combination use deviating from the SmPC (eg, cyclophosphamide) during the follow-up.

9.2.2.1 Inclusion Criteria

Patients in the participating sites are required to meet the following inclusion criteria.

Table 9.2.2-1	Inclusion Criteria
1	Male or female aged 18 years or older at the time of enrolment.
2	Clinically active LN at enrolment, as assessed by the physician.
3	Ability to understand and provide written informed consent at enrolment.
4	Initiation of voclosporin at the enrolment visit or within 120 days (4 months) before the enrolment visit, when used in accordance with the approved EU SmPC,[a] in combination with newly or previously initiated MMF (may include other prescribed combinations concomitantly, eg corticosteroids). Initiation is defined as starting voclosporin in combination with newly or previously initiated MMF (may include other prescribed combinations, eg corticosteroids) as the first LN drug, adding voclosporin to an existing LN therapy, or switching to voclosporin from an existing LN drug (including but not limited to MPA, cyclophosphamide, azathioprine, CNIs [CsA, tacrolimus], HCQ, rituximab, and/or belimumab).[b]

Abbreviations: CNIs: calcineurin inhibitors; CsA: cyclosporine A; EU: European Union; HCQ: hydroxychloroquine; LN: lupus nephritis; MMF: mycophenolate mofetil; MPA: mycophenolic acid; SmPC: Summary of Product Characteristics.

[a]Voclosporin prescriptions in accordance with the EU SmPC as assessed by the physician.

[b]The definition of voclosporin initiation is further detailed in Section 9.3.1.

9.2.2.2 Exclusion Criteria

Patients in the participating sites will be excluded if they fall under the following exclusion criterion.

Table 9.2.2-2	Exclusion Criteria
1	Participation in a clinical trial within 120 days (4 months) of enrolment
2	Concurrent dosing with a medicinal product not currently approved in EU and the United Kingdom
3	Concurrent dosing with any other CNIs (eg, tacrolimus, CsA)

Abbreviations: CNIs: calcineurin inhibitors; CsA: cyclosporine A; EU: European Union

9.2.3 Study Participation

Each enrolled patient will be followed from the start of follow-up (time zero; date of initiating voclosporin) until any of the following censoring criteria, whichever occurs first:

- End of the observation period and maximum follow-up (Q2 2030)
- Withdrawal of consent by patient for study participation (see Section 9.2.3.2)
- Site withdrawal, ie, discontinuation of participation in the study
- Lost to follow-up (see definition in Section 9.2.3.4)
- Death

- Patient enrolment in a clinical trial with an investigational drug during the follow-up. Investigational drug applies to any drug when used within (low intervention trial) or outside the terms of their marketing authorisation
- Initiating another CNI during the follow-up
- Initiating combination use deviating from the SmPC (eg, cyclophosphamide) during the follow-up

In the analysis of each respective outcome, patients are also censored at the occurrence of the outcome of interest. In the AT analyses, patients are also to be censored at the end of the risk window for the safety outcomes, which is defined as 30 days after the date of discontinuation of voclosporin treatment.

9.2.3.1 Enrolment Log

Sites will be required to complete a patient enrolment log of eligible patients at their treatment centres. Along with patients who are enrolled, this log will document why eligible patients are not included in the study, in order to assess the representativeness of the study population. Minimal, non-identifiable information will be recorded for all patients who are screened for study enrolment, but no patient-identifiable information will be recorded.

Patients will be identified only by unique patient numbers in electronic case report forms (eCRFs). Enrolment in the study is voluntary.

9.2.3.2 Discontinuation/Withdrawal Criteria

As this is a non-interventional study to collect data, no specific withdrawal criteria are specified. Patients are free to withdraw consent at any time. Patients can be withdrawn at the request of the patient, investigator, Sponsor or designee, or regulatory authority. Data will be collected up to the time of withdrawal of consent and no additional information will be collected after that time. The reason for withdrawal will be recorded in the eCRF.

The patient is free to discontinue the treatment without any prejudice. If a patient discontinues treatment with voclosporin but does not withdraw consent to participate in the study, data will continue to be recorded until end of the observation period which is also the end of the study period. The investigator can discontinue a patient's participation in the study at any time, if medically necessary. In case of occurrence of any intercurrent illness or abnormality in a laboratory assessment which, in the opinion of the investigator, warrants discontinuation of voclosporin treatment, the patient will continue in the study for data collection. In the event of discontinuation of voclosporin, physician can any time resume voclosporin treatment, if deemed appropriate as therapeutic option as per routine care. During the data collection until the end of the observation/study period, data on possible restart of voclosporin after discontinuation will also be collected

(see Section 9.3.1), as well as data on concomitant and new LN treatments (see Section 9.3.3).

9.2.3.3 Early Study Termination

The Sponsor may terminate this study early after consultation with the relevant regulatory authorities, if the study becomes futile (eg, if there is insufficient patient enrolment despite implementation of all reasonable measures to improve enrolment, including the use of additional sites and additional European countries), or if new relevant safety information emerges while the study is being conducted that negatively affects the benefit-risk balance of voclosporin.

If the Sponsor terminates or suspends the study for safety or unanticipated other reasons, prompt notification will be given to investigators, Institutional Review Board (IRB) or Independent Ethics Committee (IEC), and regulatory authorities in accordance with regulatory requirements. The Sponsor should be notified promptly if the study is terminated by the investigator or the IRB/IEC at the site.

9.2.3.4 Definition of Lost to Follow-up

As confirmed by the treating physician, patient will be considered lost to follow-up if no new data have been received or logged into source documents by the participating site for over 12 months and attempts to contact the patient and/or secondary contacts have been exhausted.

In the event a patient becomes lost to follow-up, the last data collection date will be considered the censoring date.

9.2.4 Summary of Potential Data Elements

The potential data elements planned to be collected are summarised in Table 9.2.4-1, and further detailed in Section 9.2.2 and Section 9.3.

Table 9.2.4-1 Potential Data Elements

Potential Data Elements (as available)		
	Enrolment/Baseline	**Follow-up (as available) Data Recorded at Each Routine Visit**
Informed consent	X	
Inclusion/exclusion criteria	X	
Voclosporin treatment	X	X
Demographic and medical characteristics		
Demography	X	
Height, weight, BMI	X	
Lifestyle factors: alcohol, tobacco, recreational drug use	X	
All prior comorbidities (diagnoses)	X	
Relevant procedures: renal dialysis, kidney transplant	X	X
Pregnancy status	X	
Physical examination and vital signs	X	X
History of safety outcomes	X	
SLE and LN characteristics		
Date of SLE diagnosis and LN onset, LN onset symptoms	X	
Recording of indication characteristics	X	X
ACR criteria, disease activity indices (SLEDAI-2K, PGA)	X	X
Medications		
LN treatment history including dose and reasons for dose changes, history of any other medications than LN treatments	X	
Concomitant and new LN treatments, any other concomitant and new medications than LN treatments	X	X
History of and concomitant vaccinations	X	X
Laboratory assessments: haematology, renal, liver, kidney biopsy, inflammatory biomarkers	X	X
Outcomes: Safety outcomes of interest		X
Adverse events: AE/SAEs reporting	X	
Censoring variables		X

Abbreviations: ACR: American college of Rheumatology; AE: adverse events; BMI: body mass index; LN: lupus nephritis; PGA: physician global assessment; SAE: serious adverse event; SLE: systemic lupus erythematosus; SLEDAI-2K: systemic lupus erythematosus disease activity index 2000

A detailed description of variables is provided in Section 9.3.

9.3 Variables

9.3.1 Exposure

Exposure to voclosporin will be assessed by the treating physician, as initiation of voclosporin at the enrolment visit or within 120 days (4 months) before the enrolment visit. Initiation is defined as starting voclosporin in combination with newly or previously initiated MMF, with:

- Voclosporin as the first LN drug, in combination with MMF as initiated for the first time.

  OR
- Adding voclosporin to an existing LN therapy, in combination with newly or previously initiated MMF. The existing LN therapies that voclosporin can be added to include all prescribed combinations, except for:
  - Other CNIs, as per exclusion criterion 3 (Section 9.2.3).
  - Cyclophosphamide, as per inclusion criterion 4 on use according to the SmPC (Section 9.2.3), as the safety and efficacy of voclosporin have not been established in combination with cyclophosphamide.[11]

  OR
- Switching to voclosporin (in combination with newly or previously initiated MMF) from any existing LN treatment regimen.

Being an initiator (new-user) of voclosporin will be defined by the treating physician using all available patient history available for the physician, which was considered more robust than providing a specific time period when patients would not be allowed to have prior voclosporin (ie, washout window). The specialised physicians treating LN patients are anticipated to know whether a patient has been previously treated with voclosporin. Thereby, the initiators of voclosporin are anticipated to be treatment-naïve.

The start date for voclosporin initiation (index date) will be collected from the medical records of the enrolled patients participating sites. The dose of voclosporin will also be collected from the medical records, both at treatment initiation and during follow-up (dose changes, reasons), to describe the intensity of voclosporin exposure. Further, data on temporary interruptions (dates, reasons) in voclosporin treatment will be collected from the medical records, as temporary interruptions are expected to occur as per the SmPC.[20] A temporary interruption will not qualify as a discontinuation, and thereby a patient will be considered exposed to voclosporin during the temporary interruption (applicable for the AT analysis). A temporary interruption and a discontinuation will be distinguished as per the treating physician's judgement.

Discontinuation of voclosporin (stop dates; reasons for discontinuation) will be collected from the medical records during the follow-up, which will allow considering the duration of exposure. In the AT analyses, the follow-up of patients will be restricted to the end of the risk window for the safety outcomes, defined as 30 days after the date of discontinuation of voclosporin treatment. In the ITT analyses, patients will be considered at risk until end of follow-up or censoring, whichever occurs first.

Possible restart of voclosporin after discontinuation will also be collected during the follow-up of each patient. The restarters will not, by definition, be treatment-naïve.

9.3.2 Outcome Variables

The outcomes of this PASS will be collected from the medical records of the enrolled patients in the participating sites during the follow-up. All outcome dates will be recorded. The outcomes neurotoxicity and malignancy will be coded for analysis using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA®).

Neurotoxicity: Neurotoxicity is defined as occurrence of neurological AEs that are related to voclosporin as reported by the physician. The neurotoxicity events include but are not limited to, headache, tremor, dizziness, neuralgia, migraine, paraesthesia, hypoesthesia, seizure, tension headache, disturbance in attention, and posterior reversible encephalopathy syndrome (PRES, characterised by headache, seizures, altered mental status, visual loss). Investigations, such as neuroimaging or neurophysiological examination, conducted for the management of an AE are obtained based on healthcare provider discretion. The findings pertaining to investigations can be part of AE reporting and are routinely considered when assessing causality between drug and AE.

Chronic nephrotoxicity: Chronic nephrotoxicity should be assessed when there is a decline in estimated glomerular filtration rate (eGFR) from baseline to below 60 mL/min/1.73m^2 and the decline is > 10% per year, and sustained for more than 3 months.[27,28]

Clinical judgement will be used as applicable to ensure the differentiation between the presentation of acute and chronic nephrotoxicity. This includes an assessment of attribution of decline in kidney function to primary LN disease progression.

Malignancy: Any malignancy, encompassing all malignancies.

The outcome definitions were developed in collaboration with clinicians, considering clinical practice, treatment guidelines, and outcome definitions typically used in interventional and observational studies.

9.3.3 Other Variables

Other variables detailed in Table 9.3.3-1 will be collected (as available) at baseline and during follow-up, as recorded in medical records during the visits as per routine care.

Table 9.3.3-1 Other Variables

Variables	Time period for data collection, at baseline	Collection at follow-up
Demographic and Medical Characteristics		
Demographic characteristics (sex, age, self-reported race/ethnicity [if allowed], and geographic location)	At index date (or closest before)	No
Body weight, height, and BMI	Within 90 days prior to and at index date, recording values closest to the index date	No
Lifestyle factors (use of alcohol, tobacco, and recreational drugs, if allowed)	Within 90 days prior to and at index date, recording values closest to the index date	No
All prior comorbidities (diagnoses), including immunodeficiency, renal disease, diabetes, neurological disorders (eg, chronic headache, migraine, spinal cord disease, seizures), hypertension, stroke, mood and anxiety disorders, infections, and malignancies (eg, non-Hodgkin lymphoma and Hodgkin lymphoma, myeloma and liver, cervical, lung, bladder, thyroid, stomach and brain malignancies)	Within 12 months (365 days) prior to and at index date, recording all comorbidities	No
Relevant procedures: renal dialysis, kidney transplant	At any time available in data prior to index date, excluding index date (as long back in time as available), recording all periods of dialysis and all transplants	Yes
Pregnancy status	At index date	No
Physical examination (assessment of general appearance, cardiovascular, respiratory, gastrointestinal and neurological systems followed by a targeted physical assessment [if needed]) and vital signs (body temperature, pulse rate, blood pressure, and respiratory rate)	Within 90 days prior to and at index date, using values closest to the index date	Yes
History of safety outcomes: neurotoxicity, chronic nephrotoxicity, and malignancy	Neurotoxicity and chronic nephrotoxicity: Within 12 months (365 days) prior to and at index date, all recorded events Malignancy: At any time available in data prior to index date, excluding index date (as long back in time as available), recording all diagnoses	No
SLE and LN characteristics		
Date of SLE diagnosis	At any time available in data prior to index date or at index date (as long back in time as available), recording the first diagnosis date	No

Table 9.3.3-1 Other Variables		
Variables	**Time period for data collection, at baseline**	**Collection at follow-up**
LN onset: Date of onset of LN symptoms, date of LN diagnosis	At any time available in data prior to index date or at index date (as long back in time as available), recording the first onset/diagnosis date	No
Recording of indication characteristics in medical records, including LN class III, IV or V [including mixed class III/V and IV/V], clinically active LN, eGFR < 45 mL/min/1.73m^2)	LN class and clinically active LN: At any time available in data prior to or at index date (as long back in time as available), recording values closest to the index date eGFR: Within 90 days prior to and at index date, recording values closest to the index date	Yes
Disease related signs and symptoms (ACR criteria)[14]	Within 12 months (365 days) prior to index date and at index date, recording values closest to the index date	Yes
Disease activity indices (SLEDAI-2K[15], PGA[16])	Within 12 months (365 days) prior to index date and at index date, recording values closest to the index date	Yes
Medications		
LN treatment history, including dose and reasons for dose changes: all available previous LN treatments including but not limited to corticosteroids, MMF, MPA, cyclophosphamide, azathioprine, CNIs (CsA, tacrolimus), HCQ, rituximab, and/or belimumab. Medications before initiation of voclosporin will be included regardless of discontinuation at the start or during voclosporin use	At any time available in data prior to index date, excluding index date (as long back in time as available), recording all LN treatments	No
History of any medications other than LN treatments: including those for SLE (including antimalarials [dosage and route of administration], ACE inhibitors, angiotensin receptor blockers, anticoagulants, non-steroidal anti-inflammatories, antibiotics, corticosteroids, immunosuppressants, antineoplastic agents, hormonal therapy, nervous system drugs [eg, antiepileptics, opioids], antidiabetics, and CYP3A4 inhibitors and inducers)	Within 12 months (365 days) prior to index date, excluding index date, recording all medications	No
Concomitant and new LN treatments (including doses): including but not limited to corticosteroids, MMF, MPA, azathioprine, HCQ, rituximab, and/or belimumab. This includes concomitant treatments with voclosporin, add on treatments during voclosporin treatment, and switching voclosporin treatment to another LN treatment	At index date, recording all LN treatments	Yes
Any other concomitant and new medications other than LN treatments: including those for SLE (including antimalarials [dosage and route	At index date, recording all medications	Yes

Table 9.3.3-1 Other Variables		
Variables	**Time period for data collection, at baseline**	**Collection at follow-up**
of administration], ACE inhibitors, angiotensin receptor blockers, anticoagulants, non-steroidal anti-inflammatories, antibiotics, corticosteroids, immunosuppressants, antineoplastic agents, hormonal therapy, nervous system drugs [eg, antiepileptics, opioids], antidiabetics, and CYP3A4 inhibitors and inducers)		
History of and concomitant vaccinations	Within 90 days prior to and at index date, recording all vaccinations	Yes
Laboratory assessments		
Haematology assessments (haemoglobin, red blood cell count, haematocrit, white blood cell count, white blood cell differential, and platelet count), electrolytes	Within 90 days prior to and at index date, recording all available values	Yes
Renal assessments including eGFR, UPCR, serum creatinine, BUN, and/or 24-hour proteinuria test	Within 90 days prior to and at index date, recording all available values	Yes
Liver assessments including AST, ALT, complete metabolic and lipid profile (triglycerides, cholesterol [LDL, HDL]), albumin, and bilirubin	Within 90 days prior to and at index date, recording all available values	Yes
Kidney biopsy	Within 12 months (365 days) prior to and at index date, recording all available results	Yes
Inflammatory biomarkers (anti-dsDNA, C3/C4, antinuclear antibody)	Within 90 days prior to and at index date, recording all available values	Yes
Adverse events		
AEs and SAEs, including drug-drug interactions between voclosporin and vaccines, clinically significant lab values	Reported as soon as they occur at index date or during follow-up	

Abbreviations: ACE: angiotensin-converting enzyme; ACR: American College of Rheumatology; AE: adverse event; Anti-dsDNA: anti-double-stranded deoxyribonucleic acid; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BUN: blood urea nitrogen; CNIs: calcineurin inhibitors; CsA: cyclosporine A; CYP3A4: cytochrome P450 3A4; C3 and C4: serum complement components C3 and C4; eGFR: estimated glomerular filtration rate; HCQ: hydroxychloroquine; HDL: high density lipoprotein; LDL: low density lipoprotein; LN: lupus nephritis; MMF: mycophenolate mofetil; MPA: mycophenolic acid; PGA: physician global assessment; SAEs: serious adverse events; SLE: systemic lupus erythematosus; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; UPCR: urine protein creatinine ratio

Prior and concomitant medications will be coded for analysis using the latest version of the World Health Organization (WHO) drug dictionary, the Anatomical Therapeutic Chemical (ATC) codes. Diagnoses/comorbidities will be coded for analysis using the latest version of MedDRA®.

9.3.3.1 Clinical Laboratory Tests

The findings of laboratory assessments should be assessed by the investigator and evaluated for abnormalities which may lead to treatment discontinuation. The eGFR will be calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation: GFR = $141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] _1.159 [if black], where Scr 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 Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.[29] In addition, values for eGFR obtained using other calculation formulas will be collected from the medical records, when available.

9.3.4 Censoring Variables

Censoring criteria, including withdrawal of consent by patient, site withdrawal, lost to follow-up, death, enrolment in a clinical trial with an investigational drug during the follow-up, initiating another CNI, or initiating combination use deviating from the SmPC (eg, cyclophosphamide) during the follow-up will be recorded during the follow-up. Investigational drug applies to any drug when used within (low intervention trial) or outside the terms of their marketing authorisation.

In the analysis of each respective outcome, patients are also censored, during the follow-up, at the occurrence of the outcome of interest. In the AT analyses, patients are also censored at the end of the risk window for the safety outcomes, defined as 30 days after the date of discontinuation of voclosporin treatment.

9.4 Data Sources

Data will be collected from sites in which LN patients are treated, including specialised secondary care and research centres specialised in treating LN patients. Site personnel will record all data for each study patient, from the patient's medical records, through eCRFs using an electronic data capture (EDC) system provided and approved by the Sponsor. Once written informed consent has been obtained, study site personnel will complete and enter the baseline data collection for each patient into the EDC system.

9.5 Study Size

The planned number of patients to be included in this PASS will be approximately 300 patients initiating voclosporin treatment.

Precision-based study size calculations were performed for the primary objectives, in which the 95% confidence interval (CI) was calculated for the IRs to be observed for the safety outcomes.[30] The IRs to be observed among the voclosporin exposed patients in this PASS were set to the upper bound of the 95% CI for the IRs of the safety outcomes

estimated from the results of the AURORA 1 trial.[11,31] This will allow observing potentially high incidence of the long-term safety outcomes among the voclosporin exposed patients. The precisions (95% CI) of the IRs were calculated with the following assumptions: 300 patients who initiated voclosporin by end of the 4-year enrolment, lost to follow-up 15%, and level of significance (alpha) 0.05.

The calculation was conducted using the R package Presize (presize documentation [rdrr.io]).[32] The formula is specified in the R function prec_rate (presize source: R/descriptive_stats.R [rdrr.io]).[33] The calculations were based on Barker 2002.[30]

Based on the calculations, a neurotoxicity IR of 274 per 1000 person-years (PYs; upper bound of the 95% CI in AURORA 1 trial)[11,31] could be detected with a 95% CI of 242-310 per 1000 PYs. Chronic nephrotoxicity IR of 363 per 1000 PYs (upper bound of the 95% CI in AURORA 1 trial)[11,31] could be detected with a 95% CI of 321-410 per 1000 PYs. The safety outcome any malignancy could be detected with a 95% CI of 22.8-29.2 per 1000 PYs, when the IR to be observed was set to 25.8 per 1000 PYs (estimated upper bound of the 95% CI in AURORA 1 trial).[b] [11,31]

According to the study size calculations, the possibly high IRs of the safety outcomes could be detected with a reasonable precision (95% CI) with the targeted 300 patients to be enrolled to this PASS by the end of the approximate 4-year enrolment period.

9.6 Data Management

A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning, and validation. The eCRFs will include programmable edits to obtain immediate feedback if critical data are missing, out-of-range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the EDC system and followed up for resolution.

High data quality standards will be maintained, and processes and procedures utilised to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data. All the modifications to the data will be recorded in an audit trail.

[b] As no malignancies were reported in AURORA 1, the IR was defined assuming 1 event, which resulted in an IR of 4.65 per 1000 PYs (95% CI 0.1-25.8 per 1000 PYs)

9.6.1 Data Collection

Using the eCRFs, site personnel will collect data from the patients' medical records. All variables will be collected, as available, from the patient's medical records. As a non-interventional study, there are no mandatory requirements or collection timepoints for variables. The collected data will be available in the patients' medical records as part of normal clinical practice, and all patient visits will be conducted according to the treating physician's normal clinical practice. Thus, this study does not include mandatory visits, tests, or assessments and if data is not available, it will not be solicited. Data will be collected at the time of each patient visit according to routine care, without specific data collection time points. The collected data items are detailed in Section 9.2.4 and Section 9.3.

9.6.2 Data Handling

All data collected in the patients' medical records will be entered directly into the EDC system. Prior to deployment of the study-specific EDC database, user acceptance testing will be performed. All reported data from sites participating in the study will be entered via a secure web-based EDC study database. Site personnel will be provided with secure usernames and passwords to enter study data into the EDC system. All sites will be fully trained in using the EDC system, including the eCRF completion guidelines. All participating sites will only have access to view and enter the data for their own patients. Investigators and site personnel will be able to access their account with a username and password. All eCRFs should be completed by designated, trained personnel or the study coordinator, as appropriate. In most cases, the eCRF should be reviewed, electronically signed, and dated by the investigator. All changes or corrections to eCRFs will be documented in an audit trail and an adequate explanation will be required. All participating sites will have access to the data entered by the individual site on their own enrolled patients through the EDC system.

Patient confidentiality will be strictly maintained. Patient identifying information will not be included in the database but must be maintained in a secure fashion at the treating physician's site. Data will be backed up at intervals that comply with the contract research organisation's (CRO's) standard operating procedures and details on frequency of back-ups will be provided in a study-specific data management plan.

9.6.3 Source Documents

Source documents are defined as the results of original observations and activities of the defined study assessments. Source documents will include but are not limited to patients' medical records. All source documents pertaining to this study will be maintained by the

investigators and made available for direct inspection by authorised persons. Investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents by authorised persons as defined in the informed consent form (ICF).

All data obtained during this study should be entered in the eCRFs promptly. All source documents from which eCRF entries are derived should be placed in the patient's medical records. Measurements for which source documents are usually available include laboratory assessments and biopsies (if available).

9.6.4 Access to Source Data

This study will be initiated and operated by a CRO on behalf of Sponsor. Patient-level data for all patients enrolled in the study will be provided proactively by participating sites and will be anonymised. During the study, Sponsor or their designee may make site visits to review protocol compliance, compare eCRFs and individual patient's medical records to ensure that the study is being conducted according to pertinent regulatory requirements. The eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Checking of the eCRFs for completeness and clarity, and cross-checking with source documents, may be required to monitor the progress of the study. Moreover, regulatory authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The investigator assures the CRO and the Sponsor of necessary support at all times.

9.6.5 Data Archiving and Retention

Data archiving and retention will be in accordance with Article 12.2 of the implementation regulations (EU/520/2012) from the EU. Pharmacovigilance data and documents relating to individual authorised medicinal products will be retained as long as the product is authorised and for at least 10 years after the marketing authorisation has ceased to exist. However, the documents will be retained for a longer period where EU or national laws so require.

9.7 Data Analyses

The analyses to address the study objectives will be performed in the study population. All analyses will be descriptive.

A separate statistical analysis plan (SAP) will be produced, providing detailed methods for the analyses outlined below. Any deviations from the planned analyses will be described and justified in the final study report.

9.7.1 Definition of Analysis Set

The Enrolled Set will consist of all patients fulfilling all inclusion criteria and none of the exclusion criteria.

In addition, three separate Full Analysis Sets will be formed for each outcome of interest:

- Neurotoxicity Set will consist of patients in the Enrolled Set who in addition did not have neurotoxicity 2 weeks before the index date or at index date, in order to detect incident neurotoxicity that emerged after initiating voclosporin.
- Chronic Nephrotoxicity Set will be the Enrolled Set. Patients with ongoing (at index date) or recent history of nephrotoxicity will not be excluded because of the nature of the disease with declined renal function. Instead, the main analyses on the incidence of chronic nephrotoxicity (according to primary objective) will be stratified by renal function at baseline (to be detailed in the SAP).
- Malignancy Set will consist of patients in the Enrolled Set who in addition did not have malignancy any time before index date or at index date, in order to detect incident malignancies that emerged after initiating voclosporin.

The Safety Set will consist of all study participants who have received at least 1 dose (any amount) of voclosporin during the study.

9.7.2 General Presentation of Summaries and Analyses

Statistical analysis and generation of tables, figures, study participant data listings, and statistical output will be performed using SAS® Version 9.4 or higher.

All results will be summarised with descriptive statistics. For continuous parameters, this will include number of participants with available measurements, mean, standard deviation (SD), median, minimum, and maximum and for categorical parameters, the number of participants and percentages (to one decimal place) in each category will be presented.

9.7.3 Main Analyses

For the primary objectives, the IRs per 1000 PYs (with 95% CI) for the outcomes will be calculated. The IRs will be calculated overall, and in selected time points during the

follow-up (to be detailed in the SAP). In addition, the cumulative incidence of the outcomes (i.e., incidence proportion, percentage of patients with the outcomes) will be reported, with 95% CI, for the corresponding secondary objective.

The main analyses for the outcomes neurotoxicity, chronic nephrotoxicity, and any malignancies will be performed as AT analyses (where patients are censored at the end of the risk window for the safety outcomes, defined as 30 days after the date of discontinuation of voclosporin) and ITT analyses approach (where patients will be followed regardless of discontinuation of voclosporin).

9.7.3.1 Adverse Events

All AEs will be coded according to MedDRA®, and their frequency during the study period will be presented by System Organ Class, High Level Group Term, and Preferred Term, according to MedDRA®. The data will be displayed as number of study participants experiencing the AEs, percentage of study participants experiencing the AEs, and the number of AEs. Data will also be corrected for exposure and reported by 100 PYs. The descriptive results will be presented for AEs and for AEs that were related to voclosporin.

9.7.3.2 Clinical Laboratory Data

Clinical laboratory data for liver and renal function tests as collected under standard of care treatment will be recorded. Laboratory values received by the physician through standard of care assessments that are abnormal and considered clinically significant will be reported as AEs.

9.7.3.3 Medications

Prior, concomitant, and new medications will be coded for analysis using the latest version of the WHO drug dictionary, the ATC codes.

9.7.4 Progress Report

A progress report will be developed in Q4 2027 based on data received in Q2 2027 or earlier if 50% enrolment has been reached. This report will provide an update on study progress including any potential risk for study conduct or continuance and counts of number of patients enrolled in the study at the time of the data cut.

9.7.5 Handling of Missing Data

The proportion of missing data will be reported for each measured variable in the study. Full details on handling of all missing data, which are common in observational studies, will be described separately in the SAP. This will describe the methods for identifying

where missing data methods should be applied, the techniques for identifying the type of missingness and the appropriate imputation methods to be used, if any.

9.7.6 Sensitivity Analyses

Sensitivity analyses could be conducted to assess the robustness of the methods and obtained results and will be further detailed in the SAP. The following sensitivity analyses will be considered:

- Applying alternate definitions of the outcome of chronic nephrotoxicity (see Section 9.9.3), and possibly other outcomes.
- Applying varying lag-times between the index date and the start of follow-up time to detect the outcomes (disregarding follow-up time during the lag-time), to account for possible reverse causation (ie, protopathic bias) (see Section 9.9.3).
- Repeating the main analysis in a sub-population, which excludes patients who had used other CNIs (tacrolimus and CsA) before index date.
- Repeating the main analysis in a sub-population, which excludes patients who had initiated voclosporin before enrolment, to assess the impact of potential survival and information biases due to including patients starting voclosporin treatment up to 120 days (4 months) before enrolment.
- Applying alternate approaches for handling of lost to follow-up or missing data (eg, not including the subjects' measured variables that have a large proportion of missingness).

9.7.7 Other Analyses

Other analyses will include descriptive analyses of changes in renal functions (eGFR and serum creatinine) and urine protein creatinine ratio (UPCR) during follow-up, to further characterise chronic nephrotoxicity. To further characterise the population of voclosporin-treated LN patients, change in or occurrence of other variables (Section 9.3.3) during the follow-up may also be analysed.

Among the patients who discontinued voclosporin, restart of voclosporin will be described descriptively. The incidence of the outcomes, as described for main analyses (Section 9.7.3) may be analysed among the restarters, depending on the extent of restart (to be detailed in the SAP).

Additional analyses (eg, stratified or subgroup) will be detailed in the SAP, for example by country, index year (initiation of voclosporin), baseline variables on renal function, SLE and LN characteristics, history of LN treatments, and start dose of voclosporin. The incidence of chronic nephrotoxicity will, at minimum, be stratified by renal function at baseline, to account for the differing baseline risk.

9.8 Quality Control and Quality Assurance

9.8.1 Monitoring

The Sponsor has ethical, legal, and scientific obligations to conduct this study in a detailed and orderly manner in accordance with established research principles and the guidelines for Good Pharmacoepidemiology Practices (GPP), and applicable regulatory requirements and local laws. Training in the protocol and study procedures will be conducted via telephone. As part of a concerted effort to fulfil these obligations (maintain current personal knowledge of the progress of the study), the Sponsor's monitors will visit the site to review protocol compliance and accuracy of data entered in the eCRF during the study, as well as communicate frequently via telephone and written communications. If an on-site monitoring visit is performed, the participating physician must provide the monitor with full access to all source and study documents.

9.8.2 Auditing/Inspections

The investigator is responsible for oversight and maintenance of the study records and patient source documents. These records must be readily available for audit or inspection. The Sponsor's Quality Management Unit (or representative) may conduct study site audits. Audits will include, but are not limited to, presence of required documents, the informed consent process, and comparison of CRFs with source documents. The investigator agrees to participate with audits.

Regulatory authorities may inspect the investigator during or after the study. The investigator will cooperate with such inspections and will contact the Sponsor immediately if such an inspection occurs.

9.9 Limitations of the Research Methods

This is an observational, prospective PASS conducted within real-world settings. The limitations and potential risks of bias are described below, some of which can be partly minimised at the study design stage or during data analysis but cannot be fully eliminated due to the observational nature of the study. Despite the limitations, the results of this PASS will provide important information regarding the long-term safety of voclosporin. Information obtained from this study will enhance routine pharmacovigilance and risk management activities for voclosporin by adding to our understanding of the safety profile of the drug.

9.9.1 Confounding

Due to the observational study design, causality in the observed associations will not be established. Instead, associations between drug use and risks will be assessed descriptively. In this observational PASS, no randomisation is undertaken. Further, only a voclosporin-exposed cohort is included in the study, without a comparator group. In the absence of a comparator group, confounding adjustment will not be employed. Instead, the results on the incidence of the safety outcomes will be interpreted in the context of the measured characteristics of the voclosporin-exposed patients at baseline and during follow-up, including concomitant medication use and disease severity. Considering disease severity is particularly important, because voclosporin might be reserved for patients with severe disease status and the challenge to separate the outcomes from disease progression. Particularly, the results on nephrotoxicity will be interpreted with caution considering disease severity (see stratified analysis by baseline renal function, Section 9.7.7). Further, the results will be interpreted considering other available evidence on the outcomes of voclosporin, CNIs, and other LN treatments, as well as studies on SLE and LN patients' disease progression, eg, natural history studies and other relevant publications. These measures will support in interpreting the results considering confounding factors. Yet, some uncertainly will remain in the interpretation, concerning the occurrence of the outcomes due to exposure to voclosporin, vs due to other factors, including the characteristics of voclosporin-treated patients (eg, disease severity) and disease progression during the study.

9.9.2 Selection Bias

Selection bias refers to the selective inclusion of patients who are not representative of the exposure or outcome pattern in the source population, causing distortion in the exposure-outcome relation. Although no exposure-outcome relation is studied analytically in this PASS (in the absence of a comparator group), selection bias may risk the interpretation of the results.

The selected sites are not considered a major cause of selection bias. While patients in the sites will represent urban areas more so than rural, this is not considered to cause a distortion in the exposure-outcome relation.

In this PASS, patients who consent to participate in the study are enrolled from sites, which may result in enrolling patients who may not be fully representative of all patients using voclosporin. To consider the potential for selection bias, sites will maintain screening logs of all patients meeting eligibility criteria, along with reasons for non-enrolment and lost to follow-up. While the possible non-representativeness resulting

from enrolment is not expected to distort the relation between voclosporin exposure the studied safety outcomes (causing selection bias), the risk of selection bias will be considered in the interpretation of the results.

Importantly, enrolling patients who initiated voclosporin mitigates selection bias. Including prevalent users at enrolment could results in 'depletion of susceptibles' (healthy user bias), where continuous users are survivors of earlier adverse outcomes and thereby later during their use have a lower risk of the safety outcomes.[19]

Patients are included in the study, even if they started voclosporin treatment up to 4 months prior to the enrolment visit, in order to facilitate recruitment, increase the number of included patients, and thereby mitigate random error. However, the inclusion of past initiators could result in a survival bias (patients have to be alive and healthy enough to consent at enrolment) and also information bias (critical data has to be obtained retrospectively before enrolment, including outcomes on neurotoxicity). To assess the impact of potential survival and information biases, sensitivity analyses will exclude patients who had initiated voclosporin before enrolment (see Section 9.7.6).

Informative censoring, a type of selection bias, may occur when patients are censored at discontinuation of voclosporin if the discontinuation occurred in response to change in health status (eg, deteriorating health) that was associated with the outcomes of interest (before the outcome was diagnosed). In the AT analyses for the outcomes, the follow-up time is censored at voclosporin discontinuation, when the risk of the outcomes is not considered to persist long after discontinuation. To account for the subsequent risk of informative censoring, the ITT approach without censoring at discontinuation will be applied in the sensitivity as part of main analyses (see Section 9.7.3).

9.9.3 Information Bias

The risk of information bias associated with data collection is considered limited in this PASS, since data will be collected prospectively from patients' medical records for the purpose of this study. To mitigate information bias at data collection, the sites will be trained to collect the data and established data validation procedures will be employed, especially for the most important variables (critical data, eg, outcomes) and variables which may be challenging to obtain, such as renal assessments. Capturing critical data will be considered in the eCRF design and guidelines to the sites. As part of data validation processes, the obtained data will be scrutinised for unrealistic or incomplete values, and data collection will be corrected accordingly. When the results are reported, possible remaining risk of information bias from data collection will be discussed.

Exposure misclassification, ie, whether patients are users of voclosporin or not, is not considered to risk internal validity in this PASS, as the physician's assessment of whether or not a patient initiated voclosporin is considered valid. Further, exposure misclassification is considered minimal from the fact that some patients may not use the prescribed voclosporin, because SLE and LN are severe conditions in which patients' adherence to therapy is anticipated high and the patients are monitored closely by their treating physicians. As in all non-interventional, observational studies, it is not possible to take, or request, blood samples which would be the gold standard for proof of exposure.

While the data collection is not anticipated to cause an outcome misclassification, the definition of the outcome chronic nephrotoxicity is sensitive to the chosen categorisations of eGFR to define the outcome. The used definition (decline in eGFR from baseline to below 60 mL/min/1.73m^2 and the decline is > 10% per year, and sustained for more than 3 months) was developed based on literature[27,28] and in collaboration with clinicians, and is considered to comprehensively capture chronic nephrotoxicity. However, to assess the robustness of the definition, alternate definitions may be employed in sensitivity analyses (see Section 9.7.6). In addition, other analyses will include descriptive analyses of changes in renal function during follow-up (see Section 9.7.7).

Lastly, exclusively enrolling patients who initiated voclosporin at enrolment mitigates detection bias, a type of information bias. In the chosen new-user design, new users of voclosporin are anticipated to be monitored similarly. Also, if prevalent voclosporin users were included, they could be monitored less frequently, which in turn could result in detection bias.

9.9.4 Other Biases

Protopathic bias, also called reverse causation, may arise if the initiation of voclosporin is influenced by early manifestations of an outcome of interest, before the outcome is diagnosed. To investigate the extent of reverse causation, sensitivity analyses will be considered (see Section 9.7.6) by applying varying lag-times (eg, 6 and 12 months) between the index date and the start of follow-up time to detect the outcomes. By disregarding follow-up time during the lag-time, outcome events detected shortly after initiating voclosporin (that manifested before initiating voclosporin but were detected after) are disregarded as safety outcomes related to voclosporin.

A follow-up bias may result from lost to follow-up and/or withdrawal of consent. Maintaining a low rate of lost to follow-up will decrease the risk of bias that could result, for example, if patients with safety outcomes were less likely to return to the study

healthcare provider for follow-up. In this PASS, a low lost to follow-up rate of less than 25% is expected (15% used in study size calculations, see Section 9.5), because patients with a rare, severe condition are less like to drop out. The observed lost to follow-up rate will be considered in the interpretation of the results. Further, sensitivity analyses may include alternate approaches for handling of lost to follow-up (see Section 9.7.6).

9.9.5 Random Error

The precision of the IRs of the outcomes depends on a range of parameters, including the number of patients enrolled to the study, the average follow-up time available for the patients, and the rate of lost to follow-up. The risk of random error increases and the precision of the IRs decreases (ie, the CI become wider) with lower uptake of voclosporin, fewer enrolled patients, less follow-up time per patient, and/or higher rate of lost to follow-up. The risk of random error will be discussed when reporting the results of this PASS considering the numbers of enrolled patients and the available follow-up time, including the average duration of voclosporin treatment for the AT analyses.

9.9.6 Missing Data

In this prospective study, missing data will be minimised by following the patients closely and collecting data from their medical records according to the patient's standard of care. Among the variables, critical data will be defined for validation purposes. These critical data items could be queried to confirm if complete and accurate transcription from the patient files took place. However, if data are not recorded in the patients' medical records, the data will be reported as missing. These missing data might include variables on voclosporin use (exposure), safety outcomes, of the other variables (eg, confounders). While the extent of missing data is unknown, it is possible that missing data will be frequent. The handling of missing data is described in Section 9.7.5. Further, alternative methods of handling missing data will be considered in the sensitivity analyses (see Section 9.7.6).

9.10 Amendment Policy

The investigator will not make any changes to this protocol without the Sponsor's prior written consent and subsequent approval by the IRB/IEC. Any permanent change to the protocol, whether it be an overall change or a change for specific study site(s), must be handled as a protocol amendment. Any amendment will be written by the Sponsor. Each amendment will be submitted to the IRB/IEC per applicable local regulations. Except for 'administrative' or 'non-substantial' amendments, investigators will wait for IRB/IEC approval of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of patients, the conduct or

management of the study, the study design or the quality or safety of drug(s) used in the study. However, a protocol change intended to eliminate an apparent immediate hazard to patients should be implemented immediately, followed by IRB/IEC notification within 5 working days. The Sponsor will submit protocol amendments to regulatory agencies as required.

When the IRB/IEC, investigators, and/or the Sponsor conclude that the protocol amendment substantially alters the study design and/or increases the potential risk to the patient, the currently approved written the ICF will require similar modification. In such cases, repeat informed consent will be obtained from patients enrolled in the study before expecting continued participation.

10 Protection of Human Patients

10.1 Ethical Considerations

This study must be conducted in compliance with the protocol and all other applicable local laws and regulatory requirements. Each study site will seek approval by an IRB or ethics committee (EC) according to regional requirements. The IRB/IEC will evaluate the ethical, scientific, and medical appropriateness of the study. Further, in preparing and handling CRFs, the investigator and their staff will take measures to ensure adequate care in protecting patient privacy. To this end, a patient identification code will be used to identify each patient.

10.2 Informed Consent

Written informed consent will be obtained from all patients (or their guardian or legal representative, as applicable for local laws). Consent will be documented on a written ICF. The ICF will be approved by the same IRB/IEC that approves this protocol. Each ICF will comply with applicable regulatory requirements. The investigator agrees to obtain approval from the Sponsor of any written ICF used in the study, prior to submission to the IRB/IEC.

Investigators may discuss study availability and the possibility for entry with a potential patient without first obtaining consent.

Once appropriate essential information has been provided and fully explained in layman’s language to the patient by the investigator (or a qualified designee), the IRB/IEC-approved written ICF will be signed and dated by both the patient and the person obtaining consent (investigator or designee), as well as by any other parties required by the IRB/IEC. The patient will receive a copy of the signed ICF; the original shall be kept on file by the investigator.

10.3 Confidentiality

All information generated in this study will be considered highly confidential and will not be disclosed to anyone not directly concerned with the study without the Sponsor's prior written permission. However, authorised regulatory officials and Sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records. All parties will ensure protection of patient personal data and will not include patient names on any study forms, reports, publications, or in any other disclosures, except where required by law. In accordance with local regulations in each of the study countries, patients will be informed about data handling procedures, including with respect to transfer of their data out of the European Economic Area, and asked for their consent. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. Every effort will be made to protect participant confidentiality as outlined in General Data Protection Regulation and related local requirements.

Patients will be identified only by unique patient numbers in eCRFs. Their full names may, however, be made known to a regulatory agency or other authorised officials if necessary. Enrolment in the study is voluntary.

The database will be housed in a physically and logistically secure computer system maintained in accordance with a written security policy. The system meets approved established standards for the security of health information and is validated. The system also meets the standards of the International Conference on Harmonisation (ICH) guideline E6(R1) regarding electronic study data handling and is available for audit upon request. Patient confidentiality will be strictly maintained.

In accordance with the laws and regulatory framework in each country, Ethics Committee/Ethical Review Board will be obtained. Patient informed consent/legal guardian consent will be obtained by the prescriber (study site) prior to patient enrolment into the study.

10.4 Other Good Research Practice

The study will be conducted in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (ENCePP, current version). The ENCePP Checklist for Study Protocols has been completed (ENCePP, 2018) (see Appendix 4).

The study is a PASS and will comply with the definition of the non-interventional (observational) study provided in the 2012 Guideline on Good Pharmacovigilance

Practices (GVP): Module VIII – Post-Authorisation Safety Studies (European Medicines Agency [EMA], 2013).

The study will be registered in the ENCePP electronic register of studies (ENCePP, 2010).

11 Management and Reporting of Adverse Events/Adverse Reactions

11.1 Definitions

11.1.1 Safety Information

Information from any source containing one or more of the following concepts:

- Adverse Events
- Special Situations
- Off-label use

11.1.2 Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not it is considered causally related to the medicinal product.

11.1.3 Serious Adverse Events

A serious adverse event (SAE) includes any adverse drug experience/event occurring at any dose which:

1) Results in death
2) Is life-threatening
3) Requires inpatient hospitalisation or prolongation of existing hospitalisation.
   a) Hospitalisation itself should not be reported as an SAE; whenever possible the reason for the hospitalisation should be reported.
   b) Hospitalisations or prolonged hospitalisations for social admissions (ie, those required for reasons of convenience or other nonmedical need) are not considered SAEs.
   c) Prescheduled hospitalisation to address a condition that has existed prior to the signing of the ICF should not be considered an SAE.
4) Results in persistent or significant disability or incapacity

5) Is congenital anomaly/birth defect
6) Is medically significant

Life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.

A medically significant event is an important medical event (defined as a medical event[s] that may not be immediately life-threatening or result in death or hospitalisation but, based on appropriate medical and scientific judgement, may jeopardise the patient/subject or may require intervention [eg, medical, surgical] to prevent one of the other outcomes listed in the definitions above) that might be considered serious as well. Examples of such include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias; or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

11.1.4 Special Situation

Situations related to the use of an Otsuka product which may or may not be associated with an AE such as:

- Maternal (pregnancy and breastfeeding) or paternal (via semen) exposure,
- Exposure during breastfeeding,
- Overdose/Incorrect dosage, misuse, abuse (eg: patient sharing products),
- Medication errors (eg: patient took wrong dose),
- Lack of therapeutic efficacy (eg: the product does not work),
- Occupational exposure (eg: nurse administering the product is exposed),
- Cases of suspected transmission of infectious agents,
- Use of suspected or confirmed falsified product(s) or quality defect of the product(s),
- Withdrawal reactions,
- Accidental exposure (eg: child takes parent’s product),
- Drug-drug/drug/food interactions,
- Unintentional use of product in a non-approved population (eg: paediatric or geriatric population),
- Disease progression/exacerbation of existing disease.

11.1.5 Adverse Reaction

An adverse reaction is any untoward and unintended response to a medicinal product. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out.

11.1.6 Off-label Use

Refers to situations where a product intentionally used for a medical purpose not in accordance with the authorised product information. Off-label use also includes intentional use in non-authorised population categories not indicated in the label.

11.2 Safety Reporting

The occurrence of AEs will be regularly assessed during routine patient visits. Patients should be asked the nonleading question: "How have you felt since your last visit?" All AEs (serious and non-serious) reported by the patient must be recorded on the source documents and eCRF provided by the Sponsor. Adverse event collection will begin after a patient, or parent/legal guardian, signs the ICF. All AEs must be reported after patient informed consent has been obtained, including screening failures due to AEs.

The investigator must report all SAEs to the Sponsor or Sponsor's designated safety services within 24 hours of becoming aware of the event, along with an assessment of severity and causality, by telephone, fax, or e-mail using the contact information on the cover page of this protocol. All other non-serious safety information is to be reported within 7 calendar days. The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of the study drug from the first notification of any AE. Patient confidentiality must be protected and contact information such as name, address, phone number or any other protected health information as determined by applicable local regulation must be redacted when forwarding Safety Information and supporting documentation.

All collected AEs will be summarised in the progress report and final study report.

11.2.1 Immediate Safety Reporting

All SAEs **identified or ongoing at the last contact** are to be reported to the safety contact immediately (within 24 hours of awareness) via the Study Research Safety Reporting Form. Additionally, these are recorded as such on the AE eCRF page. If updated information (eg, resolved status) on SAE status becomes available after a patient's last scheduled contact (up to last in-clinic visit for the entire study period), this must be reported to the Sponsor in the same manner.

It is expected that the investigator will provide or arrange appropriate supportive care for the patient and will provide prompt updates on the patient's status to the Sponsor. The investigator will follow the SAEs until:

- the events are resolved,
- the events have stabilised,
- the patient is lost to follow-up, or
- the patient has died.

11.2.2 Non-immediate Safety Reporting

All AEs and other safety information **identified or ongoing at the last contact** are to be reported to the safety contact within 7 calendar days from awareness via the Study Research Safety Reporting Form. The same shall be recorded from first notification of the event on the eCRF. If updated information (eg, resolved status) on safety information status becomes available after a patient's last scheduled contact (up to last in-clinic visit for the entire study period), this must be reported to the Sponsor in the same manner.

11.3 Reconciliation of Serious Adverse Events

A reconciliation of SAEs, AEs, and pregnancies between the clinical study database and the pharmacovigilance database will be performed on a monthly basis during the study period and will be completed prior to database lock.

12 Plans for Disseminating and Communicating Study Results

By signing the study protocol, the investigator agrees with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.

The results obtained within the study are the exclusive property of the Sponsor. After validation, the results will be shared with the investigators of the study. The Sponsor recognises the ethical obligation to disseminate findings of potential scientific or public health importance (eg, results pertaining to the safety of a marketed drug). Study results may be included in abstracts sent to scientific congresses and articles sent to scientific reviews. Specific plans for disseminating and communicating the study results will be produced when the results are available.

The final results of this study will be reviewed and undergo quality control process before the report will be submitted to regulatory authorities and ethics committees 12 months after study end (last patient, last study visit). The final study report will be completed

even if the study is prematurely terminated. The Sponsor will provide all participating investigators with a summary of the final study results.

The study protocol and the final study report will be included in regulatory communications as indicated in the RMP. These include Periodic Safety Update Reports and any other regulatory milestones and requirements. Study reports will be prepared using the template suggested in GVP Module VIII (EMA, Module VIII).[34]

The International Society for Pharmacoepidemiology (ISPE) Guidelines for GPP (2016, Section J)[35] state that 'there is an ethical obligation to disseminate findings of potential scientific or public health importance'; eg, results regarding the safety profile of a marketed medicinal product. Therefore, publication of study results from this PASS will be considered. Any such publications will follow established guidelines, such as those for authorship established by the International Committee of Medical Journal Editors (2014).[36] For reporting study results, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be followed.[37]

An investigator shall not publish any data (poster, abstract, manuscript, etc.) without having consulted with the Sponsor in advance.

13 References

1 Phan T, Toong C, Adelstein S. Clearing the complexity: immune complexes and their treatment in lupus nephritis. Int J Nephrol Renovasc Dis. 2011:17.

2 Almaani S, Meara A, Rovin BH. Update on lupus nephritis. Clin J Am Soc Nephrol. 2017;12(5):825-835.

3 Hanly JG, O'Keeffe AG, Su L, et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. Rheumatology. 2016;55(2):252-262.

4 Tektonidou MG, Dasgupta A, Ward MM. Risk of end-stage renal disease in patients with lupus nephritis, 1971-2015: a systematic review and bayesian meta-analysis. arthritis Rheumatol. 2016;68(6):1432-1441.

5 Yap DYH, Tang CSO, Ma MKM, Lam MF, Chan TM. Survival analysis and causes of mortality in patients with lupus nephritis. Nephrol Dial Transplant. 2012;27(8):3248-3254.

6 Costenbader KH, Desai A, Alarcón GS, et al. Trends in the incidence, demographics, and outcomes of end-stage renal disease due to lupus nephritis in the US from 1995 to 2006. Arthritis Rheum. 2011;63(6):1681-1688.

7 Eilertsen GO, Fismen S, Hanssen T-A, Nossent JC. Decreased incidence of lupus nephritis in northern Norway is linked to increased use of antihypertensive and anticoagulant therapy. Nephrol Dial Transplant. 2011;26(2):620-627.

8 Patel M, Clarke AM, Bruce IN, Symmons DPM. The prevalence and incidence of biopsy-proven lupus nephritis in the UK: Evidence of an ethnic gradient. Arthritis Rheum. 2006;54(9):2963-2969.

[9] Hermansen M-LF, Lindhardsen J, Torp-Pedersen C, Faurschou M, Jacobsen S. Incidence of systemic lupus erythematosus and lupus nephritis in denmark: a nationwide cohort study. J Rheumatol. 2016;43(7):1335-1339.

[10] Fanouriakis A, Kostopoulou M, Cheema K, et al. 2019 Update of the Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) recommendations for the management of lupus nephritis. Ann Rheum Dis. 2020;79(6):713-723.

[11] European Medicines Agency. Lupkynis. Summary of Product Characteristics.

[12] European Union (EU) Risk Management Plan (RMP) for LupkynisTM (voclosporin). Updated 8 Jul 2022.

[13] Renal response in active lupus with voclosporin (AURORA) | Study Record | Beta ClinicalTrials.gov. Accessed 7 Aug 2023. https://clinicaltrials.gov/study/NCT03021499

[14] Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken). 2012;64(6):797-808.

[15] Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol. 2002;29(2):288-291.

[16] Chessa E, Piga M, Floris A, Devilliers H, Cauli A, Arnaud L. Use of Physician Global Assessment in systemic lupus erythematosus: a systematic review of its psychometric properties. Rheumatology. 2020;59(12):3622-3632.

[17] Kuglstatter A, Mueller F, Kusznir E, et al. Structural basis for the cyclophilin A binding affinity and immunosuppressive potency of E -ISA247 (voclosporin). Acta Crystallogr Sect D Biol Crystallogr. 2011;67(2):119-123.

[18] Stalder M. In vivo evaluation of the novel calcineurin inhibitor ISATX247 in non-human primates. J Hear Lung Transplant. 2003;22(12):1343-1352.

[19] Chapter 6.1 Bias | ENCePP Guide on Methodological Standards in Pharmacoepidemiology. Accessed 7 Aug 2023. https://www.encepp.eu/standards_and_guidances/methodologicalGuide6_1.shtml

[20] European Medicines Agency. LUPKYNIS | Assessment Report. EMA/681286/2022. Updated 21 Jul 2022. Accessed 7 Aug 2023. https://www.ema.europa.eu/en/documents/assessment-report/lupkynis-epar-public-assessment-report_en.pdf

[21] Ziolkowski J, Paczek L, Senatorski G, et al. Renal function after liver transplantation: calcineurin inhibitor nephrotoxicity. Transplant Proc. 2003;35(6):2307-2309.

[22] Flechner SM, Kobashigawa J, Klintmalm G. Calcineurin inhibitor-sparing regimens in solid organ transplantation: focus on improving renal function and nephrotoxicity. Clin Transplant. 2008;22(1):1-15.

[23] Molema F, Williams M, Langendonk J, et al. Neurotoxicity including posterior reversible encephalopathy syndrome after initiation of calcineurin inhibitors in transplanted methylmalonic acidemia patients: Two case reports and review of the literature. JIMD Rep. 2020;51(1):89-104.

[24] Wu P-C, Huang I-H, Liu C-W, Huang Y-C. Topical calcineurin inhibitors and risk of lymphoma: a systematic review and meta-analysis. J Dtsch Dermatol Ges.

2021;19(9):1265-1269.

[25] Chohan R, Vij R, Adkins D, et al. Long-term outcomes of allogeneic stem cell transplant recipients after calcineurin inhibitor-induced neurotoxicity. Br J Haematol. 2003;123(1):110-113.

[26] Lam M, Zhu JW, Tadrous M, Drucker AM. Association between topical calcineurin inhibitor use and risk of cancer, including lymphoma, keratinocyte carcinoma, and melanoma: a systematic review and meta-analysis. JAMA Dermatology. 2021;157(5):549-558.

[27] Chapter 2: Definition, identification, and prediction of CKD progression. Kidney Int Suppl. 2013;3(1):63-72.

[28] Levey AS, Inker LA, Matsushita K, et al. GFR Decline as an end point for clinical trials in ckd: a scientific workshop sponsored by the national kidney foundation and the US Food and Drug Administration. Am J Kidney Dis. 2014;64(6):821-835.

[29] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604.

[30] Barker L. A comparison of nine confidence intervals for a poisson parameter when the expected number of events is ≤ 5. Am Stat. 2002;56(2):85-89.

[31] Rovin BH, Teng YKO, Ginzler EM, et al. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2021;397(10289):2070-2080.

[32] Presize documentation. Accessed 7 Aug 2023. https://rdrr.io/cran/presize/man/

[33] Presize source: R/descriptive_stats.R. Accessed 7 Aug 2023. https://rdrr.io/cran/presize/src/R/descriptive_stats.R

[34] European Medicines Agency. Guideline on good pharmacovigilance practices (GVP), Module VIII - Post-authorisation safety studies (Rev 3).

[35] Guidelines for good pharmacoepidemiology practice (GPP). Pharmacoepidemiol Drug Saf. 2016;25(1):2-10.

[36] International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. Accessed 7 Aug 2023. http://www.icmje.org/icmje-recommendations.pdf

[37] Strengthening the reporting of observations studies in epidemiology. STROBE checklists. http://www.strobe-statement.org/index.php?id=available-checklists.

14 Appendices

Appendix 1: Names of Sponsor Personnel

Report Immediately Reportable Events (SAEs, pregnancies and AEs requiring discontinuation of study drug) to:

To be confirmed

Appendix 2: Protocol Amendment(s)/Administrative Change(s)

Amendment Number: 1

Issue date: 08 Aug 2023

PURPOSE:

The purpose of this amendment was to:

- Clarify the rationale for the study design
- Update eligibility criteria to rephrase voclosporin initiation according to the EU SmPC and clarify concurrent dosing of CNIs as an exclusion criterion
- Update definition of neurotoxicity to include information on assessment of neurological investigations
- Update definition of "voclosporin initiation" for better clarity
- Addition of progress report
- Include both AT and ITT analyses as main analyses

BACKGROUND:

This PASS protocol aims to characterise and quantify long-term safety profile of voclosporin. The main outcome variables are neurotoxicity, chronic nephrotoxicity, and any malignancy, based on the RMP. The updates performed in the current protocol amendment do not change the overall objective. The amendment is performed based on comments received from the Pharmacovigilance Risk Assessment Committee (PRAC) after the submission of original protocol (v1.0).

MODIFICATIONS TO PROTOCOL:

Section affected	Description of change	Reason for change
2. List of Abbreviations	Removed "IRE" from the list	Not appearing in text
	Abbreviations ordered in alphabetical order	For consistency
4. Abstract	Updated as per changes in protocol	To maintain consistency with full protocol text
5. Amendments and Updated	Updated for Protocol Amendment 1	To reflect current changes
6. Milestones	Addition of steps regarding progress report of study	As per PRAC request a progress report is added to provide information on study progress
7. Rationale and Background	Added text regarding findings of renal biopsy sub-study	Updated the findings of renal biopsy sub-study for clarity
9.1 Study Design	Rephrased text for adult LN patients who initiated voclosporin treatment	To maintain consistency with "voclosporin initiation" definition throughout

Section affected	Description of change	Reason for change
	Updated analyses text to consider AT and ITT analysis under main analyses	As per PRAC request to include both exposure-windows (AT and ITT) under main analyses
	Updated Figure 9.1.1-1 to include “progress report”	For clarity on addition of step “progress report” in the study period
9.1.2 Rationale for the Study Design	Added text regarding prevalent users	Updated for clarity
	Provided justification for single-arm cohort	Further justification and discussion on the study design added, to address the PRAC request to potentially consider a comparator arm
9.2 Setting	Updated list of countries	Updated the list to include countries where voclosporin is available and to support patient recruitment
9.2.1 Study Period	Updated text regarding censoring criteria	For consistency
	Updated Figure 9.2.1-1	Figure updated to maintain consistency
9.2.2 Study Population	Added text “Prior to inclusion in the study, a decision would be made by the patient and the treating physician to initiate treatment with commercially available voclosporin.”	For clarity to emphasise that the study is non-interventional
	Rephrased text for adult LN patients who initiated voclosporin treatment	To maintain consistency with “voclosporin initiation” definition throughout
9.2.2.1 Inclusion Criteria	Update text regarding voclosporin initiation Updated footnote of Table 9.2.2-1	The inclusion criterion 4 and the associated footnote were edited clarify voclosporin initiation according to the EU SmPC
9.2.2.2 Exclusion criteria	Change of exclusion criterion “No concurrent dosing with medicinal product” to “Concurrent dosing with medicinal product” in Table 9.2.2-2 -Split the exclusion criterion to two points for “medicinal product not currently approved” and “CNI” in Table 9.2.2-2	Updated exclusion criteria for clarity
9.2.3 Study Participation	Addition of censoring criteria “Initiating another CNI during the follow-up” and “Initiating combination use deviating from SmPC (eg, cyclophosphamide) during the follow-up.”	To maintain consistency with the eligibility criteria
9.2.4 Summary of Potential Data Elements	Rephrased text in Table 9.2.4-1, regarding SLE and LN characteristics from “Voclosporin indication characteristics” to “Recording of indication characteristics”	Updated for clarity

Section affected	Description of change	Reason for change
9.3.1 Exposure	Updated voclosporin initiation definition	Updated definition for clarity and consistency
	Removed text “main analyses of outcomes neurotoxicity and chronic nephrotoxicity” and “The risk of these outcomes is not considered to persist beyond the risk window, while the risk of malignancies is likely to persist regardless of discontinuation” Added text “In the ITT analyses, patients will be considered at risk until end of follow-up or censoring whichever occurs first.”	Updated main analyses text as per PRAC comment to include AT and ITT analysis under main analyses
9.3.2 Outcome variables	Updated definition of neurotoxicity	The definition was revised as per PRAC request to include information on assessment of neurological investigations
	Removed examples of malignancies from definition of “any malignancy”	Removed the examples for clarity
9.3.3 Other Variables	Rephrased text for voclosporin indication in Table 9.3.3.-1	To further clarify that the variables refer to recording of the indication characteristics
	Removed “CNIs” and cyclophosphamide from concomitant treatment and updated “CY” to “cyclophosphamide” in Table 9.3.3.-1	For consistency as CNIs and combination use deviating from the SmPC are considered as censoring variables
	Removed “RBC”, “WBC” and “CY” from footnote of Table 9.3.3.-1	The abbreviations are not appearing in the table
9.3.4 Censoring Variables	Addition of text “initiating another CNI or initiating combination use deviating from the SmPC (eg, cyclophosphamide) during the follow-up”	To maintain consistency with the eligibility criteria
9.5 Study Size	Updated typographic errors from “Irs” to “IRs” and “Pys” to “PYs”	Typographic errors updated
9.7.1 Definition of Analysis sets	Updated typographic errors	Updated typographic errors
9.7.3 Main Analyses	Updated the text to include all outcomes under both analyses approach (AT and ITT)	As per PRAC request, both AT and ITT were applied to all outcomes since the different risk windows answer different scientific questions
	Updated typographic errors from “Irs” to “IRs” and “Pys” to “PYs”	Typographic errors updated
9.7.3.1 Adverse Events	Updated typographic errors from “Pys” to “PYs”	Typographic errors updated

Section affected	Description of change	Reason for change
	Added statement regarding presentation of AEs	For clarity
9.7.4 Progress Report	Addition of section and content regarding progress report development of progress report	Progress report was added to provide update on study progress
9.7.6 Sensitivity Analyses	Removed text regarding different approaches for AT and ITT	AT and ITT are included in the main analyses, thus removed from sensitivity analyses
9.7.7 Other Analyses	Provided full form of UPCR	Abbreviation error correction
9.9.1 Confounding	Added text “and other relevant publications”	Updated to include broader term for available publications
9.9.2 Selection Bias	Removed main analyses text mentioning specific outcomes	To maintain consistency, as both AT and ITT analyses are main analyses for all outcomes
9.9.3 Information Bias	Updated typographic errors	Updated typographic errors
11.2 Safety Reporting	Added text “progress report” to AE collection	Updated in alignment with inclusion of progress report
11.2.2 Non-immediate Safety Reporting	Added “Study research safety reporting form” Removed text related to “safety management plan”	Updated for clarity and as per standard process
11.3 Reconciliation of Serious Adverse Events	Updated timeline of reconciliation from “3 months” to “monthly basis”	For consistency with process
12 Plans for Disseminating and Communicating Study Results	Added text “The final results of this study with be reviewed and undergo quality control process”	Updated for clarity
	Removed full form “Good Pharmacoepidemiology Practices”	Abbreviation error correction
13. References	References updated overall in alignment with addition of citations in Section 7 and Section 9.1.2	Updated for consistency with full protocol
Appendix 4 ENCePP Checklist	Updated checklist in accordance with updated protocol text	To maintain consistency with changes made in the protocol amendment
	Updated punctuations overall	Updated punctuations overall for consistency

ADDITIONAL RISK TO THE SUBJECT: There is no additional risk to the subjects.

A complete redline version showing all changes from the previous version of the protocol will be produced and will be available upon final approval of this administrative change.

Appendix 3: List of Stand-alone Documents

A list of all investigators will be available on request.

Appendix 4: ENCePP Checklist for Study Protocols

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

Study title:

An observational post-authorisation safety study (PASS) in Europe to further characterise and quantify long-term safety profile with respect to neurotoxicity, chronic nephrotoxicity, and malignancy with use of voclosporin

EU PAS Register® number: TBC

Study reference number (if applicable): NA

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[c]	☒	☐	☐	6
1.1.2 End of data collection[d]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☐	☒	☐	-
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

1.1.4: No interim reports are planned in this PASS.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7, 8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7

[c] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[d] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	-
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	-

Comments:

2.1.4 & 2.1.5: No hypothesis are texted in this PASS.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	-
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

3.4: No measures of association are used in this PASS.

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.1
	4.2.2 Age and sex	☒	☐	☐	9.2.2
	4.2.3 Country of origin	☒	☐	☐	9.2

Section 4: Source and study populations		Yes	No	N/A	Section Number
	4.2.4 Disease/indication	☒	☐	☐	9.2.2
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.1
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

Comments:

-

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.1 9.9.3
5.3	Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.1
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.1
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	-

Comments:

5.6: No comparator in this PASS.

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.9.3
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	-

Comments:

6.4: No Health Technology Assessment outcomes are included in this PASS.

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.9.1
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9.3

Comments:

-

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.3.3 9.7.7

Comments:

-

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3.1 9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.2 9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.3 9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	-
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	-

Comments:

9.3.1: Defining exposure to voclosporin does not require coding in this PASS. 9.4: No linkage methods are used in this PASS.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☐	☐	☒	-
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	-
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.7.6
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.5
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.6

Comments:

10.1: Only descriptive analyses included in this PASS. 10.5: No analytical control of confounding as part of the study.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☐	☐	9.6 10
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9.2
12.1.2 Information bias?	☒	☐	☐	9.9.3
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9.1
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5 9.9.5

Comments:

-

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	-
13.3 Have data protection requirements been described?	☒	☐	☐	9.6.4 10.3

Comments:

13.2: No review yet.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	Appendix 2

Comments:

-

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

-

Name of the main author of the protocol: PPD

Date: dd/Month/year

Signature: _____

Investigator Agreement

I, the undersigned principal investigator, have read and understand the protocol and agree that it contains all the ethical, legal and scientific information necessary to conduct this study in accordance with the principles of Good Pharmacoepidemiology Practices and as described herein and in the Sponsor's (or designee's) Research Agreement.

I will provide copies of the protocol to all physicians, nurses and other professional personnel to whom I delegate study responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the research. I am aware that this protocol must be approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) responsible for such matters in the study facility where research will be conducted prior to commencement of this study. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in Paragraph I of the Sponsor's Research Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB- or IEC-approved protocol may be submitted to the appropriate regulatory authority/ies by the Sponsor per the relevant regional regulation(s). I agree that clinical data entered on case report forms by me and my staff may be utilized by the Sponsor in various ways such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow Sponsor monitors and auditors full access to all medical records at the research facility for patients screened or enrolled in the study.

I agree to await IRB/IEC approval before implementation of any protocol amendments to this protocol. If, however, there is an immediate hazard to patients, I will implement the amendment immediately, and provide the information to the IRB/IEC within 5 working days. Administrative changes to the protocol will be transmitted to the IRB/IEC for informational purposes only.

I agree to provide all patients with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the Sponsor any adverse experiences in accordance with the terms of the Sponsor's Research Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the Sponsor for all investigators and sub-investigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this study in a cooperative publication prior to publication of results on an individual basis.

_____

Principal or Coordinating Investigator Signature and Date

_____

Sponsor Representative Signature and Date

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PPD	Medical Affairs Approval	08-Aug-2023 14:03:46
PPD	Safety Approval	08-Aug-2023 07:14:40
PPD	Safety Approval	08-Aug-2023 07:03:16
PPD	Safety Approval	08-Aug-2023 12:16:32
PPD	QPPV Approval	08-Aug-2023 14:39:16
PPD	Regulatory Affairs Approval	08-Aug-2023 16:15:33

PPD	Safety Approval	08-Aug-2023 06:47:31
PPD	Value and Real World Evidence	08-Aug-2023 15:50:37
PPD	Safety Approval	08-Aug-2023 15:35:35
PPD	Biostatistics Approval	08-Aug-2023 14:33:47