Title Page

Title	Prospective observational study to assess the long term safety profile of venetoclax in a Swedish cohort of Chronic Lymphocytic Leukemia (CLL) patients
Protocol Version Identifier	7.0 (Protocol: P16-562) FINAL
Date of Last Version of Protocol	10 June 2021
HMA-EMA Catalogue of Real-world Data Sources and Studies Register Number (Previously EU-PAS Register)	EUPAS19010 / Study ID 49279
Active Substance	Venetoclax, ATC code: L01XX52
Medicinal Product	Venclyxto (venetoclax) (10 mg, 50 mg, 100 mg), oral administration
Product Reference	EU/1/16/1138/001-8
Procedure Number	EMEA/H/C/004106
Marketing Authorisation Holder(s)	AbbVie Deutschland GmbH & Co. KG, Knollstrasse, 67061 Ludwigshafen, Germany
Joint PASS	No
Research Question and Objectives	Primary Objective • To characterise long term safety of venetoclax, including determining the incidence of select adverse events (AEs) in CLL patients exposed to venetoclax Secondary Objectives a) To further characterise long term safety of venetoclax by describing the treated patient population stratified by factors associated with events of interest b) To describe the safety profile of venetoclax and other treatment regimens by line of therapy (LoT) c) To describe clinical characteristics of CLL patients at diagnosis, such as age, gender, staging, comorbidities, and prognostic factors (e.g., cytogenetic factors, renal and hepatic function) d) To assess occurrence of TLS and contraindicated medication use in patients who have received venetoclax in a real-world setting

	Exploratory Objective • To describe treatment regimens and sequence of therapy in patients with CLL
Country of Study	Sweden
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Marketing Authorisation Holder(s)

Marketing Authorisation Holder(s) [MAH]	AbbVie Deutschland GmbH & Co. KG, Knollstrasse, 67061 Ludwigshafen, Germany
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2.0 Abbreviations

AE	Adverse Event
AHE	Autoimmune Haematologic Event
AML	Acute Myeloid Leukaemia
ATC	Anatomical Therapeutic Chemical Classification
BCL-2	B-cell Lymphoma 2
BMI	Body Mass Index
BTKi	Bruton Tyrosine Kinase Inhibitor
CCI	Charlson Comorbidity Index
CDR	Cause of Death Register
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukaemia
CXP	Customised eXtraction Platform
DLBCL	Diffuse Large B-Cell Lymphoma
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EMR	Electronic Medical Records
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPO	Erythropoietin
EU	European Union
FCR	Fludarabine, Cyclophosphamide, and Rituximab
G-CSF	Granulocyte Colony-Stimulating Factor
GVP	Good Pharmacovigilance Practice
HL	Hodgkin Lymphoma
HMA	Heads of Medicines Agencies
ICD-10	International Classification of Diseases, 10th Revision
ICH	International Conference on Harmonisation
IR	Incidence Rate
LDH	Lactase Dehydrogenase
LoT	Line of Therapy
MAH	Marketing Authorisation Holder

MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
NBHW	National Board of Health and Welfare
NLP	Natural Language Processing
NPR	National Patient Register
PASS	Post-Authorisation Safety Study
PI	Principal Investigator
PI3Ki	Phosphoinositide 3-kinase inhibitors
PY	Patient-Year
Q	Quarter
QC	Quality Control
QPPV	Qualified Person for Pharmacovigilance
RT	Richter's Transformation
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCR	Swedish Cancer Register
SmPC	Summary of Product Characteristics
SOI(s)	Serious Opportunistic Infection(s)
SOP(s)	Standard Operating Procedure(s)
SPDR	Swedish Prescribed Drug Register
SPM	Secondary Primary Malignancies
TLS	Tumour Lysis Syndrome
TP53	Tumour Protein P53
V	Version
VEN	Venetoclax

3.0 Responsible Parties

Principal investigator	[redacted] Karolinska Institute, Stockholm, Sweden Responsibilities include giving feedback on protocol, application to the Ethical Review Board, statistical analysis plan, result interpretation and reporting, aiding in getting paperwork needed for data extraction signed, and being involved in publications.
Coordinating investigator for each country in which the study is to be performed	N/A
Sponsor contacts	AbbVie [redacted] 1 North Waukegan Rd North Chicago, IL 60064 United States
Other contacts	N/A
Vendor/Collaborator	IQVIA is responsible for carrying out the study, e.g., writing most of the protocol, statistical analysis plan, ethics application, paperwork related to data extraction, and for carrying out data extraction, data analysis, and report writing.
Investigators	Responsibilities include giving feedback on protocol, statistical analysis plan, result interpretation and reporting, aiding in getting paperwork needed for data extraction signed, and being involved in publications.
Sponsor	Review and refinement of protocol, review and refinement of statistical analysis plan, development of definitions for key events of interest, development of timelines for analysis, authorship of Executive Summary to accompany trial results, discussion on publications derived from study results.
Shared responsibilities	Authorship of Protocol Authorship of Analysis Plan Review of results and study results Publications and presentations, including to regulatory authorities

4.0 Abstract

Title: Prospective observational study to assess the long term safety profile of venetoclax in a Swedish cohort of Chronic Lymphocytic Leukemia (CLL) patients

Protocol Number/Version: 7.0

Date: 20 February 2025

Authors: IQVIA: [redacted] AbbVie: [redacted]

Rationale and Background: Chronic lymphocytic leukaemia (CLL) is the most common type of leukaemia, with an incidence of 3-8 cases per 100,000 inhabitants per year in Europe. CLL is a highly heterogeneous disease with a variable clinical course, depending on the diagnostic group in which a patient falls. While many patients never require treatment, patients with the 17p deletion have an aggressive clinical course with fast progression and shorter survival. The poor outcomes of these patients have highlighted the need to develop effective treatment for this patient group. Venetoclax, developed by AbbVie and Genentech, was initially approved by the European Medicines Agency (EMA) in 2016 as monotherapy for the treatment of CLL patients who have received at least one prior therapy for their cancer. In 2018, venetoclax was approved by the European Commission (EC) in combination with rituximab for adult CLL patients who have received at least one prior treatment. In 2020, the EC approved venetoclax in combination with obinutuzumab for adult patients who have not previously been treated for CLL. In 2022, the EMA approved ibrutinib in combination with venetoclax's indication in first-line CLL treatment. In Sweden, venetoclax was first marketed in January 2018 and approved for reimbursement in May 2018 for the CLL treatment. Since May 2021, venetoclax in combination with a hypomethylating agent has been indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia who are ineligible for intensive chemotherapy.

This study aims to characterise the long-term safety of venetoclax in CLL patients treated under real-world care. Sweden was chosen for this study due to the expected availability of granular electronic medical records (EMR) data from haematology clinics linked at a patient level to data from national health registries.

Research Question and Objectives: The aim of the study is to assess prospectively the long-term safety of venetoclax by creating a continuously monitored longitudinal cohort of CLL patients.

Primary objective: To characterise the long-term safety of venetoclax, including determining the incidence of select adverse events (AEs) in CLL patients exposed to venetoclax.

Secondary objectives: a) To further characterise long term safety of venetoclax by describing the treated patient population stratified by factors associated with events of interest; b) To describe the safety profile of venetoclax and other treatment regimens by line of therapy (LoT); c) To describe clinical characteristics of CLL patients at diagnosis, such as age, gender, staging, comorbidities, and prognostic factors (e.g., cytogenetic factors, renal and hepatic function); d) To assess occurrence of tumour lysis syndrome (TLS) and contraindicated medication use in patients who have received venetoclax in a real world setting.

Exploratory objective: To describe treatment regimens and sequence of therapy in patients with CLL.

In addition to the objectives presented above, the study contains a one-time retrospective analysis planned for and conducted in the first year of the study (reported in Interim Analysis Report 1, dated December 2019). The retrospective analysis provided specific insights into patient demographics and clinical characteristics.

Study Design: Prospective cohort study conducted over a 8-year period, running from Q1 2018 (after venetoclax has entered the Swedish market) with a maximum follow-up through Q4 2024, and final data extraction and analysis in 2025 (Year 8). The study includes patients with CLL diagnosis from 1) a national patient cohort based on data from national and population-based health registers in Sweden (Cohort 1), and 2) a sub-cohort of Cohort 1, based on patient-level data from participating haematology clinic EMRs in Sweden and cross-linked with national register data (Cohort 2).
Population: Cohort 1: Patients aged 18 years or above with a diagnosis of CLL in the Swedish Cancer Registry (SCR) between 01 January 2003 and 31 December 2022, and who are alive on 01 January 2018 i.e., prevalent CLL cases at the start of the prospective study period (01 January 2018), as well as incident cases of CLL who are diagnosed during the prospective study period (2018-2022). Cohort 2 (a sub-cohort of Cohort 1) will include CLL patients from Cohort 1 with a CLL diagnosis in an EMR within ± 90 days of the CLL diagnosis in the SCR. Two sub-cohorts of Cohort 1 and Cohort 2, i.e., Cohort 1-VEN and Cohort 2-VEN, will also be established for those patients in each cohort who have a record of venetoclax prescription/administration.
Variables: All cohorts: Patient characteristics, CLL characteristics, comorbidities, select AEs (secondary primary malignancies, Richter's transformation, serious opportunistic infections, autoimmune haematologic events, and TLS), dispensed pharmacological treatments for CLL, dispensed venetoclax contraindicated medications and mortality. Additionally for Cohort 2 and Cohort 2-VEN only (as available in the EMR data): Clinical characteristics, laboratory tests, stage (Bin and Rai for CLL), Eastern Cooperative Oncology Group status, cytogenetic aberrations, mutational status, hospital-administered drugs.
Data Sources: National health registers (National Patient Register, SCR, Swedish Prescribed Drug Register, Cause of Death Register), EMRs.
Study Size: Based on data extraction #6 (completed in Q4 2023) and Study Progress Report 6 published in March 2024, Cohort 1 (patients identified via national health registers) includes 7,543 diagnosed CLL patients, and Cohort 2 (patients identified via EMRs, sub-cohort of Cohort 1) includes 1,400 diagnosed CLL patients. By the end of 2024, the projected number of CLL patients, based on data extraction #7 (completed in Q4 2024), in Cohort 1-VEN and Cohort 2-VEN is estimated to be approximately 500 patients (or roughly 6% of Cohort 1 with a projected size of 8,265) and 80 patients (or 5% of Cohort 2 with a projected size of 1,600), respectively. As the Primary Objective describes the incidence rates (IR) of AEs of interest, the 95% confidence interval (CI) was estimated for select AEs of interest using the latest Study Progress Report 7 for a range of cohort sizes for Cohort 1-VEN and Cohort 2-VEN.
Data Analysis: Statistical analysis will be conducted separately for each objective and be descriptive in nature. Due to the limited numbers of venetoclax-treated CLL patients with available clinical data from Cohort 2 and the lack of hospital-based infusions and chemotherapy treatment information from national registries in Cohort 1, no comparative analyses are planned for this study. This also influences the availability of some variables; hence, some analyses will not be performed in both cohorts. For the Primary Objective, the number of patients, and number of events will be presented for the first occurrence of AEs. Crude IR will be computed for patients prescribed/administered venetoclax (Cohort 1-VEN and Cohort 2-VEN) according to predefined AE assessment windows. The cumulative incidence of the first AEs and its corresponding 95% CI will be calculated using Kaplan-Meier estimates, overall, and for each of the AEs if sample size allows. For Secondary Objective a), analyses for the Primary Objective will be stratified by selected patient

characteristics and risk factors (as available in the national registers and EMR data) for patients prescribed/administered venetoclax (Cohort 1-VEN and Cohort 2-VEN). Data extractions to date for the Study Progress Reports and Interim Analyses have demonstrated high proportions of missing values for some clinical characteristics from the EMR (e.g., Rai and Binet staging and Eastern Cooperative Oncology Group [ECOG] performance status). As a result, while these characteristics will be reported using descriptive summary statistics with the proportions of missing values noted, such characteristics are not possible to stratify in the analysis.

For Secondary Objective b) (Cohort 2 only), patient characteristics, comorbidities, CLL disease characteristics and treatment periods will be described for treatment regimens by LoT. In addition, the number of each AE of interest (excluding TLS) by LoT will also be described, and as the sample size allows, for patients treated with venetoclax regimens and other non-venetoclax treatment regimens according to each LoT using predefined AE assessment windows.

For Secondary Objective c), patient characteristics, CLL characteristics and comorbidities (Cohort 1, Cohort 2, Cohort 1-VEN, and Cohort 2-VEN) will be descriptively tabulated according to pre-specified baseline periods. For Cohort 2 and Cohort 2-VEN, additional CLL characteristics (e.g., disease stage, cytogenetic aberrations and mutations), clinical characteristics (e.g., blood pressure), and laboratory tests will also be tabulated (as available in the EMR data).

For Secondary Objective d), the number and proportion of patients (Cohort 1-VEN and Cohort 2-VEN) who experience TLS during treatment, by whether the TLS event occurred within the first five weeks after initiating venetoclax, and the time period of venetoclax initiation (2018-2021 and 2022-2024), along with predefined contraindicated medications use with venetoclax will be reported.

For the Exploratory Objective (Cohort 2 only), CLL treatment patterns over time will be described by the number of treatments and percentages among CLL patients; a Sankey plot will be constructed if sample size permits. In addition, proportional stacked bar plots will also be depicted for the treatment regimens, overall and by LoT, and stratified by the year of patients' 1st LoT (< 2018, 2018-2021, and 2022-2024).

Sensitivity analyses checking the robustness of Cohort 2-VEN inclusion and treatment regimen definitions will be conducted.

Milestones:	**Estimated dates**
Start of prospective data collection:	Q1 2019
End of data collection:	Q2 2025
End of patient identification period:	Q4 2022
Interim Report(s) of study results:	Basic interim study results will be provided, along with Progress Reports
Study Progress Report(s):	Annual Progress Reports 2018–2024 (beginning with the 2021 Study Progress Report, to be submitted Q1 of the following year)
Interim Analysis:	Interim Analysis Reports every second year, i.e., 2019, 2021 (submitted Q1 2022), 2023 (submitted Q1 2024)
Final Report of study results:	Q1 2026

AbbVie = AbbVie Inc; AE = Adverse Event; CI = Confidence Interval; CLL = Chronic Lymphocytic Leukemia; EC = European Commission; ECOG = Eastern Cooperative Oncology Group; EMA = European Medicines Agency; EMR = Electronic Medical Records; IR = Incidence Rate; LoT = Line of Therapy; SCR = Swedish Cancer Registry; TLS = Tumor Lysis Syndrome; VEN = Venetoclax

5.0 Amendments and Updates

Substantial amendments/updates to the study protocol after the start of data collection are summarised in the following table.

Protocol Version (Date)	Section of the Protocol	Amendment or Update	Reason
V.4 (25 March 2019)	• 4.0 Abstract • 6.0 Milestones • Annex 5 • Title Page/ Annex 4	1. Reporting timelines changed from Q3 to Q4. 2. Reference to patient diagnosis/procedure codes changed from MedDRA to ICD-10. 3. Administrative updates to the MAH name and address/updated EU QPPV contact person.	1. Reporting timelines were changed for two reasons: • waiting time to receive access to data and linking from the Swedish NBHW is longer than initially assumed; • the National Patient Register is updated annually in Q3. 2. The ICD-10 codes have been added in Annex 5 for the opportunistic infections to allow for identification of those events in the EMRs and national 'registries' records (due to absence of MedDRA codes availability in those databases). 3. Names and addresses have been updated as appropriate to keep them up to date.
V.5 (15 July 2019)	• Section 5 Amendments and Updates	1. Section revised according to the guidance for the format and content of the protocol of non-interventional post authorization safety studies (26-Sep-2012).	1. Administrative updates as requested by PRAC.
V.6.0 (10 June 2021)	• Title page • 3.0 Responsible Parties • 7.0 Rationale and Background • 9.2 Setting • 9.3.1 Exposure • 9.4.1 Study Procedures • 9.6 Data Management • 9.8 Quality Control	1. Changed "QuintilesIMS" to "IQVIA".	1. Administrative change; QuintilesIMS is now IQVIA.

Protocol Version (Date)	Section of the Protocol	Amendment or Update	Reason
	• Title page • 4.0 Abstract	1. Updated the list of authors for IQVIA.	1. Administrative change to reflect the current IQVIA study team.
	• 2.0 Abbreviations • 10.0 Protection of Human Subjects	1. Added/updated abbreviations.	1. Abbreviations added to revised study protocol when making the changes summarized below.
	• 4.0 Abstract • 6.0 Milestones	1. Reporting timelines changed from Q4 to Q1 of the subsequent year.	1. Reporting timelines were changed for three reasons: • Waiting time to receive access to data and linking from the Swedish NBHW each year continues to be longer than initially assumed, despite IQVIA's efforts to submit the annual request earlier in the calendar year; • Experience with review of the 2019 and 2020 final extracted linked datasets received from NBHW indicates that additional time is needed for review and quality control of 2021–2025 linked data sets received from the NBHW, and, if any errors or missing data are identified, for IQVIA to request and receive a corrected dataset from the NBHW; and • There are likely to be delays due to the ongoing COVID-19 pandemic related to study sites' ability to complete the EMR extraction as scheduled because of competing priorities of on-site personnel.
	• 9.3 Variables	1. Clarified CLL index date definition for patients in Cohort 1 only and for patients additionally in Cohort 2.	1. Clarification.

Protocol Version (Date)	Section of the Protocol	Amendment or Update	Reason
	• 9.8 Quality Control	1. Revised Section 9.8 Quality Control.	1. Removed references to specific IQVIA SOPs; removed language that did not pertain to quality control; made additional edits throughout section for clarity.
	• 13.0 References	1. Updated references.	1. Updated references related to the changes made to Section 9.8 Quality Control (as summarized above).
	• Annex 3. List of Protocol Signatories	1. Administrative update to list of protocol signatories due to personnel changes.	1. List of protocol signatories kept up to date.
	• Annex 4. Qualified Person for Pharmacovigilance (QPPV)	1. Administrative update to Head of QPPV and contact information.	1. Contact information for Head of QPPV kept up to date.
V.7.0 (20 February 2025)	• Title page • Marketing Authorisation Holder(s) • 3.0 Responsible Parties • 4.0 Abstract	1. Updated the list of authors for IQVIA and for the Sponsor and MAH/Sponsor contact details.	1. Administrative change to reflect the current IQVIA study team and the Sponsor team, and the current MAH/Sponsor contact details.
	• 2.0 Abbreviations	1. Added/updated abbreviations list.	1. Abbreviations added/removed as relevant for changes to V7.0.
	• 4.0 Abstract • 6.0 Milestones	1. Updated the actual dates for start and end of data collection. 2. Changed registry website name to HMA-EMA Catalogue.	1. Administrative change to reflect the actual dates scheduled for data extraction based on GVP module VIII definitions. 2. Administrative change.

Protocol Version (Date)	Section of the Protocol	Amendment or Update	Reason
	• All sections	1. All sections have been updated to use UK English. 2. Clarifications provided throughout the protocol.	1. Administrative change 2. Clarifications provided throughout the protocol in response to the changes identified below.
	• 4.0 Abstract • 7.0 Rationale and Background • 13.0 References	1. Updated information about venetoclax indications and their efficacy results with new references added for the above updates. 2. Minor wording changes for clarity, ease of reading and fluency.	1. Venetoclax received a label extension (use in combination with monoclonal antibodies) during the study period (2018 and 2020), and with ibrutinib (2022), which may affect the interpretation of the study results. 2. Administrative only.
	• Title page • 4.0 Abstract • 8.0 Research Question and Objectives • Table 1 • 9.8 Data Analysis	1. Adjustments to the objectives (Secondary a), Secondary b), Secondary d) and Exploratory) based on the analysis to be performed. 2. Added for clarification that the one-time retrospective analysis refers to data from the first Interim Analysis Report. 3. Sub-headings for primary, secondary and exploratory objectives added.	1. As stated to the PRAC in the last Study Progress Report 6 (15 March 2024), the secondary and exploratory objectives for the Final Report are only partially feasible. The rationale for the changes in each objective is as follows: • Secondary Objective a): The word "stratified" has been added to indicate that a stratified analysis will be performed. • Secondary Objective b): The comparative nature of this objective (venetoclax versus other treatments) was changed to a descriptive analysis of treatment regimen by line of therapy due to sample size limitations that preclude a comparative analysis. • Secondary Objective d): The objective statement has been changed for clarity, as causality cannot be determined nor inferred from the data available. • Exploratory objective: Due to sample size limitations and missingness of some key variables (e.g., mutations), regimens and sequence of therapy will not be described

Protocol Version (Date)	Section of the Protocol	Amendment or Update	Reason
			by patient characteristics and risk factors. 2. For clarity, it has been added that the one-time analysis planned for the study's first year refers to Interim Analysis Report 1, which has already occurred (December 2019). 3. Administrative, for clarity and ease of reading.
	• 4.0 Abstract • 9.1 Study Design • Figure 1, Figure 2, Figure 3, Figure 4, Figure 5 • Table 1, Table 2 • 9.3 Variables • 9.4 Data Sources	1. Clarification that the study will be conducted over an 8-year period, starting in 2018, with maximum follow-up of patients to the end of 2024 and then final data extraction in 2025 (Year 8) 2. Figure 1 has been updated to provide clarity on the eligibility criteria for Cohort 2 (CLL diagnosis in the EMR within +/- 90 days of a CLL diagnosis in the SCR) and sub-cohorts 1-VEN and 2-VEN added. 3. For clarity regarding the sample and cohorts under study, the following terms were added: Prevalent cases, Cohort 1-VEN, Cohort 2-VEN. 4. Study dates (including index dates, baseline periods, and follow-up periods for each objective) and data availability/dates have been updated and/or clarified in a revised Figure 2, new Table 2, and additional study schematics (Figure 3, Figure 4, and Figure 5).	1. For clarification that the study period ends in 2024 (Year 7) with data extraction and analysis in 2025 (Year 8). 2. For clarification. Also, Cohort 1-VEN and Cohort 2-VEN refer to the patients with a prescription/administration of venetoclax in Cohort 1 and Cohort 2 and are important sub-cohorts for the study. 3. The term "prevalent cases" was added to refer to patients with CLL diagnosis prior to 2018 and alive on 01 Jan 2018 (study start/time venetoclax was marketed in Sweden). See above (2) for rationale of including the terms Cohort 1-VEN and Cohort 2-VEN. 4. Clarification has been provided on key study dates and on dates of data availability for multiple data sources and the complexities of differing index, baseline, and follow-up periods for each objective. 5. In relation to changes to the objectives since v6.0, and to clarify which cohort will be used for each objective (based on data availability) 6. For clarification only. 7. Clarified that the SPDR does not include medications administered in hospitals (e.g., chemotherapy), and therefore, the full CLL treatment history cannot be captured for patients in Cohort 1. Also, that variables related to disease stage are

Protocol Version (Date)	Section of the Protocol	Amendment or Update	Reason
		5. Table 1 has been updated with the new objectives and as a result of the change of objectives, subsequent updates to which cohort(s) will be assessed for each objective. 6. Specified AEs of interest. 7. Clarifications provided on data availability for each cohort. 8. Other minor wording changes for clarity, ease of reading and fluency.	only available through EMR data (Cohort 2 and Cohort 2-VEN only). 8. For clarification only.
	• 9.1 Study Design	1. Removed the following information: a) That the SPDR includes drugs prescribed in inpatient settings. b) That patients enrolling in clinical trials of novel drugs will be captured in Cohort 2.	1. a) The SPDR does not provide information on drugs administered and/or prescribed in-hospital. b) b) Venetoclax administered and/or prescribed as part of a clinical trial is not captured in the SPDR or EMR. Also provided clarification that it is possible that patients included in the study may have had prior exposure to venetoclax as part of a clinical trial and who go on to receive venetoclax in real-world practice.
	• Figure 1 • 9.2 Setting	1. Inclusion and exclusion criteria have been explicitly stated for each cohort and sub-cohort with relevant updates made in text and in Figure 1.	1. For clarification only, no change to the overall eligibility criteria has been made.

Protocol Version (Date)	Section of the Protocol	Amendment or Update	Reason
	• 9.1 Study Design • 9.3 Variables • Table 3 • Table 4 • 9.3.1 Exposure • 9.3.2 Safety Outcomes • 9.10 Limitations	1. Removed the following terms/variables: -Costs -Progression -Radiation treatment -Underlying/multiple causes of death. 2. Tables for variables retrieved for each Cohort have been updated to reflect the data source used for each variable. 3. Medication errors was removed and replaced by TLS occurrence. Definition of TLS was added. 4. Codes for RT were added. 5. On secondary exposures, surgical procedures were removed. Stem cell transplant has also been removed. 6. Clarified in Table 3 and 4 which variables are affected by high levels of missingness	1. Rationale for removing variables/terms: -Costs: This study does not evaluate treatment costs. -Progression: This study does not evaluate treatment efficacy. -Radiation: This type of treatment is a rare treatment option for CLL -Mortality: The only information that is needed is the date of death for censoring; therefore, the underlying cause and multiple causes were removed. 2. Clarification only. 3. The TLS outcome cannot be ascertained as originally intended by whether patients are following or not their dosage schedule to determine the possibility of medication errors. TLS occurrence will be determined by ICD-10 codes or identified by free text in EMR. 4. For clarity, the ICD-10 codes to be used to assess RT were added. 5. Surgical procedures have been removed due to small numbers in counts observed to date for the interim analyses. Due to complexities with determining procedures within the line of therapy, the line of therapy will include pharmacological treatment only (given the small counts, this is not expected to affect the scientific value of the study). 6. Based on scheduled interim analysis performed, clinical variables with a high level of missingness are noted for transparency.

Protocol Version (Date)	Section of the Protocol	Amendment or Update	Reason
	• 9.5 Study procedures	1. New section added to clarify appropriate study procedures (previously documented in the data source section). 2. Update of all protocol section numbers as a result of the new protocol section added.	1. To provide clarity on study procedures aligned with NHBW requirements for analysis of national register data in Sweden. 2. Administrative change.
	• Figure 1 • 9.3 Variables • 9.3.1 Exposure • 9.6 Study Size • 9.8 Data Analysis • 9.10 Limitations	1. Any mention of a comparator treatment or group has been removed and replaced with descriptive analysis stratified by patient characteristics.	1. The reference to a comparator treatment/group was removed to align with revision of Secondary Objective b) from a comparative analysis to a descriptive analysis.

Protocol Version (Date)	Section of the Protocol	Amendment or Update	Reason
	• 9.1 Study design • 9.3 Variables • Table 4 • Table 5 • 9.3.1 Exposure • Figure 6 • Figure 7	1. Removed content about study periods from the variables section and added this to Section 9.1 Study Design. 2. Moved previous content about treatment lines and regimens from Section 9.3 Variables section to Section 9.3.1 Exposure. 3. Clarification has been added that lines of treatment are only available in Cohort 2. 4. Information and figures have been added to define treatment regimens and line of therapy (Figure 6, and Figure 7). 5. Table 2 and Figure 3, Figure 4, and Figure 5 have been added to clarify look-back periods for all objectives. 6. Updated how venetoclax treatment dose is captured.	1. For clarity, definitions of the study periods were removed from the variables section and detailed information given in the study design section. 2. For clarity, definitions of the lines of treatment and regimens were removed from the variables section and detailed information given in the Exposure section. 3. Patients' complete CLL treatment history, including inpatient medications recorded in the EMR together with data from the SPDR, can only be evaluated for Cohort 2. 4. For clarity, a definition for treatment regimens/line of therapy and regimens of interest for the study have been added. 5. Clarification only. 6. To align with how treatment doses are captured in SPDR and EMR, the text has been rephrased.
	• 9.3.1 Exposure	1. Changed the discontinuation period of (>) 90 days to (>) 60 days. 2. Noted that operational definitions for determining treatment dynamics, such as identifying treatment regimens, add-on therapy, treatment gaps, and switches are subject to change.	1. Previous gap was considered too long based on venetoclax prescription to patients. Therefore, a narrower gap of 2x the 30-day supply is proposed to allow time for temporary discontinuation of venetoclax. 2. To ensure alignment of definitions with treatment patterns in real-world clinical practice given the complexities of identifying such treatment patterns using real-world data.

Protocol Version (Date)	Section of the Protocol	Amendment or Update	Reason
	• 9.1 Study Design • 9.3.2 Safety Outcomes • 9.8 Data Analysis	1. Updated the assessment period for AEs: a) On-treatment assessment period applicable only to SOI, AHE, and TLS. b) Any time after the index date applicable only to SPM and RT. c) Removed analysis based on venetoclax duration (short and long term). d) Added assessment of safety events by time to first event. 2. Added the information on how the assessment period for the Secondary Objective b) will be carried out. 3. Table 5 added, which clarifies the data source, assessment window, and cohort for safety outcomes by objective. 4. Updates to variables to be included in the stratified analysis for Secondary Objective a).	1. For clarity, the specific safety events to be evaluated during the on-treatment period and at any time after the index period have been specified. 2. For clarity, the assessment period for Secondary Objective b) was specified. 3. For clarification only, given the complexities around multiple cohorts, assessment windows, and data sources. 4. The rationale for the updates on the list of variables to be included in the stratified analysis for Secondary Objective a) are the following: -categories for age were changed based on inclusion criteria (≥ 18 years old) and prevalence of CLL according to age. -additional stratification analysis to provide more insights about safety events and time periods. -the abnormal ranges for renal function from the Karolinska Institute Laboratory have been applied. -RT was removed since patients will be excluded from the analysis if they had the RT any time prior to the venetoclax treatment index date.

Protocol Version (Date)	Section of the Protocol	Amendment or Update	Reason
	• 9.3.3 Other Variables • 9.4 Data Sources	1. This section has been changed from "covariates" to be used in Secondary Objective b) to "other variables." 2. Moved the content about contraindicated medications from Section 9.4 to Section 9.3.3.	1. Secondary Objective b) was changed from a comparative analysis to a descriptive one. Therefore, the covariates will not be used to balance cohorts for baseline. 2. The section has been modified to reflect another variable (contraindicated medications) to be used in Secondary Objective d). The content was moved from Section 9.4 Data Sources, as the purpose of this section is to describe the various Swedish data sources and not to provide information on variables.
	• 4.0 Abstract • 9.6 Study Size	1. Study size section on estimations of cohort sizes was updated to reflect only the latest data extraction counts. 2. Subsection and tables related to study size based on Incidence rates (IR) are updated to reflect only the latest data extraction counts. 3. Comparative analysis for Incident Rate Ratio (IRR) is removed.	1. The estimated number and percentage of patients in each cohort were revised based on the latest Progress Report 6 (March 2024) and data extraction #7 (Q4 2024). 2. Estimated 95% CIs for IR were reported for a range of AE rates and different cohort sizes for Cohort 1-VEN and Cohort 2-VEN. 3. As no comparative analysis is planned for Secondary Objective b) due to sample size limitations, the sample size calculation based on IRR is not applicable and has been removed.
	• 9.7 Data Management • 9.8 Data Analysis	1. Removed sentences mentioning "confounding variables," "effect modifiers and sensitivity analysis for any variable with >10% missing data." 2. Details regarding masking rules added to general considerations in Section 9.8 Data Analysis. 3. Missing data section moved to Section 9.8.4.	1. No comparative analysis is planned, due to substantially lower cohort size for Cohort 2-VEN and masking rules that require blinding. The sensitivity analysis for missingness is not feasible. 2. For an explanation on how masking will be dealt with in the analysis. 3. Based on client agreement, missing data information has been shifted to its dedicated Section 9.8.4.

Protocol Version (Date)	Section of the Protocol	Amendment or Update	Reason
	• 4.0 Abstract • 9.8 Data Analysis	1. Details on variable-based statistical matching have been removed. 2. Added general considerations of statistical analyses. 3. Added masking rule due to NBHW privacy policy and other details on missing data. 4. Details of attrition table for Cohorts 1, 2, 1-VEN, and 2-VEN were added. 5. For all objectives and analyses, the sections have been split by cohorts: Cohort 1 & 2 or Cohort 1-VEN or 2-VEN, etc., as applicable. 6. Primary Objective 1: -Specifying that IR will only be computed should the sample size allow it. -Specifying that number of patients and number of events will be presented for the first occurrence of AEs. -IR being computed for add-on therapy and switches has been removed. -The use of other transformation method in the time-to-event analysis for the Primary objective is removed.	1. Due to low cohort sizes, missing data on key covariates, and masking rules, it is not feasible to match patient characteristics, and thus this analysis has been removed. 2. General rules regarding continuous & categorical variables were added to formalise the rules to present the analysis results. 3. Added to reflect missing data operations used for analysis and reporting small cell counts due to restrictions per the NBHW's privacy policy. 4. An attrition table, which will be a deliverable in the reports, and since it does not pertain to any particular objective, but rather to the overall study, description has been added in the newly added General Considerations section for data analysis. 5. To have clarity on which analyses are done for which cohort, as due to low sample size and data availability, variable availability is not uniform across cohorts. 6. Primary Objective 1: -Due to low cohort sizes and masking rules, only incidence rates will be computed if sample size allows. -Due to low cohort sizes, if IR cannot be produced, incidence of AEs will be assessed based on counts of events -Due to sample size restrictions, no IR for treatment deviations will be computed. -The time-to-event analyses are limited due to low counts of AEs and will be provided if sample size allows. Only the most standard transformation method (log-log transformation) will be applied.

Protocol Version (Date)	Section of the Protocol	Amendment or Update	Reason
		7. Secondary Objective a): -Clarification on characteristics to be used for stratifying occurrence of AEs. -Specifying that number of patients and number of events will be presented for the first occurrence of AEs. 8. Secondary Objective b): -Sentences were added to clarify the treatment lines being used for the descriptive analysis. -Removed sentences on comparative analysis. 9. Secondary Objective c): Formatted the section to have all analyses be split by Cohorts 1 & 2. 10. Secondary Objective d): Information added on reporting the number of patients with a record of venetoclax prescription/administration who experience TLS, time to TLS, TLS within 5 weeks of venetoclax initiation and taking concomitantly contraindicated medication. 11. Exploratory analysis: Stratification on patient characteristics and risk factors was removed. Details have been added on new outputs (Sankey plot and proportional stacked bar chart)	7. Secondary Objective a): -Data extractions to date for the Study Progress Reports and Interim Analyses have demonstrated high proportions of missing values for some clinical characteristics from the EMR data (e.g., lablaboratory tests, Rai and Binet staging, and ECOG performance status). As a result, the stratifications proposed for Secondary Objective a) have been restricted to those clinical variables where high degrees of missingness have not been observed. -Due to low cohort sizes, if IR cannot be produced, incidence of AEs will be assessed based on counts of events. 8. Secondary Objective b): -Added to highlight the new descriptive analysis of treatment lines to be made. -As no comparative analysis will be done due to low Cohort-2 VEN numbers and masking rules, these sentences were removed. 9. Secondary Objective c): -To have clarity on which analyses are done for which cohort, as due to low sample size and other reasons, variable availability is not uniform across cohorts. 10. Secondary Objective d): Previously, the TLS outcome was defined by the occurrences of medication errors. This definition is broadened to include all occurrence of TLS to enable reporting of overall TLS frequency among venetoclax-treated CLL patients, and since assessment of adherence to ramp-up (medication error) is not possible as such information cannot be reliably extracted from EMR. 11. Exploratory analysis: Due to low cohort sizes and masking

Protocol Version (Date)	Section of the Protocol	Amendment or Update	Reason
		planned. 12. Sensitivity analysis: 2 added to reflect that further analyses will be presented in the Final Report for investigating i) the role of EMR data availability on AEs for Cohort 2; and ii) robustness of regimen definitions. 13. Missing data section: Added information on missing values procedures.	rules, stratification analyses were removed. To depict the treatment patterns, these new outputs will be necessary to provide a clearer picture across the treatment index years. 12. Sensitivity analysis: i) To explore the influence of EMR data availability in Cohort 2, as this could result in patients with incomplete treatment history; ii) As treatment definitions for venetoclax and non-venetoclax-based therapies require a predefined interval for assessing combinations of treatments, the robustness of the definitions will be investigated by varying the predefined intervals selected for venetoclax and non-venetoclax regimens. 13. Information on missing data rules followed in the report.
	• Abstract • 9.1 Study Design • 9.8 Data Analysis • 9.10 Limitations	1. Details added regarding changes to strata characteristics for Secondary Objective b).	1. Due to the real-world nature of the study, data extractions to date for the Study Progress Reports and Interim Analyses have demonstrated high proportions of missing values for some clinical characteristics from the EMR. As a result, while these characteristics will be reported using descriptive summary statistics with the proportions of missing values noted in the analysis, such characteristics will not be used for the purposes of stratified analysis.

Protocol Version (Date)	Section of the Protocol	Amendment or Update	Reason
	• 9.10 Limitations	1. Removed the mitigation plan for variables with more than 20% of missingness. 2. Content added regarding missing data. 3. Content added regarding selection bias and information bias. 4. Content added regarding not being able to assess TLS in relation to medication error.	1. The sensitivity analysis for missing data was removed, and therefore the mitigation plan is no longer applicable. 2. The Limitations section has been updated to include information on data availability due to the high level of missingness in the EMR and its impact on the study analysis based on results from the Interim Analysis Report 3. 3. Additional limitations relevant to the data sources of interest were added in order to provide clarity on the potential for impact on study results and interpretation. 4. The TLS outcome cannot be ascertained as originally intended by whether patients are following or not their dosage schedule to determine the possibility of medication errors. TLS occurrence will be determined by ICD-10 codes or identified by free text in EMR.
	• 7.0 Background and Rationale • 9.6 Study Size • 13.0 References	1. Additional references included. 2. Updated reference numbers across the document.	1. Added new references in Sections 7.0 and 9.6. 2. Updated reference number related to the changes made across the document.
	• Annex 2. ENCePP checklist for study protocols	1. Adopted the ENCePP checklist from 2018 and updated the checklist according to the protocol amendments.	1. Stylistic changes for document consistency and checklist updated to reflect updates to the protocol listed above.

Protocol Version (Date)	Section of the Protocol	Amendment or Update	Reason
	• Annex 3. List of protocol signatories • Annex 4. Qualified Person for Pharmacovigilance (QPPV) • Document approval	1. Administrative updates to list of protocol signatories and QPPV due to personnel changes.	1. List of protocol signatories and contact information for Head of QPPV kept up to date.
	• Annex 5. List of CLL Pharmacological Treatments of Interest	1. Annex added.	1. In response to the treatment regimen and line of therapy being assessed for Secondary Objective b), list of treatments needed to be added.
	• Annex 6. List of Serious Opportunistic Infections	1. Reference to MedDRA codes was removed. 2. Wording updated to Serious Opportunistic Infection (rather than opportunistic serious infection).	1. MedDRA codes are not available in the national registries and EMR data. 2. Clarification only.
	• Annex 7. List of Medications Contraindicated with Venetoclax	1. Medication list updated.	1. For completeness
	• All sections	1. Formatting was updated in the entire document.	1. Formatting was applied to the entire document for consistency.

AE = Adverse Events; AHE = Autoimmune Haematologic Event; CI = Confidence Interval; CLL = Chronic Lymphocytic Leukaemia; COVID-19 = Coronavirus Disease; ECOG = Eastern Cooperative Oncology Group; EMA = European Medicines Agency; EMR = Electronic Medical Records; ENCePP = European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; EU = European Union; GVP = Good Pharmacovigilance Practice; HMA = Heads of Medicines Agencies; ICD-10 = International Classification of Diseases, 10th Revision; IR = Incidence Rate; IRR = Incidence Rate Ratio; LoT = Line of Therapy; MAH = Market Authorisation Holder; MedDRA = Medical Dictionary for Regulatory Activities; NBHW = National Board of Health and Welfare; PRAC = Pharmacovigilance Risk Assessment Committee; Q = Quarter; QPPV = Qualified Person for Pharmacovigilance; RT = Richter's Transformation; SAP = Statistical Analysis Plan; SOIs = Serious Opportunistic Infections; SOPs = Standard Operating Procedures; SPDR = Swedish Prescribed Drug Register; SPM = Second Primary Malignancy; TLS = Tumour Lysis Syndrome; VEN = Venetoclax; V = Version

6.0 Milestones

Milestones	EU-PAS Register Dates	Actual Dates
Start of prospective data collection	Q1 2018	Q1 2019*
End of data collection	Q4 2025	Q2 2025**
End of patient identification period	Q4 2022	Q4 2022
Study Progress Report 1	Q3 2018	Q3 2018
Study Progress Report 2 and Interim Analysis Report	Q3 2019	Q4 2019
Study Progress Report 3	Q3 2020	Q4 2020
Study Progress Report 4 and Interim Analysis Report	Q3 2021	Q1 2022
Study Progress Report 5	Q3 2022	Q1 2023
Study Progress Report 6 and Interim Analysis Report	Q3 2023	Q1 2024
Study Progress Report 7	Q3 2024	Q1 2025
Registration in the HMA-EMA Catalogue of real-world data sources and studies register number (formally EU-PAS registries)	Q2 2017	Q2 2017
Ethics approval for research programme	Q3 2017	Q1 2018
Final Report of study results	Q4 2025	Q1 2026

* Start of data collection: The date from which data extraction starts.

** End of data collection: The date from which data extraction ends.

EU-PAS = European Post-Authorisation Study; HMA-EMA = Heads of Medicine Agencies-European Medicines Agency; Q = Quarter

7.0 Rationale and Background

Leukaemia comprises a group of cancers usually beginning in the bone marrow, characterised by abnormally high numbers of white blood cells. There are four main types of leukaemia: acute lymphoblastic leukaemia, acute myeloid leukaemia (AML), chronic myeloid leukaemia, and chronic lymphocytic leukaemia (CLL). CLL is the most common, with an incidence of 3–8 cases per 100,000 inhabitants per year in Europe.[1,2] CLL affects B-lymphocytes, which originate in the bone marrow and develop in lymph nodes, and whose main function is to produce antibodies. CLL is a highly heterogeneous disease with

a variable clinical course,[3] depending on the diagnostic group in which a patient falls. A significant proportion of patients never require treatment, whereas others have an aggressive clinical course with fast progression and short survival. CLL patients are also at an increased risk of other forms of cancer, including non-melanoma skin cancers, malignant melanoma, and lung cancers.[4,5] Different CLL diagnostic subtypes constitute major factors that predict clinical outcomes; these subtypes are characterised mainly according to the mutational status of the immunoglobulin variable region heavy chain gene, as well as chromosomal abnormalities. Chromosomal abnormalities highly affect cell behaviour and they are grouped into mutations on chromosomes 11, 12, 13, and 17.[3]

A subset of CLL patients carry the chromosomal deletion 17p, which is associated with the worst clinical outcome and the highest risk of disease progression.[6] The 17p deletion is found in approximately 10% of CLL cases at diagnosis, but can also be acquired during the progression of the disease, particularly in patients who have received chemotherapy. Consequently, this mutation is found in approximately 30% of patients whose cancer returns after treatment.[3]

The poor outcomes in the patients with 17p deletion have been attributed to their refractoriness to conventional chemotherapy. For example, progression-free survival following treatment with fludarabine, cyclophosphamide, and rituximab (FCR regimen) was shorter for these patients as compared with treatment-naïve CLL patients without the 17p deletion (11.3 vs. 55.2 months), highlighting the need to develop effective treatments for this patient group.[7] This refractoriness to treatment has partly been attributed to the lack of normal tumour protein p53 (TP53) gene function, an important pathway for mediating the cytotoxicity of purine analogues. Accordingly, over 90% of patients harbouring the 17p deletion have concurrent TP53 mutations.[8,9] Moreover, TP53 abnormalities are key contributors to Richter's transformation (RT), the development of an aggressive and difficult-to-treat highly malignant lymphoma from CLL that occurs in 2.2%-20% of CLL cases.[10,11] The majority of cases with RT develop diffuse large B-cell lymphoma (DLBCL), further complicating treatment options.[12] Furthermore, other

secondary malignancies can develop as a result of treatment, including myelodysplastic syndrome and AML.[13]

Venetoclax, developed by AbbVie and Genentech, is a small molecule that inhibits B-cell lymphoma 2, a key regulator of apoptosis that is overexpressed in many cancers. Venetoclax was initially approved by the European Medicines Agency (EMA) in 2016 as monotherapy for the treatment of CLL patients (with and without the presence of 17p deletion or TP53 mutation), who have received at least one prior therapy for their cancer.[14] Specifically, the indication of venetoclax, according to the EMA authorisation, was the following: "Venclyxto monotherapy is indicated for the treatment of CLL in the presence of 17p deletion or *TP53* mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor. Venclyxto monotherapy is indicated for the treatment of CLL in the absence of 17p deletion or *TP53* mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor."[14] In October 2018, venetoclax was approved by the European Commission (EC) in combination with rituximab for adult CLL patients who have received at least one prior treatment.[15,16] In March 2020, the EC approved venetoclax in combination with obinutuzumab for adult patients who have not previously been treated for CLL.[16] In 2022, the EMA approved ibrutinib in combination with venetoclax's indication in first-line CLL treatment.[17,18] In Sweden, venetoclax was first marketed in January 2018 and approved for reimbursement in May 2018 for CLL treatment.[19] In addition to CLL, since May 2021, venetoclax in combination with a hypomethylating agent is indicated for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy.[20]

Venetoclax is administered orally, once per day. Venetoclax monotherapy induces an objective response in approximately 80% of patients with relapsed/refractory CLL, independent of conventional risk factors such as chromosome 17p deletion.[21,22] An overall response rate of 89% was observed in patients with relapsed/refractory CLL who received venetoclax in combination with a monoclonal antibody.[23]

The most commonly occurring adverse reactions of any grade in patients receiving venetoclax were neutropenia/neutrophil count decreased, diarrhoea, nausea, anaemia, and upper respiratory tract infection. The most frequently reported serious adverse reactions were pneumonia, febrile neutropenia, and Tumour Lysis Syndrome (TLS).[21,22] According to AbbVie's European Union (EU) Risk Management Plan, important identified risks for venetoclax are TLS, neutropenia, and serious infection, and important potential risks are embryofetal toxicity, medication error, RT, secondary primary malignancy (SPM), and severe hepatic impairment. AbbVie continues to further characterise the risks of venetoclax in its ongoing clinical trials and real-world data, including this cohort study. Venetoclax is currently under investigation as a treatment for myelodysplastic syndrome and mantle cell lymphoma.[24-26] It was originally designated as an orphan medicine by the EMA for the treatment of AML, CLL, and multiple myeloma.[27]

At the time of safety evaluation for approval (April 2016), the median follow-up for venetoclax patients was 11.4 months. While long-term safety continues to be monitored in clinical trials, AbbVie, in partnership with IQVIA, will conduct a prospective cohort study using secondary data to explore the long-term safety of venetoclax in real-world clinical settings using registry and electronic medical records (EMR) data from Sweden. Sweden was selected for this study due to the expected availability of granular EMR data from haematology clinics that can be linked with national health registers. The unique personal identification number assigned to each individual residing in the country enables data from these different sources to be linked anonymously at an individual patient level, providing unique insights into patient outcomes.

8.0 Research Question and Objectives

The aim of the study is to assess prospectively the long-term safety of venetoclax by creating a continuously monitored longitudinal cohort of CLL patients.

8.1 Primary Objective

To characterise long term safety of venetoclax, including determining the incidence of select adverse events (AEs) in CLL patients exposed to venetoclax.

8.2 Secondary Objectives

a. To further characterise long term safety of venetoclax by describing the treated patient population stratified by factors associated with events of interest.
b. To describe the safety profile of venetoclax and other treatment regimens by line of therapy (LoT).
c. To describe clinical characteristics of CLL patients at diagnosis, such as age, gender, staging, comorbidities, and prognostic factors (e.g., cytogenetic factors, renal and hepatic function).
d. To assess occurrence of TLS and contraindicated medication use in patients who have received venetoclax in a real-world setting.

8.3 Exploratory Objective

To describe treatment regimens and sequence of therapy in patients with CLL.

8.4 Other Analysis/Reporting

In addition to the objectives presented above, the study contains a one-time retrospective analysis, planned for and conducted in the first year of the study (reported in Interim Analysis Report 1, dated December 2019). The retrospective analysis provided specific insights into patient demographics and clinical characteristics. It should also be noted that each consecutive year, retrospective data of all participants has been/will be extracted and reported in the annual Study Progress Reports and Interim Analysis Reports (see Section 6.0). The present study is designed to primarily estimate AE event occurrence and does not have a priori-defined testing hypotheses.

9.0 Research Methods

9.1 Study Design

This is an observational post-authorisation safety study (PASS) to assess the long-term safety of venetoclax in patients with CLL in Sweden. The following AEs are of interest for the study:

- RT;
- SPM;
- Autoimmune haematologic event (AHE);
- Serious opportunistic infection (SOI);
- TLS.

The study is designed as a prospective[1] cohort study conducted over an 8-year period, starting in Q1 2018 (after venetoclax has entered the Swedish market) with a maximum follow-up to Q4 2024, and final data extraction and analysis in 2025 (Year 8). The study includes patients with CLL diagnosis from: (1) a national patient cohort based on data from national and population-based health registers in Sweden (Cohort 1), and (2) a sub-cohort of Cohort 1 based on patient-level EMR data from participating haematology clinics in Sweden and cross-linked with national register data (Cohort 2).

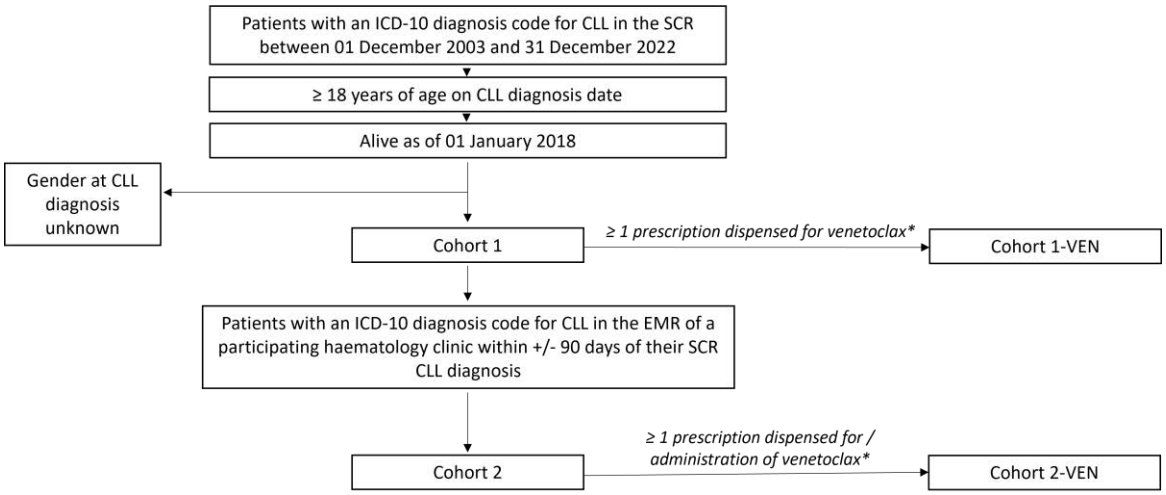
Four different compulsory national health registers will be used for data retrieval for Cohort 1. Patients aged 18 and above with a diagnosis of CLL between 01 January 2003 and 31 December 2022, and who are alive on 01 January 2018, will be included in Cohort 1. CLL diagnosis will be ascertained via International Classification of Diseases, 10th Revision (ICD-10) codes within the Swedish Cancer Registry (SCR). Individual patient data will thereafter be linked to the National Patient Register (NPR), the Swedish Prescribed Drug Register (SPDR) and the Cause of Death Register (CDR). Details on each health register are provided in Section 9.4.

[1] This study is prospective as patients on venetoclax will be followed in order to ascertain the safety of treatment ("prospective" refers to venetoclax treatment, and not to CLL diagnosis). However, each year data will be extracted in a retrospective way (i.e., already collected data will be extracted).

Cohort 2 will be a sub-cohort of Cohort 1. Patients from Cohort 1 with a CLL diagnosis in an EMR[2] (also identified via ICD-10 code) within ± 90 days of the CLL diagnosis in the SCR will be included in Cohort 2. Cohort 2 is intended to provide more granular-level clinical information from the EMRs, where available, that cannot be obtained solely from the national health registers.

Two sub-cohorts of Cohort 1 and Cohort 2, i.e., Cohort 1-VEN and Cohort 2-VEN, will also be established for those patients in each cohort who have a record of venetoclax prescription/administration. An overview of the cohorts to be assessed in this study is provided in Figure 1, with full details on the eligibility criteria for the study detailed in Section 9.2.1.

Figure 1. Diagram of Proposed Study Cohorts



* For Cohort 1, medications dispensed will be based on information collected from the SPDR, which contains information for all prescriptions dispensed to the whole population of Sweden, exclusive of over-the-counter medications or medications administered in hospitals. For patients in Cohort 2. linkage to EMR allows capture of hospital-administered drugs. Cohort 1-VEN and Cohort 2-VEN are not mutually exclusive.

CLL = Chronic Lymphocytic Leukaemia; EMR = Electronic Medical Records; ICD-10 = International Classification of Diseases, 10th Revision; SCR = Swedish Cancer Register; VEN = Venetoclax

2 Start date of EMR data availability is hospital dependent, thus site-specific restrictions of the patient population for Cohort 2 will apply. See Figure 2.

Cohort 1

Patient demographics, date of CLL diagnosis, and comorbidities, including other prior cancers, AEs, dispensed medications, and mortality data (for purposes of censoring), will be captured for Cohort 1. Safety information will be based on ICD-10 codes from the NPR and the SCR. Further details on the AEs of interest and the data source(s) for identifying each type of AE are detailed in Section 9.3.2.

Medications dispensed will be based on information collected from the SPDR, which contains information for all prescriptions dispensed to the whole population of Sweden, exclusive of over-the-counter medications or medications administered in hospitals (e.g., chemotherapy including rituximab and obinutuzumab). Since venetoclax is a prescription-only medicine, all patients with one or more dispensed prescriptions for venetoclax recorded in the SPDR will be included in Cohort 1, with the exception of patients receiving venetoclax as part of a clinical trial. It is possible that patients included in the study may have had prior exposure to venetoclax as part of a clinical trial and who go on to receive venetoclax in real-world practice.

The subset of patients in Cohort 1 with one or more prescriptions dispensed of venetoclax (recorded in the SPDR) will form Cohort 1-VEN. Additional details on the eligibility criteria for Cohort 1 and Cohort 1-VEN are provided in Section 9.2.1. A full list of variables to be assessed in Cohort 1 and Cohort 1-VEN can be found in Table 3 of Section 9.3.

Cohort 2

For patients in Cohort 2 (a subset of patients in Cohort 1 with available EMR data), linkage to EMR is intended to capture information (as available) on laboratory results, mutational status (e.g., p53 status), hospital-administered drugs (e.g., chemotherapy including rituximab and obinutuzumab), and cytogenetics, as well as safety events.

As is done with Cohort 1 (and Cohort 1-VEN), safety information will be identified via ICD-10 codes from the NPR and SCR for Cohort 2 (and Cohort 2-VEN). Additionally,

TLS will be identified from physicians' case notes in the free text of the EMR. See Section 9.3.2 for further details on the AEs of interest and the data source(s) for identifying each type of AE in Cohort 2 and Cohort 2-VEN.

Information on Rai and Binet staging, Eastern Cooperative Oncology Group (ECOG) performance status, del(17p), del(11q), del(13q), trisomy 12, TP53 (tumour protein p53), and immunoglobulin heavy chain variable region gene mutation may also be captured from the physician case notes if available. The use of physician case notes along with laboratory values from the EMR (i.e., lactase dehydrogenase [LDH] levels, renal and hepatic functions) can potentially provide additional insights into the frequency and characterisation of the study AEs. The process for extracting variables from the free text of case notes will be done using natural language processing (NLP) software.

It is intended that Cohort 2 will enrich the description of patient characteristics and disease management. However, due to the real-world nature of the study, data extractions to date for the Study Progress Reports and Interim Analyses have demonstrated high proportions of missing values for the aforementioned clinical characteristics from the EMR. As a result, while these characteristics will be reported using descriptive summary statistics with the proportions of missing values noted in the analysis (see Section 9.8), such characteristics will not be used for the purposes of stratified analysis.

The subset of patients in Cohort 2 with one or more prescriptions of (recorded in the SPDR) or administrations of (recorded in the EMR) venetoclax will form Cohort 2-VEN. Additional details on the eligibility criteria for Cohort 2 and Cohort 2-VEN are provided in Section 9.2.1. A full list of variables to be assessed in Cohort 2 and Cohort 2-VEN can be found in Table 4 in Section 9.3.

Table 1 provides an overview of which cohort will be used for each objective. As full CLL drug treatment history (including hospital-administered drugs) can only be ascertained by linking the SPDR and the EMR, Secondary Objective b) and the exploratory objective for the study, which will describe treatment regimens, can only be assessed for Cohort 2.

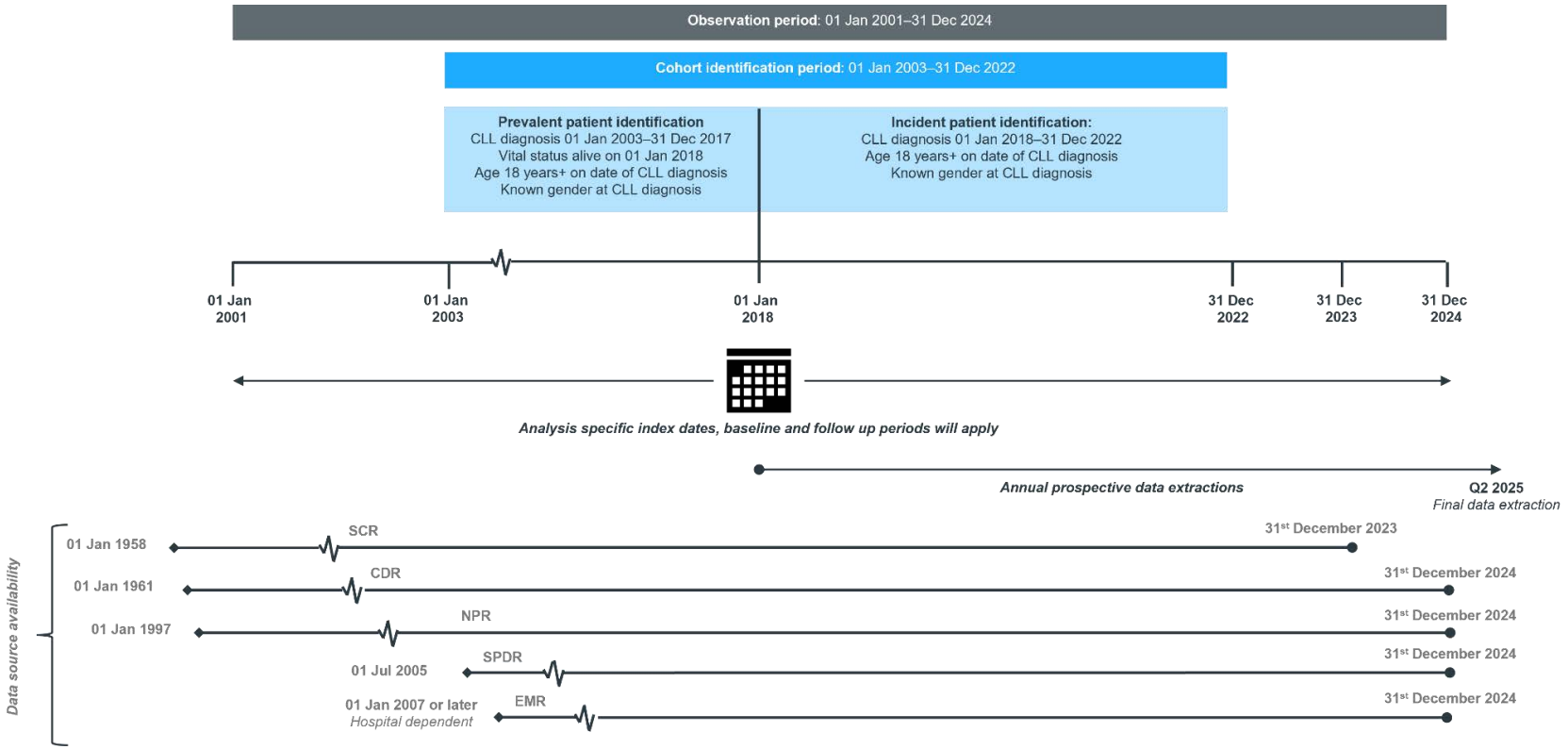
Table 1. Overview of Which Cohort(s) Will Be Used for Each Study Objective

Objective	Research Question	Cohort(s)
Primary Objective	To characterise long term safety of venetoclax, including determining the incidence of select adverse events in CLL patients exposed to venetoclax.	Cohort 1-VEN Cohort 2-VEN
Secondary Objective a)	To further characterise long term safety of venetoclax by describing the treated patient population stratified by factors associated with events of interest.	Cohort 1-VEN Cohort 2-VEN
Secondary Objective b)	To describe the safety profile of venetoclax and other treatment regimens by LoT.	Cohort 2
Secondary Objective c)	To describe clinical characteristics of CLL patients at diagnosis such as age, gender, staging, comorbidities, and prognostic factors (e.g., cytogenetic factors, renal and hepatic function).	Cohort 1 Cohort 2 Cohort 1-VEN Cohort 2-VEN
Secondary Objective d)	To assess occurrence of TLS and contraindicated medication use in patients who have received venetoclax in a real-world setting.	Cohort 1-VEN Cohort 2-VEN
Exploratory objective	To describe treatment regimens and sequence of therapy in patients with CLL.	Cohort 2

CLL = Chronic Lymphocytic Leukaemia; LoT = Line of Therapy; TLS = Tumour Lysis Syndrome; VEN = Venetoclax

Figure 2 provides an overview of the overall study design, along with the data availability periods for each of the data sources to be used in the study.

Figure 2. Study Overview and Data Availability



Data availability: The final data extraction for the study will take place in Q2 2025**.** A 3- to 6-month data lag exists for all national registers except the SCR, which has a data lag of approximately 13 months. A minimal data lag for EMRs exists (<3 months). For the final analysis, it is anticipated that data for all sources will be available by

31 December 2024 with the exception of the SCR, which will be 31 December 2023. However, delays are possible and may impact 2024 data availability. EMR data availability is hospital dependent, thus, site-specific restrictions of the patient population for Cohort 2 will apply.

CDR = Cause of Death Register; CLL = Chronic Lymphocytic Leukaemia; EMR = Electronic Medical Records; NPR = National Patient Register; Q2 = Quarter 2, SCR = Swedish Cancer Register; SPDR = Swedish Prescribed Drug Register

The cohort identification period for the study is 01 January 2003 to 31 December 2022. Patients with a CLL diagnosis after 31 December 2022 will not be included. The study will include both patients who have been diagnosed with CLL prior to the start of the prospective study (i.e., prior to 01 January 2018) and who were alive on 01 January 2018, i.e., prevalent cases, as well as incident cases of CLL who are newly diagnosed between 01 January 2018 and 31 December 2022 and who meet all of the study eligibility criteria as detailed in Section 9.2.1. It should be noted that for Cohort 1, patients with a diagnosis of CLL in the SCR from 2003 to 2022 will be included; however, due to EMR data availability starting from 2007 onwards, not all patients in Cohort 1 will be eligible for Cohort 2, given that an EMR CLL diagnosis that occurs within ± 90 days of the patients SCR CLL diagnosis is required for inclusion into Cohort 2.

In order to ensure that all patients can have the required look-back period to ascertain comorbidities of interest prior to CLL diagnosis (a 2-year look-back period[3]), prevalent patients diagnosed with CLL prior to 01 January 2003[4] will not be included. The start of the study observation period is therefore 01 January 2001. Differences in data availability among the national registers exist; thus, the maximum follow-up of patients included in the study will be 31 December 2024 (end date of data availability in the SPDR, NPR, and EMR).

A one-time retrospective data extraction, planned for and conducted in the first year of the study (reported in Interim Analysis Report 1, dated December 2019), was carried out, providing specific insights into patient demographics and clinical characteristics of the prevalent patients included in the study. Extraction of prospective data took place annually between 2018 and 2024. The final data extraction is planned for Q2 2025.

Analysis-specific index dates, baseline, and follow-up time windows will be defined depending on the objective. As such, patients are allowed to have multiple index dates for the study dependent on the objective being assessed. The baseline and follow-up periods

3 Data availability in the NPR is restricted to the 2 years prior to the CLL diagnosis in the SCR.
4 Complete data (availability of both inpatient and outpatient specialist encounters) in the NPR began nationwide on 01 January 2001.

will also differ depending on the objective and/or outcome of interest. Table 2 details the relevant index dates and time periods for each objective, which are also visualised in Figure 3, Figure 4, and Figure 5.

Table 2. Overview of Study Index Dates, Baseline and Follow-up Periods by Study Objective

Relevant Objective(s)	Index Date	Indexing Period	Cohort (s)	Baseline Period	Follow-Up Period/Assessment Window(s)
Primary objective Secondary Objective a) Secondary Objective d)	**VEN treatment index date:** Defined as the date of 1st venetoclax prescription/administration (Figure 3).	01 January 2018 to 31 December 2024	Cohort 1-VEN	**Patient demographics:** At VEN treatment index date. **Comorbidities:** From 2 years prior to CLL diagnosis date up to and including VEN treatment index date.	**Treatment exposure window:** From VEN treatment index date to the earliest of VEN discontinuation emigration, death, or end of data availability. **RT and SPM assessment window:** From VEN treatment index date to the earliest of date of the AE, emigration, death, or end of data availability. **AHE, SOI & TLS assessment window:** From VEN treatment index date to the earliest of date of the AE, VEN discontinuation + 30 days, emigration, death, or end of data availability.
			Cohort 2-VEN	**Patient demographics:** At VEN treatment index date. **Comorbidities:** From 2 years prior to CLL diagnosis date up to and including VEN treatment index date. **Cytogenetic mutations:** From CLL diagnosis date up to and including VEN treatment index date. **Disease stage & laboratory test results:** 6 months prior to and including VEN treatment index date.	

Relevant Objective(s)	Index Date	Indexing Period	Cohort (s)	Baseline Period	Follow-Up Period/Assessment Window(s)
Secondary objective c)	**CLL index date:** Defined as the date of CLL diagnosis (Figure 4).	01 January 2003 to 31 December 2022	Cohort 1 Cohort 1-VEN	**Patient demographics:** At CLL index date. **Comorbidities:** 2 years prior to and including CLL index date.	N/A
			Cohort 2 Cohort 2-VEN	**Patient demographics:** At CLL index date. **Comorbidities**: 2 years prior to and including CLL index date. **Clinical characteristics:** 6 months prior to and including CLL index date.	

Relevant Objective(s)	Index Date	Indexing Period	Cohort (s)	Baseline Period	Follow-Up Period/Assessment Window(s)
Secondary objective b)	**LoT index date:** Defined as the initiation of a new LoT. Patients can have multiple LoT index dates, one for each LoT for CLL they received, i.e., LoT 1, LoT 2, LoT 3, etc. (Figure 5).	On or after 01 January 2007 (hospital dependent*) to 31 December 2024	Cohort 2*	**Patient demographics:** At each LoT index date **Comorbidities:** For each LoT index date, comorbidities will be assessed in the 2 years prior to and including the LoT index date.	**Treatment exposure assessment window:** From LoT index date to the earliest of LoT end date, emigration, death, or end of data availability. **RT and SPM assessment window:** From LoT index date to the earliest of date of the AE, emigration, death, or end of data availability. **AHE & SOI assessment window:** From LoT index date to the earliest of date of the AE, LoT end date + 30 days, emigration, death, or end of data availability.
Exploratory objective					**Treatment sequencing/utilisation assessment window:** From 1st LoT index date to the earliest date of emigration, death, or end of data availability.

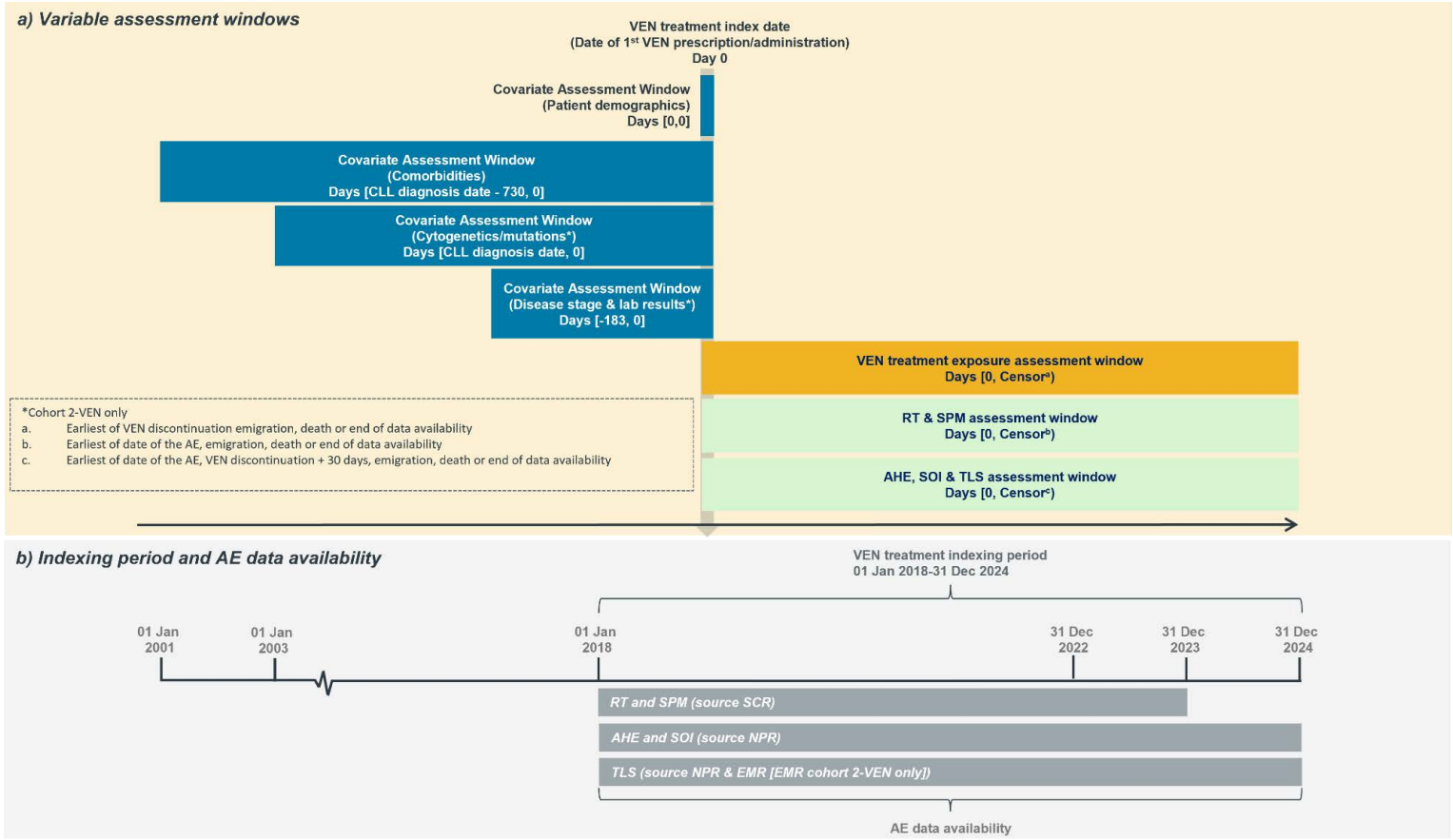
* Start of EMR data availability is hospital dependent and will be on or after 01 January 2007. Data availability for different modules of the EMR may also differ within the hospital. In order to be able to determine full drug treatment history/LoT sequencing, only patients in Cohort 2 diagnosed with CLL after the start of data availability for medication modules in the participating clinics EMR will be included.

AE = Adverse Event; AHE = Autoimmune Haematologic Event; CLL = Chronic Lymphocytic Leukaemia; EMR = Electronic Medical Records; LoT = Line of Therapy; N/A = Not Applicable; RT = Richter's Transformation; SOI = Serious Opportunistic Infection; SPM = Second Primary Malignancy; TLS = Tumour Lysis Syndrome; VEN = Venetoclax

For AEs that are expected to develop over a short duration after treatment commences (AHE, SOI, TLS), AEs will be assessed from the treatment index date (VEN treatment index date or LoT index date as appropriate for the objective) until the earliest of 30 days post VEN/LoT discontinuation[5] (see Section 9.3.1.1 for details of how discontinuation will be derived), emigration, death, or end of data availability regardless of any change to treatment during that period. For AEs that are expected to develop over a longer duration after treatment commences (RT and SPM), AEs will be assessed from the treatment index date (VEN treatment index date or LoT index date as appropriate for the objective) until the end of follow-up (earliest of emigration, death or end of data availability) regardless of any change to treatment. In order to provide some context regarding the occurrence of AEs in relation to CLL drug treatment changes, the occurrence of AEs will be stratified according to changes in drug treatment before and after the occurrence of the AEs for Cohort 2 and Cohort 2-VEN (stratifications are fully specified in Section 9.8.2.2 and Section 9.8.2.3).

5 Should a new LoT for CLL be started within the 30 days post discontinuation, the AE would be counted in both LoT episodes.

Figure 3. Study Schematic for Venetoclax Treatment: Indexing, Variable Assessment Windows, and AE Data Availability

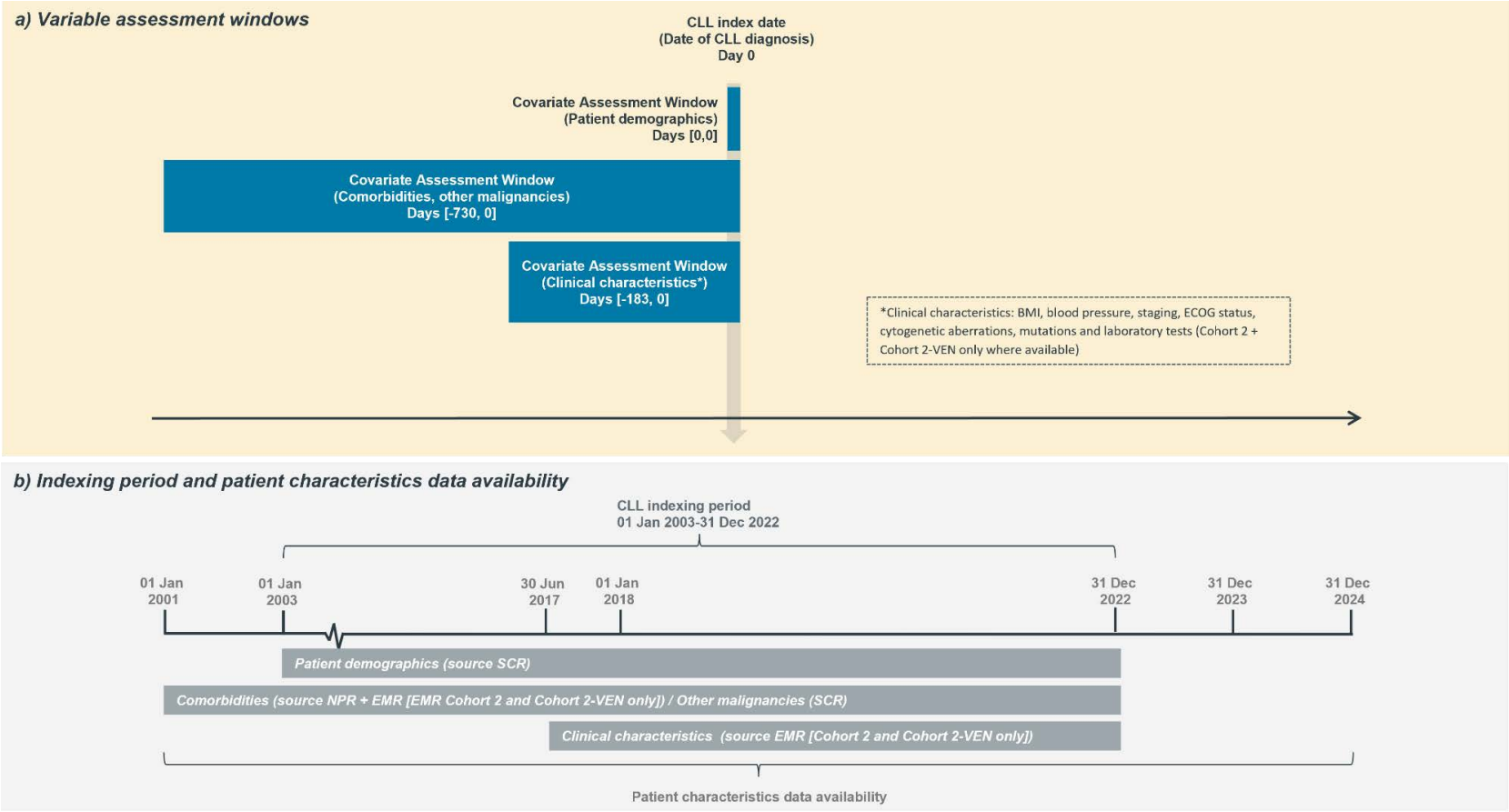


VEN treatment dates: VEN treatment will be identified in the SPDR for Cohort 1-VEN, and in the SPDR and EMR for Cohort 2-VEN. Definitions for VEN treatment (including VEN treatment index date, treatment and discontinuation dates) are provided in Table 2 and Section 9.3.

AE data availability: RT and SPM will be identified from the SCR; AHE, SOI and TLS will be identified from the NPR; TLS will also be identified in the EMR for patients in Cohort 2-VEN.

AE = Adverse Event; AHE = Autoimmune Haematologic Event; CLL = Chronic Lymphocytic Leukaemia; EMR = Electronic Medical Records; NPR = National Patient Register; RT = Richter's Transformation; SCR = Swedish Cancer Register; SOI = Serious Opportunistic Infection; SPM = Second Primary Malignancy; TLS = Tumour Lysis Syndrome; VEN = Venetoclax

Figure 4. Study Schematic for Patient Characterisation: Indexing, Variable Assessment Windows, and Data Availability

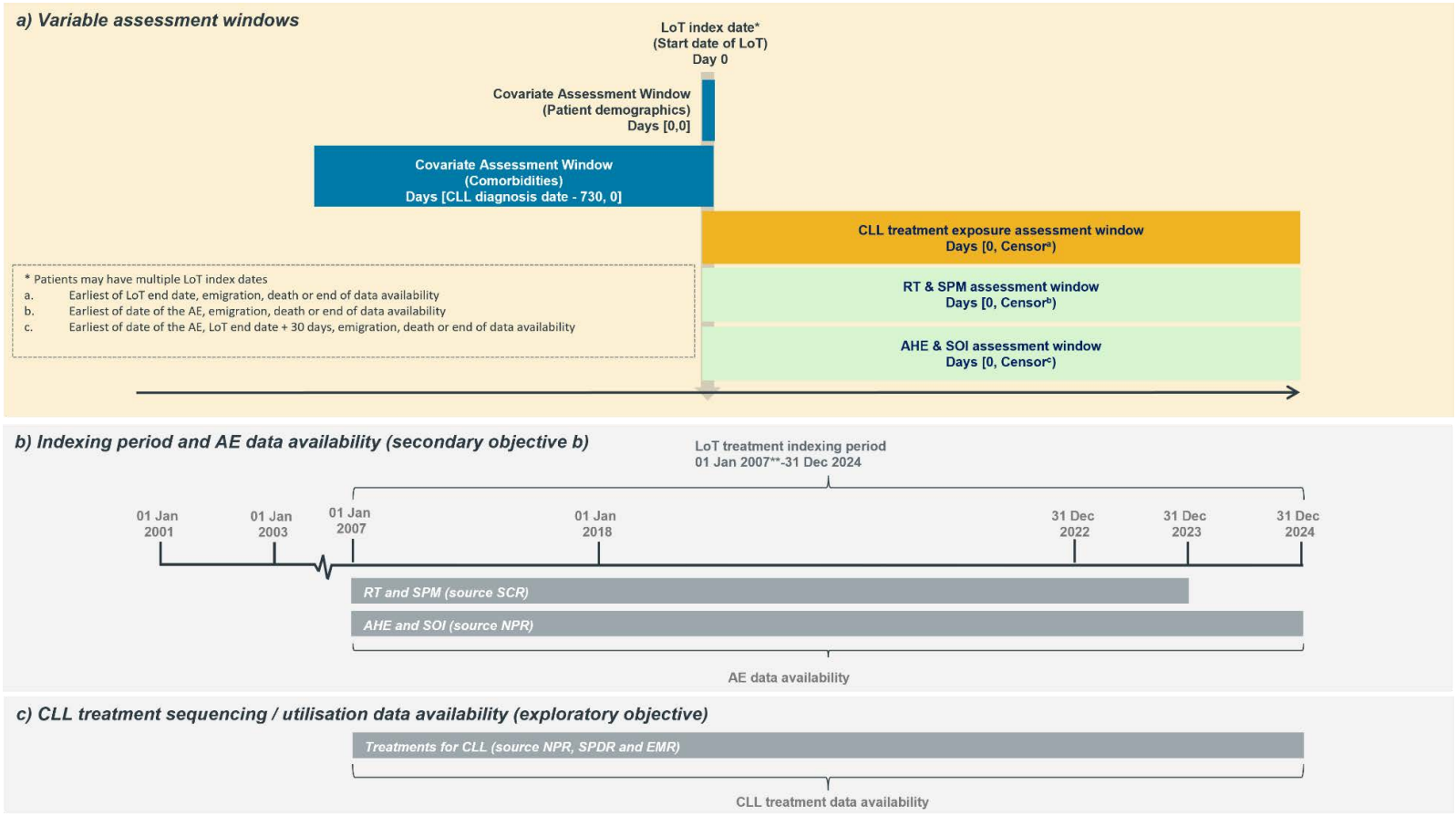


CLL diagnosis: CLL diagnosis date (CLL index date) will be identified in the SCR for Cohort 1 and Cohort 1-VEN, and in the EMR for Cohort 2 and Cohort 2-VEN.

Patient characteristics: Further details of the patient characteristics to be assessed, including data sources to be used for assessing patient characteristics are provided in Table 3 and Table 4 of Section 9.3.

BMI = Body Mass Index; CLL = Chronic Lymphocytic Leukaemia; ECOG = Eastern Cooperative Oncology Group; EMR = Electronic Medical Records; NPR = National Patient Register; SCR = Swedish Cancer Register; VEN = Venetoclax

Figure 5. Study Schematic for LoT: Indexing, Variable Assessment Windows, and Data Availability



* **LoT treatment dates**: Lines of therapy will be identified in the SPDR and EMR. Definitions for identifying LoT, including index, treatment and end dates for each LoT are provided in Table 2 and Section 9.3.

** Start of EMR data availability is hospital dependent and will be on or after 01 January 2007 thus the LoT indexing period will between 01 January 2007 and 31 December 2024.

AE data availability: RT and SPM will be identified from the SCR; AHE and SOI will be identified from the NPR.

AE = Adverse Event; AHE = Autoimmune Haematologic Event; CLL = Chronic Lymphocytic Leukaemia; EMR = Electronic Medical Records; LoT = Line of Therapy; NPR = National Patient Register; RT = Richter's Transformation; SCR = Swedish Cancer Register; SOI = Serious Opportunistic Infection; SPDR = Swedish Prescribed Drug Register; SPM = Second Primary Malignancy; VEN = Venetoclax

9.2 Setting

9.2.1 Eligibility Criteria

The source population will be a national cohort of patients with a diagnosis of CLL in the SCR. The source cohort will be used to form two cohorts (Cohort 1 and Cohort 2). Cohort 1 will include all patients diagnosed with CLL in the SCR between 01 January 2003 and 31 December 2022. Cohort 2 will be a sub-cohort of Cohort 1 and include CLL patients in Cohort 1 from participating haematology clinics in Sweden. Cohort 2 is intended to provide a more granular and in-depth collection of clinical patient data (where available) than can be captured using the national registers alone. Since Cohort 2 will include only patients from the participating haematology clinics in Sweden, its representativeness to the national population will be determined by comparing it to Cohort 1.

Two further sub-cohorts of patients from each Cohort 1 and Cohort 2, who have a record of venetoclax prescription/administration will be formed (Cohort 1-VEN and Cohort 2-VEN). Detailed inclusion and exclusion criteria for each cohort are provided below.

9.2.1.1 Cohort 1

Patients must meet all the following inclusion criteria to be included in Cohort 1:

- Diagnosis of CLL (ICD-10: C91.1 Chronic lymphocytic leukaemia of B-cell type and/or morphology code: 9823/3) in the SCR between 01 January 2003 and 31 December 2022 (the cohort identification period)
- Alive on 01 January 2018
- 18 years or older on the CLL diagnosis date

Patients will be excluded from Cohort 1 if they meet one or more of the following criteria:

- Missing age and/or gender at CLL diagnosis date

9.2.1.2 Cohort 2

Patients must meet all the following inclusion criteria to be included in Cohort 2:

- Be a member of Cohort 1
- CLL diagnosis (ICD-10: C91.1) in the EMR of a participating haematology clinic that is recorded within ± 90 days of the CLL diagnosis in the SCR

There are no additional exclusion criteria for Cohort 2.

9.2.1.3 Cohort 1-VEN

Patients must meet all the following inclusion criteria to be included in Cohort 1-VEN:

- Be a member of Cohort 1
- Have one or more dispensed prescriptions for venetoclax in the SPDR during the VEN treatment indexing period (01 January 2018 to 31 December 2024 - Figure 3).

There are no additional exclusion criteria for Cohort 1-VEN.

9.2.1.4 Cohort 2-VEN

Patients must meet all the following inclusion criteria to be included in Cohort 2-VEN:

- Be a member of Cohort 2
- Have one or more dispensed prescriptions for venetoclax in the SPDR, and/or one or more administrations of venetoclax in the EMR during the VEN treatment indexing period (01 January 2018 to 31 December 2024 - Figure 3).

There are no additional exclusion criteria for Cohort 2-VEN.

9.3 Variables

Variables that will be obtained from the data sources and used to assess the study objectives are presented in Table 3 for Cohort 1 and Cohort 1-VEN and Table 4 for

Cohort 2 and Cohort 2-VEN. Accompanying codes lists for the study variables, e.g., ICD-10 codes, will be provided in the SAP.

Table 3. List of Variables Retrieved for Cohort 1 and Cohort 1-VEN

	Variables Collected	Data Source
Patient characteristics	Sex Geographical region	SCR
CLL characteristics	CLL diagnosis date Age at CLL diagnosis	SCR SCR (Date of birth)
	Age at treatment start Duration of CLL disease at treatment start	SPDR (treatment start)
Comorbidities	Diagnoses included in CCI	NPR
	Other malignancies	SCR
AE	RT (occurrence and date) SPM (occurrence and date)	SCR
	AHE (occurrence and date) SOI (occurrence and date) TLS* (occurrence and date)	NPR
Treatments for CLL	Pharmacological treatments for CLL (e.g., dispensed medications), date(s) of treatment	SPDR
	Haematological treatments (blood transfusion, EPO, G-CSF, intravenous iron preparation, human normal immunoglobulin), date(s) of treatment	NPR
Other treatments	Contraindicated medications*, date(s) of treatment	SPDR
Mortality	Date of death (for censoring of follow-up)	CDR

* Data extraction for Cohort 1-VEN only.

AE = Adverse Event; AHE = Autoimmune HaematologicHematologic Event; CCI = Charlson Comorbidity Index; CDR = Cause of Death Register; CLL = Chronic Lymphocytic LeukaemiaLeukemia; EPO = Erythropoietin; G-CSF = Granulocyte Colony-Stimulating Factor; NPR = National Patient Register; RT = Richter's Transformation; SCR = Swedish Cancer Register; SOI = Serious Opportunistic Infection; SPDR = Swedish Prescribed Drug Register; SPM = Second Primary Malignancy; TLS = Tumour Lysis Syndrome; VEN = Venetoclax

Table 4. List of Variables Retrieved for Cohort 2 and Cohort 2-VEN

	Variables Collected	Data Source
Patient characteristics	Sex Geographical region	SCR
Clinical characteristics*	BMI (weight, height) Systolic/Diastolic blood pressure	EMRs
Lab tests*	Blood counts (including neutrophil counts) Hepatic, renal function, LDH	EMRs
CLL characteristics	CLL diagnosis date Age at CLL diagnosis	SCR (date of birth) EMRs (CLL diagnosis date)
	Age at treatment index Duration of CLL disease at treatment start	SPDR/EMR (treatment start)
	Stage (Bin and Rai for CLL)* ECOG status* Cytogenetic aberrations (e.g., Del(17p))* Mutations (e.g., TP53)*	EMRs
Comorbidities	Diagnoses included in CCI	NPR, EMRs
	Other malignancies	SCR
AE	SPM (occurrence and date) RT (occurrence and date)	SCR
	SOI (occurrence and date) AHE (occurrence and date)	NPR
	TLS** (occurrence and date)	NPR, EMRs
Treatments for CLL	Pharmacological treatments for CLL (e.g., dispensing drugs), date(s) of treatment	SPDR, EMRs
	Chemotherapy, date(s) of treatment Immunotherapy for cancer, date(s) of treatment	EMRs
	Haematologic treatments (blood transfusion, EPO, G-CSF, intravenous iron preparation, human normal immunoglobulin), date(s) of treatment	NPR, EMRs
Other treatments	Contraindicated medications**, date(s) of treatment	SPDR/EMRs
Mortality	Date of death (for censoring of follow-up)	CDR

* Interim Analysis identified high levels of missingness for these variables. Reporting of these variables is therefore dependent on data availability.

** Data extraction for Cohort 2-VEN only.

AE = Adverse Event; AHE = Autoimmune Haematologic Event; BMI = Body Mass Index; CCI = Charlson Comorbidity Index; CDR = Cause of Death Register; CLL = Chronic Lymphocytic Leukaemia; ECOG = Eastern Cooperative Oncology Group; EMR = Electronic Medical Record; EPO = Erythropoietin; G-CSF = Granulocyte Colony-Stimulating factor; LDH = Lactate Dehydrogenase; NPR = National Patient Register; RT = Richter's Transformation; SCR = Swedish Cancer Register; SOI = Serious Opportunistic Infection; SPDR = Swedish Prescribed Drug Register; SPM = Second Primary Malignancy; TLS = Tumour Lysis Syndrome; TP53 = Tumour Protein P53; VEN = Venetoclax

The same information might be available from different sources. Since the EMR system is the primary source for reporting into the national registers and recording errors that could occur when data is reported into the national registers, the hospital EMR data will be considered the optimal source. For most variables, the preferred order of reliability will be the following: 1) the hospital EMR data, 2) the SCR, and 3) the NPR.

9.3.1 Exposure

The primary exposure of interest is treatment with venetoclax, identified by Anatomical Therapeutic Classification (ATC) code L01XX52 in the SPDR (Cohort 1-VEN, Cohort 2-VEN) and EMR (Cohort 2-VEN). Note that venetoclax administered and/or prescribed as part of a clinical trial will not be captured in the SPDR or EMR. For Secondary Objective b) treatment regimen by LoT will be considered the exposure of interest (Cohort 2 only).

Initial exposure to venetoclax and other CLL drug treatments will be defined as any record of prescription/administration of the product during the observation period (01 January 2001 to 31 December 2024 – see Figure 2) without prior record of prescription/administration of the same product in the available patient's history. A patient will be considered exposed to venetoclax / a LoT starting on their venetoclax treatment / LoT index date through until the first of: discontinuation of venetoclax / LoT, the end of the study period, emigration, or death. See Section 9.3.1.1.1 for how the duration of treatment exposure will be determined. See Table 2 for further details on exposure assessment windows. While not common, retreatment with venetoclax may occur; identifications of retreatment and whether retreatment should be considered as a separate exposure will be determined by subject matter expertise.

Operational definitions for determining treatment dynamics, such as identifying treatment regimens, lines of therapy, add-on therapy, treatment gaps, and switches, will be derived and pre-specified in accordance with treatment guidelines and in conjunction with subject matter experts prior to any analysis taking place. Given the real-world nature of the study, it is anticipated that refinement of the definitions will need to be an iterative process during the analysis phase of the study to ensure alignment of definitions with treatment patterns in real-world clinical practice. The process of refining the definitions will apply only to the study exposures. Outcomes will remain fully blinded ensuring study results are not influenced in any way throughout the process.

The breadth of information that will be captured from different sources (national health registers and EMRs) will allow for accurate measurement of exposures of interest. To ensure the validity of exposure measurement, subject matter experts will be included in the study to provide scientific input. In addition, data extraction will be performed by trained and experienced IQVIA personnel.

9.3.1.1 Drug Treatment Regimens and Lines of Therapy (Cohort 2)

Drug regimens and treatment lines can only be assessed for Cohort 2 and Cohort 2-VEN, as patients' complete CLL treatment history is captured from EMR (data on administered in-hospital medications [e.g., chemotherapy]) together with the SPDR (data on prescribed/dispensed medications). The complete list of CLL drug treatments, i.e., exposures of interest for identifying treatment regimens, is provided in Annex 5.

The treatment regimens of interest for the study are shown in Figure 6. Regimens will be assigned based on the order shown (1-3) in Figure 6 and thus will be mutually exclusive. The hierarchy of treatment regimen categories (Category i–iii) reflects the different levels of granularity with which the regimen could be reported. While the aim is to report to the most granular category feasible for each regimen type (1-3), it is acknowledged that due to small counts and required masking rules (see Section 9.8.1), such a greater category of granularity may not be possible, and a lesser category of regimen granularity may need to be reported.

The following treatment regimens will be used to determine CLL drug treatments for Cohort 2 during the assessment window for each LoT (see Table 2 for details of assessment windows):

Regimen Type 1: Venetoclax regimens:

- Category i: Defined as any treatment regimen with a prescription or administration of venetoclax.
  - Category ii: Venetoclax regimens will be further classified into venetoclax monotherapy or venetoclax-based combination therapy.
    - Category iii: Venetoclax-based combination therapy will be further classified as: venetoclax plus rituximab or obinutuzumab; venetoclax plus Bruton tyrosine kinase inhibitor (BTKi) (including venetoclax plus ibrutinib); or venetoclax plus Phosphoinositide 3-kinase inhibitors (PI3Ki) (including venetoclax plus idelalisib).

Regimen Type 2: BTKi regimens:

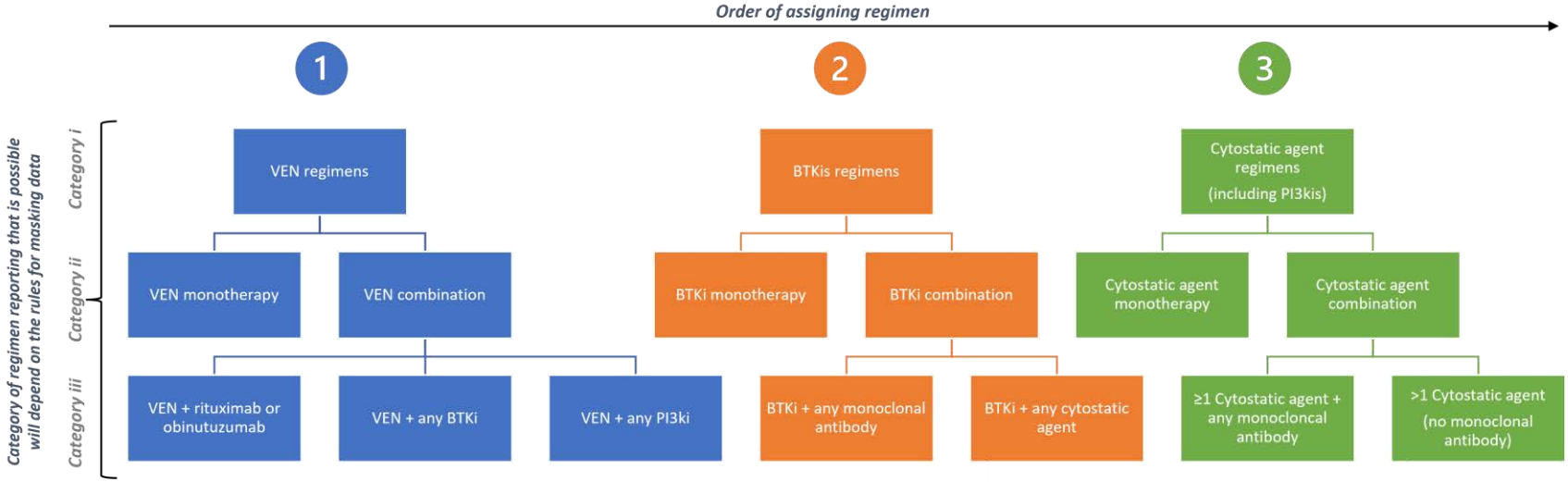
- Category i: Defined as any treatment regimen with a prescription or administration of one or more BTKi (including ibrutinib or acalabrutinib).
  - Category ii: BTKi regimens will be further classified into BTKi monotherapy or BTKi-based combination therapy.
    - Category iii: BTKi-based combination therapy will be further classified as: any BTKi plus any monoclonal antibody(s); or any BTKi plus any cytostatic agent(s). It should be noted that the combination of BTKi plus venetoclax is excluded from the BTKi regimens (Type 2) and is part of the venetoclax regimens (Type 2).

Regimen Type 3: Cytostatic agent regimens (including PIK3i):

- Category i: Defined as any treatment regimen with a prescription or administration of one or more cytostatic agents (including idelalisib, chlorambucil, bendamustine, fludarabine, cyclophosphamide, doxorubicin, or vincristine).

- Category ii: Cytostatic agent regimens will be further classified into monotherapy or cytostatic agent-based combination therapy.
  - Category iii: Cytostatic agent-based combination therapy will be further classified as: cytostatic agent(s) plus other cytostatic agent(s); cytostatic agent(s) plus monoclonal antibody (including FCR and bendamustine plus rituximab). It should be noted that the combinations of cytostatic agents plus BTKi, and venetoclax plus idelalisib are excluded from the cytostatic regimens and are part of the BTKi regimens (Type 2) and venetoclax regimens (Type 1) respectively.

Figure 6. Treatment Regimens of Interest and Assignment of Mutually Exclusive Regimen Types



Assignment of regimens: Regimens will be assigned based on the order of assignment shown (1-3) and thus will be mutually exclusive. The hierarchy of treatment regimen category (i-iii) reflects the different levels of granularity with which the regimen could be reported. While the aim is to report to the highest possible granularity depicted for each regimen type (1-3), it is acknowledged that due to small counts and the required masking rules, such a greater category of granularity may not be possible, and a lesser category of regimen granularity may need to be reported.

BTKi = Bruton Tyrosine Kinase Inhibitor; PIK3i = Phosphoinositide 3-kinase Inhibitors; VEN = Venetoclax

9.3.1.1.1 Definition of Treatment Duration, Add-On Therapy, Gaps, and Switches

The patient will be assumed to be exposed to the drug of interest (venetoclax or other CLL-related drug) for a period equal to the duration of the dispensed prescription, starting on the date of earliest dispensing. No delay in exposure following the date of dispensed prescription will be assumed. The end date of dispensed prescription use will be calculated using the estimated daily dose and the number of tablets prescribed to estimate the presumed days of supply. For hospital-administered treatments, for which a prescription does not apply, treatment duration will be calculated according to the administered drug module in the EMR.

Treatment with a drug is assumed to be discontinued if the gap between the last day of the treatment and the next prescription for the drug of interest is more than (>) 60 days. Treatment episodes will be defined as consecutive prescriptions without gaps of > 60 days. Generally, a debulking therapy, administered prior to a specific regimen, will not be considered part of a regimen

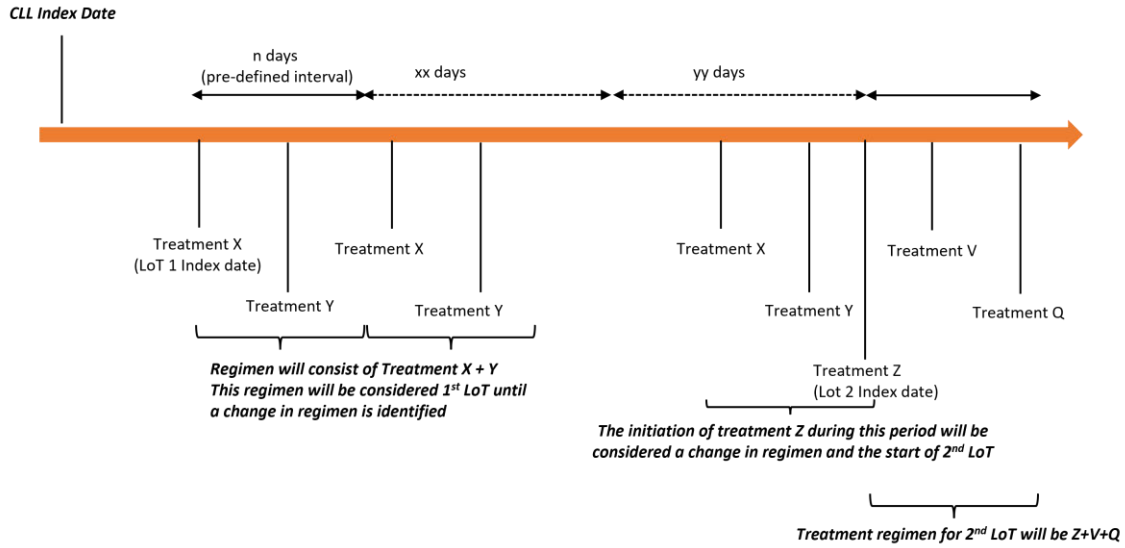
9.3.1.1.2 Defining LoT (Cohort 2 only for Secondary Objective b and Exploratory Objective)

The start date of the 1st LoT (1st LoT index date) will be defined as the earliest date of a prescription or administration of any CLL-related drug(s) (see Annex 5) following the CLL index date. To define a treatment regimen, a pre-defined number of days in which CLL drug treatments are prescribed/administered will be set. The regimen will then be defined as the single CLL drug or combination of drugs prescribed/administered during that predefined interval following the 1st LoT index date.

When a change in regimen is identified (for example., the addition of a new drug to the existing regimen, a switch to a new treatment, or re-initiation of the same CLL-related drug regimen after a period of treatment discontinuation [discontinuation is defined in Section 9.3.1.1.1]), this constitutes the start date of the 2nd LoT (2nd LoT index date). The new regimen will again be identified as the single CLL drug or combination of drugs

prescribed/administered during the predefined interval following the 2nd LoT index date. The same process will be used to identify subsequent lines of treatments and regimens. An illustrative example of how LoT and regimen will be assigned can be found in Figure 7.

Figure 7. Illustrative Example of Assigning LoT



CLL = Chronic Lymphocytic Leukaemia; LoT = Line of Therapy

Swedish national treatment guidelines for CLL, as well as input from clinical experts, will provide guidance for defining the predefined interval for identifying treatment regimens. The following intervals are initially proposed but are subject to change during the development of the operational definitions for defining regimens, LoT, and treatment changes:

- Venetoclax-based regimens: An interval of 90 days will be applied, with a sensitivity analysis of 60 days (see Section 9.8.3.2).
- For non-venetoclax-based regimens: An interval of 35 days will be applied, with a sensitivity analysis of 28 days (see Section 9.8.3.2).

9.3.2 Safety Outcomes

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Serious adverse events consist of an AE that results in death, is life-threatening, requires inpatient hospitalisation, or results in prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is a medically important event or reaction, according to International Conference on Harmonisation (ICH) E3D guidelines.

For this study, select AEs of interest will be retrieved from previously collected data (i.e., secondary data). The primary outcome is the incidence of select AEs in CLL patients treated with venetoclax. These events of interest will be identified based on ICD-10 diagnosis codes (from the NPR and SCR) and free-text searches of physician case notes in the EMRs (TLS only). Specifically:

- SPM – any new cancer diagnosis (ICD-10 classification codes C00.x – C97, D37.x – D48.x) sourced from the SCR
- RT – defined as progression of CLL to a more aggressive form of lymphoma, i.e., a diagnosis code for DLBCL (ICD-10: C83.3) or Hodgkin lymphoma (ICD-10: C81) sourced from the SCR
- SOI – defined as per Annex 6 sourced from the NPR
- AHE – defined per ICD-10 classification codes as "D59.1 Other autoimmune hemolytic anaemias" and "D69.3 Idiopathic thrombocytopenic purpura" sourced from the NPR
- TLS – defined per ICD-10 classification codes as "E88.3" sourced from the NPR or identified in the free text of physician case notes in the EMR (Cohort 2-VEN only).

For Secondary Objective b) the outcome is the incidence of SPM, RT, SOI, and AHE (as defined above) in CLL patients treated with different treatment regimens by LoT.

The operational definitions and assessment windows for the AEs are summarised in Table 5.

Table 5. Data Source and Availability, Assessment Windows, and Operational Definitions for AEs of Interest

Adverse Event	Data Source	Assessment Window	Cohort	Operational Definition
RT*	SCR – end of data availability: 31-Dec-2023	**Primary Objective/Secondary Objective A** START: Venetoclax treatment index date END**: First of date of outcome, emigration, death, end of SCR data availability	Cohort 1-VEN Cohort 2-VEN	A diagnosis code for DLBCL (ICD-10: C83.3) or HL (ICD-10: C81)
		Secondary Objective B START: LoT index date END: First of date of outcome, emigration, death, end of SCR data availability	Cohort 2	
SPM	SCR – end of data availability: 31-Dec-2023	**Primary Objective/Secondary Objective A** START: Venetoclax treatment index date END**: First of date of outcome, emigration, death, end of SCR data availability	Cohort 1-VEN Cohort 2-VEN	A diagnosis code for a non-CLL malignancy (ICD-10: C00-C97 [Malignant neoplasms], excluding C91.1 [CLL]; D37-D48 [Neoplasms of uncertain or unknown behaviour])
		Secondary Objective B START: LoT index date END: First of date of outcome, emigration, death, end of SCR data availability	Cohort 2	
AHE	NPR – end of data availability: 31-Dec-2024**	**Primary Objective/Secondary Objective A** START: Venetoclax treatment index date END: First of date of outcome, emigration, death, discontinuation of venetoclax plus 30 days, end of NPR data availability	Cohort 1-VEN Cohort 2-VEN	A diagnosis code for an AHE (ICD-10: D59.1 [Other autoimmune haemolytic anaemias] or D69.3 [Idiopathic thrombocytopenia purpura])
		Secondary Objective B START: LoT index date END: First of date of outcome, emigration, death, LoT end date plus 30 days, end of NPR data availability	Cohort 2	

Adverse Event	Data Source	Assessment Window	Cohort	Operational Definition
SOI	NPR – end of data availability: 31-Dec-2024**	**Primary Objective/Secondary Objective A** START: Venetoclax treatment index date END: First of date of outcome, emigration, death, discontinuation of venetoclax plus 30 days, end of NPR data availability	Cohort 1-VEN Cohort 2-VEN	ICD-10 diagnosis code(s) for an SOI that occurred during an inpatient hospitalisation. The complete list of ICD-10 diagnosis codes that were used to identify SOIs can be found in Annex 6. For the SOIs that required 2 or more ICD-10 diagnosis codes, the codes must have occurred during the same hospitalisation stay for an inpatient encounter.
		Secondary Objective B START: LoT index date END: First of date of outcome, emigration, death, LoT end date plus 30 days, end of NPR data availability	Cohort 2	
TLS	NPR – end of data availability: 31-Dec-2024** EMR– end of data availability: 31-Dec-2024	**Primary Objective/Secondary Objective A** START: Venetoclax treatment index date END: First of date of outcome, emigration, death, discontinuation of venetoclax plus 30 days, end of NPR data availability	Cohort 1-VEN Cohort 2-VEN	A diagnosis code for TLS (ICD-10: E88.3); or identified in the free text of the EMR using text mining (applies to Cohort 2-VEN only)***.
	NPR – end of data availability: 31-Dec-2024** SPDR/ end of data availability: 31-Dec-2024 EMR– end of data availability: 31-Dec-2024	**Secondary Objective D** START: Venetoclax treatment index date END: First of date of outcome, emigration, death, discontinuation of venetoclax plus 30 days, end of NPR data availability (applies to patients in Cohort 1/Cohort 1-VEN only), end of SPDR data availability, end of EMR data availability (applies to Cohort 2/Cohort 2-VEN only)		

* Patients will be excluded from the analysis for RT if they have records of RT any time prior to the VEN treatment index date (Primary and Secondary Objective a) and any time prior to the 1st LoT index date (Secondary Objective b).

** NPR data are typically updated in June for the prior year; however, the updates can be completed earlier or later. For Final Report, the expectation is to receive data until 31 December 2024 from the NPR at time of final extraction in Q2 2025.

*** The complete list of keywords that are used to identify TLS in the EMR can be found in the SAP.

AE = Adverse Event; AHE = Autoimmune Haematologic Event; ATC = Anatomical Therapeutic Chemical; CLL = Chronic Lymphocytic Leukaemia; DLBCL = Diffuse Large B-cell Lymphoma; EMR = Electronic Medical Record; HL = Hodgkin Lymphoma; ICD-10 = International Classification of Disease, 10th Edition; LoT = Line of Therapy; SCR = Swedish Cancer Registry; NPR = National Patient Register; RT = Richter's Transformation; SAP = Statistical Analysis Plan; SOI(s) = Serious Opportunistic Infection(s); SPDR = Swedish Prescribed Drug Register; SPM = Second Primary Malignancy; TLS = Tumour Lysis Syndrome; VEN = Venetoclax

For patients prescribed/administered venetoclax, the above-listed AEs will be assessed within the following periods:

1. On-treatment assessment period (applicable to SOI, AHE, and TLS): time from the VEN treatment index date until 30 days post-venetoclax discontinuation (regardless of whether patients switch to other therapy within that time period), emigration, death or end of data availability, whichever occurs first.
2. Any time after VEN-initiation (applicable to SPM and RT): time from VEN treatment index date until emigration, death, or the end of data availability, whichever occurs first, regardless of whether patients switch to other therapy.

Given this approach, the assessment of the occurrence of AEs will be stratified according to different time periods and changes in CLL-related drug treatments before and after the VEN treatment index date. Full details of these stratifications are provided in Section 9.8.2.2.

A similar approach for assessment of the occurrence of AEs by LoT (Secondary Objective b) will be used to assess the listed safety events among treatment regimens in Cohort 2. Full details of the stratifications for Secondary Objective b) are provided in Section 9.8.2.3.

9.3.3 Other Variables

Details for medications that are contraindicated for use with venetoclax treatment will be collected as below:

- A list of predefined contraindicated medications listed in the summary of product characteristics (SmPC) for use with venetoclax has been established based on the venetoclax SmPC (see Annex 7). If there are one or more prescriptions dispensed for contraindicated medications for a patient, start and stop dates of the medication(s) will be determined.
- Based on start and stop dates of venetoclax, it will be determined if the contraindicated medication was taken during treatment with venetoclax.

- For instances where contraindicated medication was taken during treatment with the venetoclax treatment, analysis will be performed to assess if any TLS occurred in the treatment period.

9.4 Data Sources

Four national health registers in Sweden will be used to retrieve health information pertaining to the identified CLL patients. These registers are governed by the Swedish National Board of Health and Welfare (NBHW) and reporting information to them is compulsory for all health care professionals. Rigorous validation work is constantly ongoing from the health authority in order to ensure that data is complete, comprehensive, and of the highest quality possible. There is a large number of scientific publications based on the data sources that will be used in this study.[28-30] All the data will, nevertheless, be reviewed in the data management process in order to ensure the completeness of the data.

Since the EMR system is the primary source for reporting into the national registers and recording errors may occur when data is reported into the national health registers, the EMR data will be considered the "gold standard." Thus, in case of potential duplication of the same data from multiple sources, the EMR data will be considered the primary source for the analysis. Any potential discrepancy between data sources will be documented.

Furthermore, the SCR has been validated in a study.[22,31] The study concluded that the overall completeness of the register is very high (i.e., > 96%) and comparable to other high-quality registers in Northern Europe and that any potential underreporting will be without major impact for most uses in epidemiological or public health studies. Despite the anticipated high reliability and validity of the source data used in the proposed study, the data collected will be scrutinised in the data extraction and management process in order to ensure the completeness of the data. In particular, cross-validation will be made based on the different coding classification systems.

A summary of the data availability for each of the Swedish national health registers and the EMRs of participating haematology clinics (Table 6) and details on the different registries are provided in Section 9.4.1.

Table 6. Summary of Data Availability for the Swedish National Health Registers and EMRs of the Participating Haematology Clinics

Data Source	Start Date of Available Data	Start Date of Data Extraction for the Study	End Date of Data Last Extraction for the Study
SCR	01 January 1958*	01 January 1958*	31 December 2023
NPR**	01 January 1987	01 January 1997	31 December 2024
SPDR	01 July 2005	01 July 2005	31 December 2024
CDR	01 January 1952	01 January 1961	31 December 2024
EMRs of participating haematology clinics	2007 or later***	2007 or later***	31 December 2024

* Cases diagnosed before 01 January 2003 will be excluded from the analysis.

** NPR data are typically updated in June for the prior year; however, the updates can be completed earlier or later. Coverage for outpatient non-primary care began nationwide in 2001.

*** The start dates of EMR data availability by module for each clinic region will be provided in the SAP.

CDR = Cause of Death Register; EMR = Electronic Medical Records; NPR = National Patient Register; SAP = Statistical Analysis Plan; SCR = Swedish Cancer Register; SPDR = Swedish Prescribed Drug Register

9.4.1 National Health Registers

9.4.1.1 Swedish Cancer Registry

The SCR was introduced in 1958 and collects information from the time of diagnosis on all diagnosed cancer patients across Sweden. The registry receives data reported from all oncology/haematology clinics across Sweden, and the data are verified by oncologists and pathologists at regional oncology research centres across the country prior to reporting into the national registry. The SCR is updated annually in January.

9.4.1.2 Swedish National Patient Register

The Swedish NPR dates back to 1964. From 1987, there is information on all completed inpatient admissions in publicly operated hospitals, and the collection of outpatient care

data began in 1997. The collection of specialised outpatient care data began in 2001. The key variables are diagnosis (ICD-9/10 code), sex, age, region, hospital visits, specialty visits, and hospital admission and discharge dates. In addition, detailed data is available on all medical procedures and surgeries performed in the inpatient and outpatient specialist setting in Sweden. The NPR is updated annually in June.

9.4.1.3 Cause of Death Register

The National CDR in Sweden allows for the study of mortality in any patient population of interest. The statistics on causes of death comprise all deaths, covering all residents in the country, whether the person in question was a Swedish citizen or not, and irrespective of whether the deaths occurred in Sweden or not (i.e., deaths will be reported even if they occurred in a third country). The main variables included in the register are: social security number, home district, sex, date of death, underlying cause of death, nature of the injury, multiple causes of death, marked if autopsied or not, and if so, what kind; marked if operated on within four weeks before death; marked if injury/poisoning; marked if alcohol related; marked if narcotic related; and code for diabetes. In this study, the CDR will be used to assess mortality in the defined patient population for censoring.

9.4.1.4 Swedish Prescribed Drug Register

The SPDR contains information about unique patient identifiers for all prescriptions dispensed to the whole population of Sweden (~10.5 million inhabitants) since 2005. There are details on the sex, age, and residency of the patients included in the register. For prescribed drugs, the register includes data on dispensed items, substance, brand name, formulation, package size, dispensed amount, dosage, expenditure, and reimbursement. There is also information on the date of prescribing and dispensing, as well as the prescriber's profession and practice. All drugs are classified according to the ATC code. There is no information on over-the-counter medications for drugs used or administered in hospitals. In order to evaluate the indication, the SPDR data will be linked to the NPR, which includes ICD-10 diagnosis codes associated with all inpatient and outpatient (specialist) health care contacts, as well as national coverage.

9.4.2 EMR Data

Haematology clinic EMR data include unique longitudinal details around patient characteristics, laboratory test results, clinical progression, treatments, and outcomes. The inclusion of EMR data is intended to enable access to, and analysis of, more granular clinical data that are not captured in the national registers (e.g., cytogenetic and mutation analysis data, information on hospital-administered treatments [such as chemotherapy], and other treatments, and physician notes regarding TLS) when recorded and available as part of real-world care. EMR data availability is hospital dependent; thus site-specific restrictions of patient populations for Cohort 2 will apply.

EMR data will be extracted using the PYGARGUS Customised eXtraction Platform (CXP) 3.0 and extraction programs specifically adapted from PYGARGUS CXP 3.0 for the present research study in the hospital EMR settings chosen.

The PYGARGUS CXP 3.0 is an application intended for extracting relevant data from health care documentation systems. PYGARGUS CXP 3.0 supports extraction from hospitals, general practitioners, and other health care providers. The information that can be extracted with CXP includes, for example, information on patient demographics, diagnoses, medications and prescriptions, laboratory test results, and results from pathology/cytology.

9.4.3 Data Linkage and Data Privacy

Linkage across the national health registers will be carried out at the national authority using personal identification numbers that each Swedish citizen carries from birth to death, and other residents can get if planning to live more than 1 year in Sweden. The health registers that will be used in this study are all governed by the Swedish Health Authority and are updated annually, except the SPDR, which is updated monthly. The linkage is performed in accordance with national and EU data privacy legislation and handled by the Swedish Health Authority. The patient-level data that will be accessed by IQVIA are therefore de-identified, and thus the integrity of the individual patient is

protected. Longitudinal individual patient data from the EMR cohort will be linked to the pre-specified set of national health registers described above.

9.5 Study Procedures

This study will comply with all applicable laws, regulations, and guidance regarding patient protection, including patient privacy. Individual informed consent will not be obtained since this is a non-interventional population-based study. However, certain other precautions will be taken, including:

- Ensuring data is pseudonymised
- Ensuring final analysis data is pseudonymised
- Ensuring possibility of linkage back to individually identified patients is impossible when the final study database is available (anonymised)
- Obtaining ethical committee approval for use of data as proposed (e.g., the review of and extraction of information from individual medical charts) records for the proposed use ahead of study initiation

Specifically, the following steps are taken with regard to data extraction:

- Exports of CXP result in two types of files: the analysis files and a key code file. The content of the analysis files is anonymous, which means that the social security number (*personnummer*) has been replaced with an internal patient identification (CXP number). The key code file contains a link between the patient's identity (social security number) and internal patient identification from the analysis files. The key code file is handled and stored always by a third party, which in most cases is the Principal Investigator (PI). This is to keep it separated from the analysis result. This file is used for linking to other registers.
- Disclosure of the analysis files and the key code file should be kept apart (i.e., they are saved on two separate hard drives). Both hard drives must in turn be encrypted.
- The hard disk that contains the key code file is provided to the PI, who subsequently sends it to the NBHW.

- The hard disk with the analysis files is submitted to the responsible person at IQVIA/PYGARGUS. Once all the extractions are made, the various databases are linked together into one database. Data cleansing is done in this database before it is submitted to the NBHW. With data cleansing, all data disclosure of an individual, such as personal identification number, is cleared away. The study database is then sent to the NBHW, along with the file description. The key code file is sent separately.
- The NBHW combines the data of the study database with data from other registers, according to an agreement, and returns the linked dataset in the form of Statistical Analysis System (SAS) files to IQVIA. Such returning of data means that data is disclosed by the NBHW and that such disclosure is subject to OSL. The NBHW returns the data connected to an identification number, which only they will hold and have access to, i.e., that number that replaces the identifying number in the key code file. It is, thus, only the NBHW that is able to identify which individual can be connected with a certain individual's dataset.

9.6 Study Size

9.6.1 Cohort Size Estimates and Updates *(based on recent study reports)*

Cohort 1 and Cohort 1-VEN

For Cohort 1, prevalent cases of CLL who were still alive on 01 January 2018 were included in a retrospective data set covering patients diagnosed prior to 2018. Starting from the year 2018, a prospective dataset has been built by adding newly diagnosed CLL patients from 01 January 2018 to 31 December 2022 (i.e., incident cases). Patients then have the potential to be followed for an additional one to two years, until 31 December 2023 for the SCR and until 31 December 2024 for the NPR, SPDR, EMR, and CDR (see Section 9.1 and Figure 2 for more details).

Updated counts from data extraction #7 (completed in Q4 2024) show that by the end of 2024, approximately 8,265 CLL patients are projected to be included in Cohort 1, of

which 500 are expected to receive venetoclax (or 6% of Cohort 1). The projected sample size estimates for Cohort 1 provided in earlier protocol versions (6,400 for Cohort 1 in protocol v6.0) have hence been achieved.

Cohort 2 and Cohort 2-VEN

At the time of original protocol development (v1.0 2017), the anticipated Cohort 2 size was based on the assumption that ten to fifteen haematology clinics in Sweden would agree to participate in the study. However, the number of CLL patients projected to be included in Cohort 2 has since been revised downward to reflect challenges with site recruitment (*seven hospitals were ultimately included in the study*) and the fact that not all of the estimated prevalent CLL patients in each county of interest will meet the study inclusion criterion for Cohort 2 (i.e., have an EMR CLL diagnosis that occurs within ± 90 days of their SCR CLL diagnosis) given that the EMR data for diagnosis roughly start from 2007 onwards[6]. Local practice guidelines during the Covid-19 pandemic also restricted the use of venetoclax, which along with lower site enrolment, has led to lower-than-expected numbers of venetoclax patients in Cohort 2.

These revised numbers (based on data extraction #7 completed in Q4 2024) show that by the end of 2024, approximately 1,600 CLL patients are estimated to be included in Cohort 2, of which 80 are expected to receive venetoclax (or 5% of the revised Cohort 2).

Table 7 provides detailed information on patient counts for all cohorts from data extraction #6 (completed in Q4 2023 with cohort identification through to 2021, and as reported in the latest Study Progress Report v6.0, dated March 2024) and revised estimates from data extraction #7 (completed in Q4 2024 with cohort identification through to 31 December 2022, i.e., the end of the cohort identification period). Note, patient numbers and consequently the length of observed follow-up are increasing across both cohorts.

6 **Footnote**:
For Cohort 1, the diagnosis of CLL from SCR would be from 2003, though EMR data starts from 2007 onwards, making not all cohort 1 patients to be eligible for Cohort 2.

Table 7. Patient Count Projection in the Number of CLL Patients by the end of 2024**

Cohort	Current Number of CLL Patients after Data Extraction #6* (Cohort Identification to 31 Dec 2021)	Revised Numbers of CLL Patients by the End of the Cohort Identification Period (to 31 Dec 2022) Based on Data Extraction #7**
Cohort 1	7,543	8,265
Cohort 2	1,400	1,557
Cohort 1-VEN	307	500
Cohort 2-VEN	38	75

* Table based on data presented in the Study Progress Report 6.0 dated March 2024.

** Based on data extraction #7 (completed in Q4 2024) as presented in Study Progress Report #7.

CLL = Chronic Lymphocytic Leukaemia; Q = Quarter; VEN = Venetoclax

9.6.2 Precision Estimates for Incidence Rates (Primary Objective)

For the Primary Objective, incidence rates (IR) for the AEs of interest among venetoclax-exposed CLL patients will be calculated separately for Cohort 1-VEN and Cohort 2-VEN (see Section 9.8 for more details on analysis).

Because these AEs vary widely in frequency, from rare to more common, the IR 95% confidence intervals (CI) are computed using Byar's approximation method[32,33] for higher-frequency events (AHE) and exact methods for rare events to ensure accurate inference (other AEs of interest).[34-36]

To ensure that both rare and more common events are adequately captured, margins of error of 0.05, 0.1, 0.2, and 0.3 around the IR estimates will be evaluated. These margin of error values are deliberately broad to account for the possibility of sparse event counts in smaller cohorts and to ensure that the CIs are sufficiently precise for clinical interpretation.

Because the final mean duration of venetoclax exposure will be unknown until the final data extraction and linkage in Q2 2025, the following mean durations were used for the precision calculations: 0.5 years, 1 year (corresponds to the fixed-dose duration for first-

line treatment with venetoclax), 2 years (corresponds to the fixed-dose duration for second-line treatment with venetoclax), and 3 years.

Estimated IR with 95% CIs for select AEs of interest using a range of sample sizes of 500, 525, 575, and 600 for Cohort 1-VEN, and 75, 80, 85, and 90 for Cohort 2-VEN are provided in Table 8 and Table 9, respectively. The anticipated IR of SOI, SPM, TLS, RT, and AHE are 1.2, 2.7, 3.0, 6.3, and 23.7 per 100 person-years (PY), respectively.[37-40]

The 95% CI reported in Table 8 and Table 9 provide a range of plausible values for the true IR of safety events of interest in the actual population. These ranges account for different feasible accrual scenarios in a real-world setting. The chosen sample sizes allow the estimation of IRs with the specified margins of error across all AEs and several exposure durations.

For example, considering a margin of error of 0.05 and a mean duration of VEN exposure of 0.5 years, in Cohort 1-VEN (N = 500), the 95% CI is 2.6 to 3.1 for an observed IR of 3.0 for TLS (Table 8), suggesting that we can be 95% confident that the true population IR for TLS falls within this range of CI. Similarly for Cohort 2-VEN (N = 75), also considering a margin of error of 0.05 and a mean duration of VEN exposure of 0.5 years, the 95% CI is 1.8 to 4.5 (Table 9). The wider intervals observed in Cohort 2-VEN reflect the increased uncertainty associated with the smaller sample sizes in this cohort.

Table 8. Estimated 95% CI for IR for the AEs of Interest Using a Range of Probable Sizes and Exposure Durations for Cohort 1-VEN

Cohort Size	Mean Duration of VEN Exposure (years)	Margin of Error	Incidence Rates (per 100 Person-Years)				
			SOI	SPM	TLS	RT	AHE
			1.2	2.7	3.0	6.3	23.7
500	0.5	0.05	0.6-1.1	2.2-2.7	2.6-3.1	6.1-6.6	23.5-24.0
		0.1	0.6-1.2	2.2-2.8	2.6-3.2	6.1-6.7	23.4-24.0
		0.2	0.5-1.3	2.1-2.9	2.5-3.3	6.0-6.8	23.3-24.1
		0.3	0.5-1.4	2.0-3.0	2.4-3.4	5.9-6.9	23.2-24.2
	1	0.05	0.9-1.2	2.6-2.9	2.9-3.2	6.2-6.5	23.6-23.9
		0.1	0.8-1.2	2.5-2.9	2.8-3.2	6.1-6.5	23.5-23.9
		0.2	0.8-1.3	2.4-3.0	2.7-3.3	6.0-6.6	23.4-24.0
		0.3	0.7-1.5	2.3-3.1	2.6-3.4	5.9-6.7	23.3-24.1
	2	0.05	1.1-1.3	2.6-2.8	2.9-3.1	6.2-6.4	23.6-23.8
		0.1	1.0-1.3	2.6-2.9	2.9-3.2	6.2-6.5	23.5-23.8
		0.2	1.0-1.5	2.5-3.0	2.8-3.3	6.1-6.6	23.4-23.9
		0.3	0.9-1.6	2.4-3.1	2.7-3.4	6.0-6.7	23.3-24.0
	3	0.05	1.1-1.3	2.6-2.8	2.9-3.1	6.2-6.4	23.6-23.8
		0.1	1.1-1.3	2.6-2.8	2.9-3.1	6.2-6.4	23.6-23.8
		0.2	1.0-1.4	2.5-2.9	2.8-3.2	6.1-6.5	23.5-23.9
		0.3	0.9-1.5	2.4-3.1	2.7-3.3	6.0-6.6	23.4-24.0
525	0.5	0.05	1.0-1.5	2.5-3.0	2.5-3.0	6.1-6.6	23.5-24.0
		0.1	0.9-1.5	2.4-3.0	2.5-3.0	6.1-6.6	23.4-24.0
		0.2	0.8-1.6	2.4-3.1	2.4-3.1	6.0-6.7	23.3-24.1
		0.3	0.8-1.7	2.3-3.2	2.3-3.2	5.9-6.8	23.2-24.2
	1	0.05	1.0-1.3	2.6-2.9	2.9-3.2	6.2-6.5	23.6-23.9
		0.1	1.0-1.4	2.5-2.9	2.8-3.2	6.1-6.5	23.5-23.9
		0.2	0.9-1.5	2.4-3.0	2.7-3.3	6.0-6.6	23.4-24.0
		0.3	0.8-1.6	2.3-3.1	2.6-3.4	5.9-6.7	23.3-24.1

Cohort Size	Mean Duration of VEN Exposure (years)	Margin of Error	Incidence Rates (per 100 Person-Years)				
			SOI	SPM	TLS	RT	AHE
			1.2	2.7	3.0	6.3	23.7
	2	0.05	1.1-1.3	2.6-2.8	2.9-3.1	6.2-6.4	23.6-23.8
		0.1	1.0-1.3	2.6-2.9	2.9-3.2	6.2-6.4	23.5-23.8
		0.2	1.0-1.5	2.5-3.0	2.8-3.3	6.1-6.5	23.4-23.9
		0.3	0.9-1.6	2.4-3.1	2.7-3.4	6.0-6.7	23.3-24.0
	3	0.05	1.1-1.3	2.6-2.8	2.9-3.1	6.2-6.4	23.6-23.8
		0.1	1.1-1.3	2.6-2.8	2.9-3.1	6.2-6.4	23.6-23.8
		0.2	1.0-1.4	2.5-2.9	2.8-3.2	6.1-6.5	23.5-23.9
		0.3	0.9-1.5	2.4-3.0	2.7-3.3	6.0-6.6	23.4-24.0
575	0.5	0.05	0.9-1.3	2.3-2.7	2.6-3.1	6.1-6.6	23.5-24.0
		0.1	0.8-1.4	2.2-2.8	2.6-3.1	6.1-6.6	23.5-24.0
		0.2	0.8-1.5	2.1-2.9	2.5-3.2	6.0-6.7	23.4-24.1
		0.3	0.7-1.6	2.1-3.0	2.4-3.3	5.9-6.8	23.3-24.2
	1	0.05	0.9-1.2	2.6-2.9	2.9-3.2	6.2-6.4	23.6-23.8
		0.1	0.9-1.3	2.5-2.9	2.8-3.2	6.1-6.5	23.5-23.9
		0.2	0.8-1.4	2.4-3.0	2.7-3.3	6.0-6.6	23.4-24.0
		0.3	0.7-1.5	2.4-3.1	2.6-3.4	5.9-6.7	23.3-24.1
	2	0.05	1.1-1.3	2.6-2.8	2.9-3.1	6.2-6.4	23.6-23.8
		0.1	1.0-1.3	2.6-2.9	2.9-3.1	6.2-6.4	23.5-23.8
		0.2	1.0-1.4	2.5-3.0	2.8-3.3	6.1-6.5	23.4-23.9
		0.3	0.9-1.6	2.4-3.1	2.7-3.4	6.0-6.6	23.3-24.0
	3	0.05	1.1-1.3	2.6-2.8	2.9-3.1	6.2-6.4	23.6-23.8
		0.1	1.1-1.3	2.6-2.8	2.9-3.1	6.2-6.4	23.6-23.8
		0.2	1.0-1.4	2.5-2.9	2.8-3.2	6.1-6.5	23.5-23.9
		0.3	0.9-1.5	2.4-3.0	2.7-3.3	6.0-6.6	23.4-24.0

Cohort Size	Mean Duration of VEN Exposure (years)	Margin of Error	Incidence Rates (per 100 Person-Years)				
			SOI	SPM	TLS	RT	AHE
			1.2	2.7	3.0	6.3	23.7
600	0.5	0.05	0.8-1.3	2.5-2.9	2.5-2.9	6.1-6.6	23.5-23.9
		0.1	0.8-1.3	2.5-3.0	2.5-3.0	6.1-6.6	23.5-24.0
		0.2	0.7-1.4	2.4-3.1	2.4-3.1	6.0-6.7	23.4-24.1
		0.3	0.7-1.6	2.3-3.2	2.3-3.2	5.9-6.8	23.3-24.2
	1	0.05	1.1-1.3	2.6-2.9	2.9-3.1	6.2-6.4	23.6-23.8
		0.1	1.0-1.4	2.5-2.9	2.8-3.2	6.1-6.5	23.5-23.9
		0.2	0.9-1.5	2.4-3.0	2.7-3.3	6.0-6.6	23.4-24.0
		0.3	0.8-1.6	2.4-3.1	2.6-3.4	5.9-6.7	23.3-24.1
	2	0.05	1.1-1.3	2.6-2.8	2.9-3.1	6.2-6.4	23.6-23.8
		0.1	1.1-1.3	2.6-2.9	2.9-3.1	6.2-6.4	23.5-23.8
		0.2	1.0-1.4	2.5-3.0	2.8-3.2	6.1-6.5	23.4-23.9
		0.3	0.9-1.6	2.4-3.1	2.7-3.4	6.0-6.6	23.3-24.0
	3	0.05	1.1-1.3	2.6-2.8	2.9-3.1	6.2-6.4	23.6-23.8
		0.1	1.1-1.3	2.6-2.8	2.9-3.1	6.2-6.4	23.6-23.8
		0.2	1.0-1.4	2.5-2.9	2.8-3.2	6.1-6.5	23.5-23.9
		0.3	0.9-1.5	2.4-3.0	2.7-3.3	6.0-6.6	23.4-24.0

AHE = Autoimmune HaematologicHematologic Event; RT = Richter's Transformation; SOI = Serious Opportunistic Infection; SPM = Second Primary Malignancy; TLS = Tumour Lysis Syndrome; VEN = Venetoclax

Table 9. Estimated 95% CI for IR for the AEs of Interest Using a Range of Probable Sizes and Exposure Durations for Cohort 2-VEN

Cohort Size	Mean Duration of VEN Exposure (years)	Margin of Error	Incidence Rates (per 100 Person-Years)				
			SOI	SPM	TLS	RT	AHE
			1.2	2.7	3.0	6.3	23.7
75	0.5	0.05	0.0-1.9	1.8-4.5	1.8-4.5	4.4-7.2	20.4-23.2
		0.1	0.0-2.0	1.8-4.6	1.8-4.6	4.4-7.2	20.4-23.2
		0.2	0.0-2.1	1.7-4.7	1.7-4.7	4.3-7.3	20.3-23.3
		0.3	0.0-2.2	1.6-4.9	1.6-4.8	4.2-7.5	20.2-23.4
	1	0.05	0.0-1.0	2.2-3.6	2.2-3.6	4.9-6.3	23.2-24.6
		0.1	0.0-1.0	2.1-3.7	2.2-3.7	4.8-6.3	23.1-24.7
		0.2	0.0-1.1	2.1-3.8	2.1-3.8	4.7-6.4	23.0-24.8
		0.3	0.0-1.2	2.0-3.9	2.0-3.9	4.6-6.5	22.9-24.9
	2	0.05	0.4-1.2	2.4-3.2	2.4-3.2	5.7-6.5	23.4-24.2
		0.1	0.4-1.2	2.4-3.2	2.4-3.2	5.7-6.5	23.4-24.2
		0.2	0.4-1.3	2.3-3.3	2.3-3.3	5.6-6.6	23.3-24.3
		0.3	0.3-1.4	2.2-3.4	2.2-3.4	5.5-6.8	23.2-24.4
	3	0.05	0.7-1.2	2.5-3.0	2.5-3.0	6.1-6.6	23.5-24.0
		0.1	0.7-1.3	2.4-3.1	2.4-3.1	6.0-6.7	23.4-24.1
		0.2	0.6-1.4	2.3-3.2	2.3-3.2	5.9-6.8	23.3-24.2
		0.3	0.5-1.5	2.2-3.3	2.3-3.3	5.8-6.9	23.2-24.3
80	0.5	0.05	0.0-1.8	1.7-4.3	1.7-4.3	4.2-6.7	21.6-24.3
		0.1	0.0-1.9	1.7-4.3	1.7-4.3	4.1-6.8	21.6-24.3
		0.2	0.0-2.0	1.6-4.4	1.6-4.4	4.0-6.9	21.5-24.4
		0.3	0.0-2.1	1.5-4.6	1.5-4.6	4.0-7.0	21.4-24.5
	1	0.05	0.0-0.9	2.1-3.4	2.1-3.4	5.8-7.1	23.2-24.6
		0.1	0.0-1.0	2.0-3.5	2.0-3.4	5.7-7.2	23.2-24.6
		0.2	0.0-1.0	1.9-3.6	1.9-3.6	5.6-7.3	23.1-24.7
		0.3	0.0-1.1	1.8-3.7	1.9-3.7	5.6-7.4	23.0-24.8
	2	0.05	0.4-1.1	2.2-3.0	2.3-3.0	6.0-6.8	23.4-24.1
		0.1	0.4-1.1	2.2-3.0	2.2-3.0	6.0-6.8	23.4-24.2
		0.2	0.3-1.2	2.1-3.1	2.1-3.1	5.9-6.9	23.3-24.3
		0.3	0.3-1.4	2.0-3.2	2.0-3.2	5.8-7.0	23.2-24.4

Cohort Size	Mean Duration of VEN Exposure (years)	Margin of Error	Incidence Rates (per 100 Person-Years)				
			SOI	SPM	TLS	RT	AHE
			1.2	2.7	3.0	6.3	23.7
85	3	0.05	0.7-1.2	2.3-2.8	2.7-3.2	6.1-6.6	23.5-24.0
		0.1	0.6-1.2	2.3-2.9	2.7-3.3	6.0-6.7	23.4-24.1
		0.2	0.6-1.3	2.2-3.0	2.6-3.4	5.9-6.8	23.3-24.2
		0.3	0.5-1.4	2.1-3.1	2.5-3.5	5.9-6.9	23.2-24.3
	0.5	0.05	0.0-1.7	1.6-4.0	1.6-4.0	3.9-6.3	22.8-25.3
		0.1	0.0-1.7	1.6-4.1	1.6-4.1	3.9-6.4	22.8-25.4
		0.2	0.0-1.9	1.5-4.2	1.5-4.2	3.8-6.5	22.7-25.5
		0.3	0.0-2.0	1.4-4.3	1.4-4.3	3.7-6.6	22.6-25.6
	1	0.05	0.0-0.9	1.9-3.2	1.9-3.2	5.4-6.7	23.2-24.5
		0.1	0.0-0.9	1.9-3.3	1.9-3.2	5.4-6.8	23.2-24.6
		0.2	0.0-1.0	1.8-3.4	1.8-3.4	5.3-6.9	23.1-24.7
		0.3	0.0-1.1	1.7-3.5	1.7-3.5	5.2-7.0	23.0-24.8
	2	0.05	0.4-1.0	2.1-2.8	2.7-3.4	6.0-6.7	23.4-24.1
		0.1	0.4-1.1	2.1-2.8	2.7-3.4	6.0-6.8	23.4-24.2
		0.2	0.3-1.2	2.0-3.0	2.6-3.6	5.9-6.9	23.3-24.3
		0.3	0.3-1.3	1.9-3.1	2.5-3.7	5.8-7.0	23.2-24.4
	3	0.05	0.6-1.1	2.2-2.7	2.6-3.1	6.1-6.6	23.5-24.0
		0.1	0.6-1.1	2.1-2.7	2.5-3.1	6.1-6.6	23.4-24.0
		0.2	0.5-1.2	2.0-2.8	2.4-3.2	6.0-6.8	23.3-24.1
		0.3	0.5-1.4	2.0-2.9	2.3-3.3	5.9-6.9	23.2-24.2
90	0.5	0.05	0.0-1.6	1.5-3.8	1.5-3.8	3.7-6.0	22.9-25.3
		0.1	0.0-1.7	1.5-3.8	1.5-3.8	3.7-6.0	22.8-25.3
		0.2	0.0-1.8	1.4-4.0	1.4-4.0	3.6-6.1	22.7-25.4
		0.3	0.0-1.9	1.3-4.1	1.3-4.1	3.5-6.2	22.6-25.5
	1	0.05	0.7-1.9	1.8-3.0	1.8-3.0	5.1-6.4	23.2-24.5
		0.1	0.7-2.0	1.8-3.1	1.8-3.1	5.1-6.4	23.2-24.5
		0.2	0.6-2.1	1.7-3.2	1.7-3.2	5.0-6.5	23.1-24.6
		0.3	0.6-2.3	1.6-3.3	1.6-3.3	4.9-6.6	23.0-24.7
	2	0.05	0.9-1.5	2.0-2.6	2.5-3.2	6.1-6.7	23.4-24.1
		0.1	0.8-1.6	2.0-2.7	2.5-3.3	6.0-6.8	23.4-24.1
		0.2	0.8-1.7	1.9-2.8	2.4-3.4	5.9-6.9	23.3-24.2
		0.3	0.7-1.8	1.8-2.9	2.3-3.5	5.8-7.0	23.2-24.3

Cohort Size	Mean Duration of VEN Exposure (years)	Margin of Error	Incidence Rates (per 100 Person-Years)				
			SOI	SPM	TLS	RT	AHE
			1.2	2.7	3.0	6.3	23.7
	3	0.05	0.9-1.4	2.4-2.9	2.8-3.3	6.1-6.6	23.5-24.0
		0.1	0.9-1.5	2.4-2.9	2.7-3.3	6.1-6.6	23.5-24.0
		0.2	0.8-1.6	2.3-3.1	2.7-3.4	6.0-6.7	23.4-24.1
		0.3	0.7-1.7	2.2-3.2	2.6-3.5	5.9-6.8	23.3-24.2

AHE = Autoimmune HaematologicHematologic Event; RT = Richter's Transformation; SOI = Serious Opportunistic Infection; SPM = Second Primary Malignancy; TLS = Tumour Lysis Syndrome; VEN = Venetoclax

9.7 Data Management

Data management for this study will be conducted using standard IQVIA processes. These processes will take into consideration any data governance imposed on the data sources, including any plans to handle the data outside of the institution or country of origin. IQVIA will adhere to all local and regional laws on data protection and privacy. Datasets and analytic programs will be stored at the database level and analysed locally, according to IQVIA procedures, with access restricted to study personnel. IQVIA confidentiality agreements are signed by all employees and include data protection and strict prohibitions on reidentification attempts.

This study will follow the relevant chapters of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and the ICH guidelines for data management. In addition, the data will be checked for consistency in terms of range of values, units of measurement, and relevance of clinical information.

9.8 Data Analysis

9.8.1 General Considerations

Summary statistics will be generated and reported as mean, standard deviation, 5th percentile, 25th percentile, median, interquartile range, 75th percentile, and 95th percentile for continuous variables, and as frequencies and percentages (%) for categorical variables, unless otherwise specified. The present study is primarily designed

to estimate IRs for the AEs of interest and does not have a priori-defined testing hypotheses. Results will be summarised in tables and/or figures in Microsoft® (MS) Excel format.

All analyses in Section 9.8.2 will be conducted in SAS® (SAS Institute Inc., Cary, NC) using the version that is current (at least version 9.4) when the analyses are completed.

Data from the national health registers and participating haematology clinics are subject to small cell reporting restrictions per the NBHW's privacy policy; thus, cells with a value of < 5 will be masked. Additionally, a cell(s) with a count ≥ 5 may need to be modified (e.g., > X) to prevent the calculation of a masked cell's count.

An attrition table showing how patients qualified for Cohort 1, Cohort 2, Cohort 1-VEN, and Cohort 2-VEN will be provided. The distribution of time exposed to venetoclax and database follow-up post-venetoclax initiation (using 31 December of the prior year at the time of analysis to calculate, e.g., for the final analysis using 31 December 2024) will also be reported.

Due to the limited numbers of venetoclax-treated CLL patients with available clinical data from Cohort 2 and the lack of hospital-based infusions and chemotherapy treatment information from national registries in Cohort 1, no comparative analyses are planned for this study. This also influences the availability of some variables, and hence certain analyses will not be performed in both cohorts (see Table 1).Stratifications are, however, proposed to understand AE risk among venetoclax-treated patients.

Interim safety analyses are being conducted every second year (see Section 6.0). Tabulations of AEs frequencies will be produced along with the scheduled Progress Reports.

When reporting LoT, if masking prohibits reporting analysis of each LoT separately (i.e., 1st LoT, 2nd LoT, 3rd LoT, etc.), 2nd LoT and later lines will be combined into one category (i.e., 1st LoT and 2+ LoT will be reported).

9.8.2 Analysis by Objectives

9.8.2.1 Primary Objective

To characterise long term safety of venetoclax, including determining the incidence of select AEs in CLL patients exposed to venetoclax

Cohort 1-VEN and Cohort 2-VEN:

For Cohort 1-VEN and Cohort 2-VEN, the number of patients, and number of events will be presented for the first occurrence of AEs.

Should sample size allow, crude IRs (per 100 PY) and their corresponding 95% CIs will be calculated and reported per unit of observational time, e.g., PY. For the calculation of crude IRs, the denominator will be the pooled person-time of all the patients within the cohort. The 95% confidence limits will be calculated assuming normality on the log scale or by calculating exact Poisson confidence limits as needed. All first events occurring during the follow-up period will be counted in the total number of events. The numerator will be the number of first AEs of all patients within the cohort.

The crude IR per 100 PY will be defined as the number of first events during follow-up divided by the total number of PY at risk and multiplied by 100 as under:

$$IR = \frac{number\ of\ first\ events\ during\ follow\ up}{total\ person-years\ at\ risk\ during\ follow\ up}\ x\ 100$$

Table 5 summarises the assessment windows to calculate the number of venetoclax PY at risk for different AEs.

The distribution of duration from index date to first event, including median days to reach first AE and other relevant statistics as detailed in Section 9.8.1 will be reported for both cohorts.

Cumulative incidence of first events and its corresponding 95% CI will be calculated using the Kaplan-Meier estimates, overall and for each of the AEs, if the sample size

allows. The 95% CIs will be calculated using the log-log transformation of the survival function. The percentage of patients with an AE will be calculated for each month after the therapy index date and stratified by each type of AE, if sample size allows.

9.8.2.2 Secondary Objective a)

To further characterise long term safety of venetoclax by describing the treated patient population stratified by factors associated with events of interest

Cohort 1-VEN:

The number of patients and number of events will be presented for the first occurrence of AEs, along with the crude IRs (as calculated above for the Primary Objective) stratified by the following variables for Cohort 1-VEN (as sample size allows):

- Age (years) of patients at VEN treatment index date will be categorised as follows: 18-64, 65-74, 75+
- Charlson Comorbidity Index (CCI) at CLL index date and VEN treatment index date
  - 0
  - 1
  - 2
  - 3
  - ≥ 4
- Time between CLL index date and VEN treatment index date: 0-5 years; 6-9 years; 10+ years
- Sex: males, females
- For the AHE and SOI outcomes only, whether the patient had ≥ 1 AHE or SOI, respectively, in the 6 months prior to the VEN treatment index date
- Occurrence of the AEs will be stratified within the following time periods* (yes/no), with a limitation that CLL treatments administered at hospital will not be captured and therefore some misclassification might occur:
  - During venetoclax exposure

- After venetoclax discontinuation

* For each time period described above, the duration between the VEN treatment index date and the AE occurrence will be reported via appropriate summary statistics (as detailed in Section 9.8.1).

Cohort 2-VEN:

For Cohort 2-VEN only, the number of patients and number of events will be presented for the first occurrence of AEs, along with crude IRs, additionally stratified by the following variables (as sample size allows):

- Treatment regimen: venetoclax monotherapy, venetoclax-based combination therapy
- Number of therapy lines received prior to VEN treatment index date: 0 lines (no treatment received), 1 line, 2 lines, 3 lines, or 4 or more lines
- Renal function: abnormal estimated glomerular filtration rate <80 mL/min/1.73 m^2 if 18–50 years of age or <60 mL/min/1.73 m^2 if ≥ 51 years of age
- For the AHE and SOI outcomes only, whether the patient had ≥1 AHE or SOI, respectively, in the six months prior to the VEN treatment index date
- For the RT and SPM outcomes only, whether the patient received other, non-venetoclax pharmacological treatment following the VEN treatment index date but prior to the occurrence of the AE of interest (yes/no)
- Occurrence of the AEs will be stratified by CLL treatment history:
  - CLL treatment-naïve prior to VEN treatment index date
  - CLL treatment experienced prior to VEN treatment index date
    - Prior CLL regimens (i.e., regimens received prior to VEN treatment index date)
- Occurrence of the AEs will be stratified within the following time periods* (yes/no):
  - During venetoclax exposure
    - Received other CLL treatment prior to AE
  - After venetoclax discontinuation

- After venetoclax discontinuation and before the start of a subsequent CLL treatment
- After venetoclax discontinuation and after the start of a subsequent CLL treatment

* For each time period described above, the duration between the VEN treatment index date and the AE occurrence will be reported via appropriate summary statistics (as detailed in Section 9.8.1).

Data extractions to date for the Study Progress Reports and Interim Analyses have demonstrated high proportions of missing values for some clinical characteristics from the EMR data (e.g., laboratory tests, Rai and Binet staging, and ECOG performance status). As a result, the stratifications proposed for Secondary Objective a) have been restricted to those clinical variables where high degrees of missingness have not been observed.

9.8.2.3 Secondary Objective b)

To describe the safety profile of venetoclax and other treatment regimens by LoT

Cohort 2 only:

Baseline patient characteristics, comorbidities, CLL disease and treatment periods will be described for treatment regimens by LoT for Cohort 2. The list of variables to be used in the analysis will be as follows:

- Age at LoT index date
- Sex: males, females
- CCI at CLL index date and LoT index date (0, 1, 2, 3, ≥ 4)
  - Due to the chronic nature of many comorbidities, and since not all chronic conditions will be recorded at each patient visit/interaction, a look-back period of 2 years prior to and including the start of each LoT (each LoT index date) will be used. See Table 2 for further details on assessment windows for CCI and other patient characteristics.
- Period of CLL diagnosis (i.e., CLL index date): 01 January 2007 to 31 December 2012; 01 January 2013 to 31 December 2017; 01 January 2018 to 31 December 2022

- Time from CLL diagnosis (i.e., CLL index date) to LoT initiation (i.e., each LoT index date)
- LoT time exposed: Defined as duration of exposure, i.e., period from each LoT start date until the LoT end date (see Section 9.3.1.1)
- Time to next LoT: Defined as time between LoT start date and the start date of the next LoT (see Section 9.3.1.1)
- Occurrence of the AEs will be stratified within the following time periods (yes/no):
  - During the LoT
  - After LoT and before the start of a new LoT
  - After LoT and after the start of a new LoT

In addition, the number of AEs of interest (excluding TLS) will also be described by LoT, and as sample size allows, for patients treated with venetoclax regimens and treated with other non-venetoclax treatment regimens (e.g., BTKIs) according to each LoT. See Section 9.3.1.1 for a description of treatment regimens of interest and how lines of therapy are to be derived. See Table 5 for time windows relevant to the assessment of each AE.

9.8.2.4 Secondary Objective c)

To describe clinical characteristics of CLL patients at diagnosis, such as age, gender, staging, comorbidities, and prognostic factors (e.g., cytogenetic factors, renal and hepatic function)

Cohort 1 and Cohort 1-VEN:

Patient characteristics, CLL characteristics and comorbidities (Table 3) at CLL index date will be presented for Cohort 1 and Cohort 1-VEN according to pre-specified baseline periods (Table 2).

Cohort 2 and Cohort 2-VEN:

Patient characteristics, CLL characteristics and comorbidities (Table 4) at CLL index date will be presented for Cohort 2 and Cohort 2-VEN according to pre-specified baseline periods (Table 2). For Cohort 2 and Cohort 2-VEN additional CLL characteristics (disease stage and cytogenetic aberrations and mutations), clinical characteristics (e.g., blood pressure), and laboratory tests (Table 4), where available, will be described according to pre-specified baseline periods (Table 2).

9.8.2.5 Secondary Objective d)

To assess occurrence of TLS and contraindicated medication use in patients who have received venetoclax in a real-world setting

Cohort 1-VEN:

The number and proportion of patients in Cohort 1-VEN who experience TLS will be reported:

- Overall
- By whether the TLS event occurred within the first five weeks after initiating venetoclax (i.e., after the VEN treatment index date).
- By time period of venetoclax initiation (i.e., VEN treatment index date):
  - 2018–2021
  - 2022–2024

Duration between the VEN treatment index date and the first TLS event will also be reported for Cohort 1-VEN. Distribution of duration from the VEN treatment index date to the first TLS event will be described via appropriate summary statistics (as detailed in Section 9.8.1).

In addition, the number and proportion of TLS events in patients taking venetoclax concomitantly with a contraindicated medication will also be tabulated.

Cohort 2-VEN:

The number and proportion of patients in Cohort 2-VEN who experience TLS will be reported:

- Overall
- By whether the TLS event occurred within the first 5 weeks after initiating venetoclax (i.e., after the VEN treatment index date)
- By whether the TLS event occurred while taking venetoclax concomitantly with a contraindicated medication
- By time period of venetoclax initiation (i.e., VEN treatment index date):
  - 2018–2021
  - 2022–2024

Duration between the VEN treatment index date and the first TLS event will also be reported for Cohort 2-VEN. Distribution of duration from the VEN treatment index date to the first TLS event be described via appropriate summary statistics (as detailed in Section 9.8.1).

Patients in Cohort 2-VEN who experience TLS within the first 5 weeks after initiating venetoclax (i.e., after the VEN treatment index date) will be additionally described as follows:

- Setting of the venetoclax exposure prior to the TLS event (outpatient; clinic/inpatient; both outpatient and clinic/inpatient)
- Dispensed formulations filled during dose titration (weeks 1–4)
- Early maintenance prescription, stratified by week 1–4 titration completion.

In addition, the number and proportion of TLS events in patients taking venetoclax concomitantly with a contraindicated medication will also be tabulated.

9.8.2.6 Exploratory Objective

To describe treatment regimens and sequence of therapy in patients with CLL

Cohort 2 only:

CLL treatment patterns over time for Cohort 2 will be described as the number and proportions of patients who receive a particular drug regimen from January 2007 to December 2024 (see Table 2).

Patients' journey from the first to the third LoT will be described in a Sankey plot and an accompanying tabulation showing the number of treatments and percentages. The Sankey plot will be provided, including the treatment regimen in each LoT. Any of the treatment regimens that are masked due to low cell counts (see Section 9.8.1) will be recategorised into an "all other treatment regimens" category.

In addition, a stacked bar plot showcasing the proportions of treatment regimens across all treatment index years (2007-2024) and stratified by year of patient's 1st LoT index date (< 2018, 2018-2021, 2022-2024), overall, and by LoT, will also be depicted.

See Section 9.3.1.1 for details on reporting of treatment regimens. Should the data not lend itself to visualisation via Sankey diagrams and/or stacked bar plots (i.e., due to rules on masking), a tabulated output of the number and proportion of patients by regimen and LoT will be produced, overall and stratified by the year of the patient's 1st LoT index date (< 2018, 2018-2021, and 2022-2024).

9.8.3 Sensitivity Analyses

9.8.3.1 Sensitivity Analysis 1

Ideally, the EMR systems of each participating haematology clinic would have full coverage in the EMR medication module(s), starting from patients' CLL index date through to their VEN treatment index date. However, this will not be possible for all patients in Cohort 2 given that the EMR medication module(s) have become available in a

staggered fashion with respect to EMR module diagnosis dates. This might then result in patients with incomplete treatment history.

Hence, for the Final Report, sensitivity analyses utilising Cohort 2 will be conducted to explore the role of EMR modules availability regarding CLL treatment history on AE outcomes. The analyses for Primary Objective (as mentioned in Section 9.8.2.1) will be redone using a different Cohort 2-VEN inclusion criteria as was used previously in the Interim Report 3, dated March 2024. Following are the additional inclusion criteria:

- Be a member of Cohort 2-VEN; and
- Have up to 2 years of coverage in the EMR medication module(s) immediately prior to the VEN treatment index date to assess for prior CLL therapies received (if any). Specifically, patients must have coverage in the EMR medication module(s) as follows:
  - For patients with a VEN treatment index date that occurs > 2 years after their CLL index date, must have:
    - At least 2 years of coverage in the EMR medication module(s) immediately prior to the VEN treatment index date; and
    - Not emigrated in the 2 years immediately prior to or on the VEN treatment index date.
- For patients with a VEN treatment index date that occurs ≤ 2 years after their CLL index date must have:
    - Coverage in the EMR medication module(s) starting on the CLL index date through to the VEN treatment index date (inclusive); and
    - Not emigrated in the time between the CLL index date and VEN treatment index date (inclusive).

9.8.3.2 Sensitivity Analysis 2

This sensitivity analysis will be done to study the robustness of the treatment regimen operational definitions used in the main study, where a predefined number of days in which CLL treatments are prescribed/administered is used to define a regimen: 35 days

for non-venetoclax regimens and 90 days for venetoclax regimens. The analyses for Secondary Objectives a) and b) (Section 9.8.2.2 and Section 9.8.2.3, respectively) will be repeated, wherever applicable, by changing the treatment regimen definition for non-venetoclax regimens from 35 days to 28 days and venetoclax regimens from 90 days to 60 days.

For this sensitivity analysis, the treatment regimen will be defined as the single CLL drug (monotherapy) or combination of drugs (polytherapy) used within 28 days for non-venetoclax therapies and 60 days for venetoclax, after initiation of the first CLL treatment after CLL diagnosis. To properly document the implications of changing the treatment regimen definitions, this will be done in three stages and results tabulated for each:

a). change definition for venetoclax to 60 and keep non-venetoclax therapies to be 35 days

b). keep definition for venetoclax to 90 and change non-venetoclax therapies to be 28 days

c). change definitions for both venetoclax and non-venetoclax therapies to 60 and 28 days, respectively.

In order to ensure alignment of definitions with treatment in real-world clinical practice (see Section 9.3.1), please note that the intervals detailed here (including those for the sensitivity analysis) are those initially proposed, but will be subject to change during the iterative development of the operational definitions for defining regimens, LoT, and treatment changes.

9.8.4 Missing Data

Missing data occur where a variable is directly reported as missing or unavailable, where a variable observation is blank, where the extracted data may not be interpretable, or where the value is considered to be missing because of data inconsistency or out-of-range results.

In general, missing data will not be imputed. The extent of missing data will be assessed and summarised descriptively. The number and proportion of missing data for each measured variable will be presented. In descriptive analyses, patients with missing data will not be included in the denominator for the calculation of percentages. Variables that have complete missing values will be excluded from the analyses. If a variable is missing for only some of the patients, a missing data category will be added and utilised in the analysis.

Longitudinally, it is not possible to identify the presence of missing values. For example, for a variable like body mass index (BMI), it cannot be ascertained if measurements were taken at three different time points but only recorded for the first one. Therefore, we assume that a value remains true until evidence in the data shows that it is not. However, this last observation carried forward approach risks misclassification if a patient has, in fact, changed value, but this was unrecorded. However, this change is only relevant if the treating physician is aware of it.

Incomplete dates (from the free text of the EMR) will be re-coded as summarised below:

- If only month and year are reported: March 2018 will be re-coded as 15 March 2018
- Beginning of March 2018 will be re-coded as 1 March 2018
- End of March 2018 will be re-coded as 31 March 2018

For the TLS-related outcomes, TLS events without a date or with an incomplete date will be captured and reported but not described further.

In addition, if a code is not found for a specific drug / disease, then the data is not assumed to be missing. The absence of codes will be interpreted as an absence of diagnosis or an absence of dispensed prescription.

9.9 Quality Control

This study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigour and follow the generally accepted research practices described in the following documents:

1. Guideline on good pharmacovigilance practices (GVP) – Module VIII – Postauthorization safety studies, Revision 3 (EMA 2017)[41]
2. International Society of Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practice[42]
3. Guidelines for good database selection and use in pharmacoepidemiology research.[43]

The study will also be conducted according to the standard operating procedures (SOPs) of IQVIA, AbbVie, the NBHW, and the participating haematology sites.

At IQVIA, at the study level, all aspects of the study, from the development of the protocol to the reporting of the results, will be conducted within the framework of IQVIA's Quality Management System. Quality control (QC) will be implemented based on QC checklists developed for the study, which will cover the study methodology, SAP, SAS programming, CXP programs used to extract data from the EMRs of the participating haematology clinics, data management and analysis, study results, conclusions, Study Progress Reports, and Interim and Final Study Reports. Furthermore, the QC checklists will be completed by appropriately qualified and trained subject matter experts. The result of the execution of the individual QC steps will be documented and will include identified outages, if any, as well as the execution of any required corrective action (if necessary). Finally, the QC checklists will be subjected to a final review and approval for sufficiency and completeness from the Principal in Charge of the study and retained in the study master file.

9.10 Limitations of the Research Methods

9.10.1 Missing Data

The national health registers included in this study are mandatory registries linked together through the use of mandatory personal identifiers. For most variables, only a small proportion of the data is expected to be missing.

Since Interim Analysis Report 1, a high proportion of missing values has been observed for several variables of interest obtained from the EMR, including laboratory tests, disease stage (Rai and Binet staging and ECOG performance status), cytogenetic aberrations, mutations, and clinical characteristics (blood pressure and BMI). Strategies to reduce the level of missing values have been applied, e.g., a longer time window for the baseline period for the definition of the cytogenetic aberrations and mutations. However, the missing values for key variables from the EMRs are still high. Given that linkage to EMR for the study was intended to provide additional granularity in clinical data than the national registers alone and provide additional insights into the frequency and characterisation of AEs, the extent of missing data will prevent the conduct of some of the analyses originally planned for this study, e.g., comparative analysis for Secondary Objective b). Full details of the original objectives impacted are provided and discussed in Progress Report 7 (submitted at the same time as this protocol amendment). This current protocol now reflects the analysis that can and will be conducted.

As a result of the high levels of missing data, the stratification of the occurrence of AEs by patient characteristics and risk factors is limited to those variables where high levels of missingness have not been observed. Thus, the potential confounding on occurrence of AEs by patients underlying disease characteristics cannot be assessed in this study.

This study intended to assess potential medication errors that can result in unfavourable outcomes, i.e., TLS. It has since been established that whether patients are following or not their dosage schedule to determine the possibility of medication errors is not possible, as such information cannot be reliably extracted from the EMRs of participating clinics. Therefore, the definition for TLS has been broadened to include all occurrences of TLS to

enable reporting of overall TLS frequency among VEN-treated CLL patients (see Section 9.3.2).

9.10.2 Selection Bias

Cohort 1 is based on data from four national and compulsory health registers in Sweden and covers all patients with a diagnosis of CLL in the registry in this country, which will prevent any potential selection bias within Cohort 1.

Cohort 2, a sub-cohort of Cohort 1, is based on patients from select participating haematology clinics in Sweden with limited geographical coverage. The selection of clinics for inclusion in the study was planned in order to provide a representative sample of the CLL population in the country. However, clinical participation was lower than expected; thus, the CLL patients in Cohort 2 may not be representative of the national CLL population. In order to assess the impact of any such selection bias, patient characteristics for Cohort 1 and 2 will be compared in Secondary Objective c).

9.10.3 Information Bias

The use of automated health databases for research has limitations, particularly regarding misclassification of the treatment and outcome variables. For example, while automated health databases provide detailed information on dispensed medications, actual use cannot be determined. Thus, it is possible that patients may fill a prescription for venetoclax and never take it. Further, patients who discontinue their medication before finishing the entire prescription will be indistinguishable from those patients who take the entire prescription. Additionally, because there is no days' supply or duration variable in the SPDR, a proxy for duration will be used that may lead to misclassification of drug exposure. Misclassification of diagnoses is also a potential issue. For example, there is the potential for the under- or misreporting of information to the national health registers. An absence of a diagnosis code will be considered as an absence of the condition.

For patients in Cohort 1, medications administered in the hospital/clinic inpatient setting will not be captured. Thus, there could be misclassification of venetoclax exposure for

those patients in Cohort 1 who receive venetoclax at the hospital; this could include CLL patients who are at the highest risk for TLS. Further, we will not be able to fully characterise these patients' CLL treatment histories, as CLL treatments administered exclusively in the inpatient setting will not be captured by the NPR or SPDR. The cohorts to be used for each objective have therefore been selected based on the availability of data that can adequately address the objective.

Additionally, the EMR systems of the participating haematology clinics will not have full coverage in the EMR medication module(s) for all patients in Cohort 2, starting from patients' CLL index date through to their venetoclax treatment index date, depending on when the EMR medication module(s) came online for each participating haematology clinic. Sensitivity analyses utilising Cohort 2 will be conducted to explore the role of EMR module availability regarding CLL treatment history on AE outcomes (see Section 9.8.3.1).

For Cohort 2, it may be possible for a patient to start treatment for their CLL after the SCR CLL diagnosis date but before the EMR CLL diagnosis date (i.e., the CLL index date for patients in Cohort 2). This would most likely occur if a patient initially sought care and was started on treatment for CLL at a non-participating haematology clinic and then transferred their care to a participating haematology clinic. However, given that the EMR CLL diagnosis date must be within ± 90 days of the SCR diagnosis date, this scenario is not anticipated to happen often, if at all. Note also that it will not be possible to definitively determine whether a patient received treatment (or not) at another, non-participating haematology clinic, as only medications filled at outpatient pharmacies and/or administered at the participating haematology clinics will be captured.

The NPR only covers inpatient and outpatient specialist care. Thus, comorbidities of interest that may be more likely to be captured in a general practitioner setting (e.g., hypertension, diabetes) are likely to be under-represented in our results. Additionally, data availability in the NPR is restricted to the 2 years prior to the CLL diagnosis in the SCR. Given the chronic nature of many comorbidities, which may not be captured in all

interactions with a health care professional, it is possible some chronic comorbidities may not be captured, thus underestimating CCI.

Patients in Cohort 2 may leave the haematology clinic at some point during their follow-up, e.g., a patient initially seen at a smaller, participating clinic may transfer to a larger, non-participating university clinic for their CLL care. Because there is no "continuous enrolment" variable for the EMR, these patients may look indistinguishable from patients who are seen less frequently. Thus, it is possible that full EMR follow-up is not available for some patients. This will be mitigated, in part, by the data from the national health registers.

Emigration/immigration status is only available for the most recent emigration/immigration. Thus, a patient moving in and out of Sweden multiple times will look identical to a patient who has only moved in and/or out of Sweden once. Thus, there may be some missing baseline and follow-up time for these patients.

9.11 Other Aspects

Not applicable (N/A).

10.0 Protection of Human Subjects

This study will comply with all applicable laws, regulations, and guidance regarding patient protection, including patient privacy and confidentiality.

The study will be submitted to ethical review boards for approval. Regulatory authorities will be notified and approval sought as required by local laws and regulations.

Individual informed consent will not be required since this is a non-interventional population-based study which imposes no health risk to the participants. Data in this study will be collected using the CXP extraction tool, which extracts relevant predefined data from the EMRs. Furthermore, data for Cohort 1 will be collected, linked, and handled by the NBHW according to their standard procedures for register-based research and linking of data. Data will be de-identified by NBHW before it is handed out for analysis.

10.1 Informed Consent

This study will comply with all applicable laws, regulations, and guidance regarding patient protection, including patient privacy. Individual informed consent will not be required since this is a non-interventional population-based study that imposes no health risk to the participants. Data in this study will be collected using the CXP extraction tool, which extracts relevant predefined data from the EMRs.

10.1.1 Consent and Collection of Specimens for Future Biomedical Research

N/A.

11.0 Management and Reporting of Adverse Events/Adverse Reactions

This study involves the extraction of information from national registers (ICD-10 codes) and EMRs (ICD-10 codes and free-text searches). Information pertaining to adverse reactions will not be particularly discovered as the study does not involve identifiable patient data associated with an AbbVie drug. Adverse reactions/AEs will be reported to competent authorities in accordance with the provisions of GVP Modules VI and VIII. Since the study is only based on secondary data, the reporting of suspected adverse reactions in the form of individual case safety reports is not required (see GVP Module VI). Reports of AEs will be summarised as part of any Interim Safety Analysis and in the Final Study Report.

12.0 Plans for Disseminating and Communicating Study Results

The study has been registered in the Heads of Medicine Agencies (HMA)-EMA Catalogue of real-world data sources (formally known as the ENCePP) e-register of studies by the Marketing Authorisation Holder (MAH) under the number EUPAS19010.[44]

Annual Study Progress Report will be prepared yearly from 2018. Interim Safety Analysis Reports will be conducted every second year starting from 2019.

A Final Study Report will be written in MS Word format using AbbVie's template and following STrengthening the Reporting of OBservational studies in Epidemiology and GVP recommendations.[44,45] The final study report will be submitted to the Committee for Medical Products for Human Use/EMA within one year after the study conclusion.

Study findings will be submitted to a scientific congress (to be specified later). Publications are expected to result from this study and be submitted to a peer-reviewed journal.

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Annex 1. List of Stand-Alone Documents

There are no stand-alone documents for this protocol.

Annex 2. ENCePP Checklist for Protocols

Adopted by the ENCePP Steering Group on 15 October 2018.

Study title: Prospective observational study to assess the long term safety profile of venetoclax in a Swedish cohort of Chronic Lymphocytic Leukemia (CLL) patients
HMA-EMA Catalogue of real-world studies number: EUPAS19010 Study ID 49279 **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[7]	☒	☐	☐	6
1.1.2 End of data collection[8]	☒	☐	☐	6
1.1.3 Progress Report(s)	☒	☐	☐	6
1.1.4 Interim Report(s)	☒	☐	☐	6
1.1.5 Registration in the HMA-EMA Catalogue of real-world studies	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7
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
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 generalized)	☒	☐	☐	8

7 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.
8 Date from which the analytical dataset is completely available.

Section 2: Research question	Yes	No	N/A	Section Number
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no a priori hypothesis?	☒	☐	☐	8

Comments:

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)	☒	☐	☐	9.8
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:

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9
4.2.2 Age and sex	☒	☐	☐	9
4.2.3 Country of origin	☒	☐	☐	9
4.2.4 Disease/indication	☒	☐	☐	9
4.2.5 Duration of follow-up	☒	☐	☐	9

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.1 and 9.2

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 categorizing 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
5.3 Is exposure categorized according to time windows?	☒	☐	☐	9.1, 9.8
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☒	☐	9.3

Comments:

5.5 Some AEs are assessed using on-treatment exposure due to the acute nature of the outcome, while others with latent nature are assessed with an intention to treat approach i.e studied as any time since exposure initiation. 5.6 The occurrence of selected adverse events in patients exposed to treatments other than venetoclax will be described with no direct comparison made with venetoclax-exposed patients.

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

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
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)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.8
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.10
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.10

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, subgroup analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

The occurrence of selected adverse events in patients exposed to treatments other than venetoclax will be described with no direct comparison made with venetoclax-exposed patients.

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)	☒	☐	☐	9.3/9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3/9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3/9.4
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)	☒	☐	☐	9.3/9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3/9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, comorbidity, co-medications, lifestyle)	☒	☐	☐	9.3/9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3/9.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3/9.4/ Annex 5/ Annex 6
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3/9.4/ Annex 7
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.8
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.6
10.3 Are descriptive analyses included?	☒	☐	☐	9.8

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.4 Are stratified analyses included?	☒	☐	☐	9.8
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.8
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.8
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.8.4
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.8.3

Comments:

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)	☒	☐	☐	9.5
11.2 Are methods of quality assurance described?	☒	☐	☐	9.5
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

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?	☒	☐	☐	9.10
12.1.2 Information bias?	☒	☐	☐	9.10
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).	☒	☐	☐	9.10
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)	☒	☐	☐	9.6

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
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.5

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

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: _____

Date: 06/February/2025

Signature: _____

Annex 3. List of Protocol Signatories

Name	Title	Functional Area
[redacted]		Global Epidemiology
		Product Safety Team
		Regulatory
		Pharmacovigilance

Annex 4. Qualified Person for Pharmacovigilance (QPPV)

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Annex 5. List of CLL Pharmacological Treatments

List of CLL Pharmacological Treatments of Interest

Cytostatic agents	Trade name	ATC code	Hospital administered
Chlorambucil*	Leukeran	L01AA02	
Bendamustine	Ribovact	L01AA09	X
Fludarabine	Fludara	L01BB05	X
Cyclophosphamide**	Sendoxan	L01AA01	X
Doxorubicin (hydroxy-daunorubicin)	Adriamycin, Caelyx, Myocet, others	L01DB01	X
Vincristine	Oncovin, Vincasar, Marqibo, others	L01CA02	X
Monoclonal antibody immunotherapy			
Rituximab	Mabthera, Ritemvia, Rixathon	L01FA01	X
Ofatumumab	Arzerra	L01FA02 L04AG12	X
Obinutuzumab	Gazyva, Gazyvaro	L01FA03	X
Alemtuzumab	Lemtrada, Campath, MabCampath	L04AG06	X
PIK3i			
Idelalisib	Zydelig	L01EM01	
BTKi			
Ibrutinib	Imbruvica	L01EL01	
Acalabrutinib	Calquence	L01EL02	
BCL-2 inhibitor			
Venetoclax	Venclyxto	L01XX52	
Immunomodulatory			
Lenalidomide	Revlimid	L04AX04	
Nitrogen mustard alkylating agent			
Trofosfamide***	Genoxal Trofosfamida	L01AA07	

* Chlorambucil is an orally administered chemotherapy. The drug can be captured in the SPDR and EMR.

** Can be given in tablet form or IV; when combined with rituximab, will be IV-administered.

*** Trofosfamide is an uncommon treatment for CLL.

ATC = Anatomical Therapeutic Chemical; BCL-2 = B-cell Lymphoma 2; BTKi = Bruton Tyrosine Kinase Inhibitor; CLL = Chronic Lymphocytic Leukaemia; EMR = Electronic Medical Records; IV = Intravenously; PIK3i = Phosphoinositide 3-kinase inhibitor; SPDR = Swedish Prescribed Drug Register

Annex 6. List of Serious Opportunistic Infections

List of Medical Terms to be Used to Identify Serious Opportunistic Infections.

Serious opportunistic infections (SOI) have been listed according to International Classification of Diseases, 10th Revision (ICD-10) codes. As Swedish health registries will record these diagnoses using ICD-10 codes, and as one ICD-10 can map to multiple SOIs, each SOI has been matched to one or multiple ICD-10 codes.

Serious Opportunistic Infection	ICD-10 Code	Category
Aeromonas infection	A04.8	Other specified bacterial intestinal infections
	A49.8	Bacterial infection of unspecified site
	A41.4	Sepsis due to anaerobes
	A41.5	Sepsis due to other Gram-negative organisms
Allescheriosis	B48.2	Allescheriasis. Infection due to *Pseudallescheria boydii*
Alternaria infection	B48.7	Opportunistic mycoses
Aspergilloma	B44.0	Invasive pulmonary aspergillosis
	B44.1	Other pulmonary aspergillosis
	B44.8	Other forms of aspergillosis
Aspergillosis oral	B44.8	Other forms of aspergillosis
	B44.2	Tonsillar aspergillosis
Aspergillus infection	B44.9	Aspergillosis, unspecified
	B44.7	Disseminated aspergillosis
Atypical mycobacterial lower respiratory tract infection	A31.0	Pulmonary mycobacterial infection
	J40	Bronchitis, not specified as acute or chronic
	J41.0	Simple chronic bronchitis
	J41.1	Mucopurulent chronic bronchitis
	J41.2	Mixed simple and mucopurulent chronic bronchitis

Serious Opportunistic Infection	ICD-10 Code	Category
Atypical mycobacterial pneumonia	A31.0	Pulmonary mycobacterial infection
	J15.8	Other bacterial pneumonia
Atypical mycobacterium pericarditis	A31.8	Other mycobacterial infections
	I30.1	Infective pericarditis
Bacillary angiomatosis	A44.8	Other forms of bartonellosis
	A44.1	Cutaneous and mucocutaneous bartonellosis
BK virus infection	B33.8	Other specified viral diseases
	B34.8	Other viral infections of unspecified site
Botryomycosis	A49.8	Other bacterial infections of unspecified site
	A48.9	Other specified bacterial diseases
Brachyspira infection	A04.8	Other specified bacterial intestinal infections
	A49.8	Bacterial infection of unspecified site
	A69.8	Other specified spirochaetal infections
Brevibacterium infection	A42.9	Actinomycosis, unspecified
	A48.9	Other specified bacterial diseases
	A49.8	Bacterial infection of unspecified site
Bronchopulmonary aspergillosis	B44.0	Invasive pulmonary aspergillosis
	B44.1	Other pulmonary aspergillosis
Burkholderia cepacia complex infection	A49.8	Other bacterial infections of unspecified site
	J16.8	Pneumonia due to other specified infectious organisms
Burkholderia cepacia complex sepsis	A41.5	Sepsis due to other Gram-negative organisms
Campylobacter colitis	A04.5	*Campylobacter* enteritis
	A09.0	Other and unspecified gastroenteritis and colitis of infectious origin
Candida endophthalmitis	B37.8	Candidiasis of other sites
Candida osteomyelitis	B37.8	Candidiasis of other sites
Candida pneumonia	B37.1	Pulmonary candidiasis
Candida retinitis	B37.8	Candidiasis of other sites
Candida sepsis	B37.7	Candidal sepsis

Serious Opportunistic Infection	ICD-10 Code	Category
Capnocytophaga infection	A49.8	Other bacterial infections of unspecified site
Central nervous system fungal infection	G96.8	Other specified disorders of central nervous system
Cerebral aspergillosis	B44.8	Other forms of aspergillosis
Cerebral candidiasis	B37.8	Candidiasis of other sites
	G02.1+B37.5	Meningitis in mycoses + candidial meningitis
	G05.2 + B37.8	Encephalitis, myelitis, and encephalomyelitis in other infectious and parasitic diseases classified elsewhere+candiniasis of other sites
Cerebral fungal infection	G02.1 + B37.5/B38.4	Meningitis in mycoses + candidial meningitis/coccidioidomycosis meningitis
	G03.8	Meningitis due to other specified causes
	G02.1 + B49	Meningitis in mycoses + unspecified mycosis
	G05.2 + B49	Encephalitis, myelitis, and encephalomyelitis in other infectious and parasitic diseases classified elsewhere + unspecified mycosis
Cerebral toxoplasmosis	G05.2 + B58.2	Encephalitis, myelitis, and encephalomyelitis in other infectious and parasitic diseases classified elsewhere + toxoplasma meningoencephalitis
	G02.8 + B58.2	Meningitis in other specified infectious and parasitic diseases classified elsewhere + toxoplasma meningoencephalitis
Chronic pulmonary histoplasmosis	B39.1	Chronic pulmonary histoplasmosis capsulati
Coccidioides encephalitis	B38.9	Coccidioidomycosis, unspecified
	G04.8	Other encephalitis, myelitis, and encephalomyelitis
	G05.2 + B38.9	Encephalitis, myelitis, and encephalomyelitis in other infectious and parasitic diseases classified elsewhere + Coccidioidomycosis, unspecified
Coccidioidomycosis	B38.9	Coccidioidomycosis, unspecified
Colitis herpes	B00.8	Other forms of herpesviral infection
	A08.5	Other specified intestinal infections
Cryptococcal cutaneous infection	B45.2	Cutaneous cryptococcosis
Cryptococcal fungaemia	B45.7	Disseminated cryptococcosis
Cryptococcosis	B45.9	Cryptococcosis unspecified

Serious Opportunistic Infection	ICD-10 Code	Category
Cutaneous coccidioidomycosis	B38.3	Cutaneous coccidioidomycosis
Cytomegalovirus chorioretinitis	B25.8	Other cytomegaloviral diseases
Cytomegalovirus colitis	B25.8	Other cytomegaloviral diseases
	A09.0	Other and unspecified gastroenteritis and colitis of infectious origin
Cytomegalovirus duodenitis	B25.8	Other cytomegaloviral diseases
	A09.0	Other and unspecified gastroenteritis and colitis of infectious origin
Cytomegalovirus enteritis	B25.8	Other cytomegaloviral diseases
	A09.0	Other and unspecified gastroenteritis and colitis of infectious origin
Cytomegalovirus enterocolitis	B25.8	Other cytomegaloviral diseases
	A09.0	Other and unspecified gastroenteritis and colitis of infectious origin
Cytomegalovirus gastritis	B25.8	Other cytomegaloviral diseases
	A09.0	Other and unspecified gastroenteritis and colitis of infectious origin
Cytomegalovirus gastroenteritis	B25.8	Other cytomegaloviral diseases
	A09.0	Other and unspecified gastroenteritis and colitis of infectious origin
Cytomegalovirus gastrointestinal infection	B25.8	Other cytomegaloviral diseases
	A09.0	Other and unspecified gastroenteritis and colitis of infectious origin
Cytomegalovirus gastrointestinal ulcer	K27 + B25.8	Peptic ulcer, site unspecified+ other cytomegaloviral diseases
Cytomegalovirus hepatitis	B25.1 + K77.0	Cytomegaloviral hepatitis + liver disorders in infectious and parasitic diseases classified elsewhere
Cytomegalovirus infection	B25.9	Cytomegaloviral disease, unspecified
Cytomegalovirus mucocutaneous ulcer	L99 + B25.8	Other disorders of skin and subcutaneous tissue in diseases classified elsewhere + other cytomegaloviral diseases
Cytomegalovirus myelomeningoradiculitis	B25.8	Other cytomegaloviral diseases

Serious Opportunistic Infection	ICD-10 Code	Category
Cytomegalovirus myocarditis	B25.8	Other cytomegaloviral diseases
	I41.1 + B25.8	Myocarditis in viral diseases classified elsewhere + other cytomegaloviral disease
Cytomegalovirus oesophagitis	K23 + B25.8	Disorders of oesophagus in diseases classified elsewhere + other cytomegaloviral diseases
Cytomegalovirus pancreatitis	B25.2 + K87.1	Cytomegaloviral pancreatitis + disorders of pancreas in diseases classified elsewhere
Cytomegalovirus pericarditis	I30.1 + B25.8	Infective pericarditis + other cytomegaloviral diseases
Cytomegalovirus syndrome	B25.9	Cytomegaloviral disease, unspecified
	B25.8	Other cytomegaloviral diseases
Cytomegalovirus urinary tract infection	N39.0 + B25.8	Urinary tract infection, site not specified + Other cytomegaloviral diseases
Cytomegalovirus viraemia	B25.9	Cytomegaloviral disease, unspecified
Disseminated cryptococcosis	B45.7	Disseminated cryptococcosis
Disseminated cytomegaloviral infection	B25.9	Cytomegaloviral disease, unspecified
	B25.8	Other cytomegaloviral diseases
Disseminated tuberculosis	A19.9	Miliary tuberculosis, unspecified
	A19.1	Acute miliary tuberculosis of multiple sites
	A19.2	Acute miliary tuberculosis, unspecified
	A19.8	Other miliary tuberculosis
Encephalitis *cytomegalovirus*	G05.1 + B25.8	Encephalitis, myelitis, and encephalomyelitis in viral diseases classified elsewhere + other cytomegaloviral diseases
Encephalitis fungal	G04.8 + B49	Other encephalitis, myelitis, and encephalomyelitis + mycosis, unspecified
Endocarditis candida	B37.6 + I39.8	candidal endocarditis + endocarditis, valve unspecified, in diseases classified elsewhere
Endocarditis histoplasma	I39.8 + B39.9	Endocarditis, valve unspecified, in diseases classified elsewhere + histoplasmosis, unspecified
Enterococcal gastroenteritis	B95.2 + A09.0	Streptococcus group D and enterococcus as the cause of diseases classified to other chapters + other and unspecified gastroenteritis and colitis of infectious origin

Serious Opportunistic Infection	ICD-10 Code	Category
Enterocolitis fungal	B48.7	Opportunistic mycoses
	A09.0 + B49	Other and unspecified gastroenteritis and colitis of infectious origin + unspecified mycosis
Exserohilum infection	B48.8	Other specified mycoses
Eye infection toxoplasmal	B58.0 + H32.0	Toxoplasma oculopathy + chorioretinal inflammation in infectious and parasitic diseases classified elsewhere
Fungaemia	B49	Unspecified mycosis
Fungal abscess central nervous system	G96.8	Other specified disorders of central nervous system
	B48.8	Other specified mycoses
Fungal oesophagitis	K20 + B49	Oesophagitis + unspecified mycosis
Fungal retinitis	H32.0 + B49	Chorioretinal inflammation in infectious and parasitic diseases classified elsewhere +unspecified mycosis
Fungal sepsis	B37.7	Candidial sepsis
	A41.8	Other specified sepsis
Fungal tracheitis	J04.1/J42 + B49	Acute/chronic tracheitis + unspecified mycosis
Funguria	R82.7 + B49	Abnormal findings on microbiological examination of urine + unspecified mycosis
Fusarium infection	B48.7	Opportunistic mycoses
	B48.8	Other specified mycoses
Gastritis fungal	K29.6 + B49	Other specified gastritis + unspecified mycosis
Gastritis herpes	K29.6 + B00.8	Other specified gastritis + other forms of herpesviral infection
Gastroenteritis *cryptococcal*	A09.0 + B45.8	Other and unspecified gastroenteritis and colitis of infectious origin + other forms of cryptococcosis
Gastrointestinal candidiasis	B37.8	Candidiasis of other sites
Gastrointestinal fungal infection	A09.0 + B49	Other and unspecified gastroenteritis and colitis of infectious origin + unspecified mycosis
Genital herpes simplex	A60.0	Herpesviral infection of genitalia and urogenital tract
	A60.9	Anogenital herpesviral infection, unspecified
Granulicatella bacteraemia	A48.8	Other specified bacterial diseases

Serious Opportunistic Infection	ICD-10 Code	Category
Granulicatella infection	A48.8	Other specified bacterial diseases
Hepatic candidiasis	B37.8	Candidiasis of other site
Hepatic infection fungal	B48.8	Other specified mycoses
Hepatitis B reactivation	B18.0 or B18.1	Chronic viral hepatitis B with delta agent/without
Hepatitis toxoplasmal	B58.1 + K77.0	Toxoplasma hepatitis + liver disorders in infectious and parasitic diseases classified elsewhere
Hepatosplenic candidiasis	B37.8	Candidiasis of other sites
Herpes oesophagitis	K20 + B00.8	Oesophagitis + other forms of herpesviral infection
Herpes ophthalmic	B00.5	Herpesviral ocular disease
Herpes pharyngitis	B00.2	Herpesviral gingivostomatitis and pharyngotonsillitis
Herpes sepsis	B00.7	Disseminated herpesviral disease
	A41.8	Other specified sepsis
Herpes simplex colitis	A09.0 + B00.8	Other and unspecified gastroenteritis and colitis of infectious origin + other forms of herpesviral infection
Herpes simplex encephalitis	B00.4	Herpesviral encephalitis
Herpes simplex gastritis	A09.0 + B00.8	Other and unspecified gastroenteritis and colitis of infectious origin + other forms of herpesviral infection
Herpes simplex hepatitis	B17.8 + B00.8	Other specified acute viral hepatitis + other forms of herpesviral infection
Herpes simplex meningitis	B00.3 + G02.0	Herpesviral meningitis + meningitis in viral diseases classified elsewhere
Herpes simplex meningoencephalitis	B00.4 + G05.1	Herpesviral encephalitis + encephalitis, myelitis, and encephalomyelitis in viral diseases classified elsewhere
Herpes simplex meningomyelitis	B00.4 + G05.1	Herpesviral encephalitis + encephalitis, myelitis, and encephalomyelitis in viral diseases classified elsewhere
Herpes simplex necrotising retinopathy	B00.5	Herpesviral ocular disease
Herpes simplex otitis externa	H62.1 + B00.1	Otitis externa in viral diseases classified elsewhere + herpesviral vesicular dermatitis

Serious Opportunistic Infection	ICD-10 Code	Category
Herpes simplex pharyngitis	B00.2	Herpesviral gingivostomatitis and pharyngotonsillitis
Herpes simplex pneumonia	J16.8 + B00.8	Pneumonia due to other specified infectious organisms + other forms of herpesviral infection
Herpes simplex sepsis	B00.7	Disseminated herpesviral disease
	A41.8	Other specified sepsis
Herpes simplex visceral	B00.8	Other forms of herpesviral infection
Herpes zoster cutaneous disseminated	B02.7	Disseminated zoster
	B02.8	Zoster with other complications
Herpes zoster disseminated	B02.7	Disseminated zoster
Herpes zoster meningitis	B02.1 + G02.0	Zoster meningitis + meningitis in viral diseases classified elsewhere
Herpes zoster meningoencephalitis	B02.0 + G05.1	Zoster encephalitis + encephalitis, myelitis, and encephalomyelitis in viral diseases classified elsewhere
Herpes zoster meningomyelitis	B02.1 + G05.1	Zoster meningitis + encephalitis, myelitis and encephalomyelitis in viral diseases classified elsewhere
Herpes zoster meningoradiculitis	B02.1 + G05.2	Zoster meningitis + encephalitis, myelitis, and encephalomyelitis in viral diseases classified elsewhere
Herpes zoster necrotising retinopathy	B02.8	Zoster with other complications
Herpes zoster oticus	B02.8	Zoster with other complications
Herpes zoster pharyngitis	J02.8 + B02.8	Acute pharyngitis due to other specified organisms + zoster with other complications
Histoplasmosis	B39.9	Histoplasmosis, unspecified
Histoplasmosis cutaneous	B39.1	Histoplasmosis, unspecified
Histoplasmosis disseminated	B39.3	Disseminated histoplasmosis capsulati
	L08.8	Other specified local infections of skin and subcutaneous tissue
HIV viraemia	B24	Unspecified HIV disease
	B23.8	HIV disease resulting in other specified conditions

Serious Opportunistic Infection	ICD-10 Code	Category
Infection in an immunocompromised host	B99	Other and unspecified infectious diseases
Intestinal tuberculosis	A18.3	Tuberculosis of intestines, peritoneum, and mesenteric glands
JC virus infection	B34.4	Papovavirus infection, unspecified site
Kaposi's sarcoma AIDS related	B21.0	HIV disease resulting in Kaposi sarcoma
Kaposi's varicelliform eruption	B00.0	Eczema herpeticum
Listeria encephalitis	A32.1 + G05.0	Listerial meningitis and meningoencephalitis + encephalitis, myelitis, and encephalomyelitis in bacterial diseases classified elsewhere
Listeria sepsis	A32.7	Listerial sepsis
Lower respiratory tract herpes infection	B00.8	Other forms of herpesviral infection
Lymphadenitis fungal	I88.8	Other nonspecific lymphadenitis
Malassezia infection	B48.8	Other specified mycoses
	B36.0	Pityriasis versicolor
Meningitis *aspergillus*	G02.1 + B44.8	Meningitis in mycoses + other forms of aspergillosis
Meningitis *candida*	G02.1 + B37.5	Meningitis in mycoses + candidial meningitis
Meningitis *coccidioides*	G02.1 + B38.4	Meningitis in mycoses + coccidioidomycosis meningitis
Meningitis *cryptococcal*	G02.1 + B45.1	Meningitis in mycoses + cerebral cryptococcosis
Meningitis *exserohilum*	G02.1	Meningitis in mycoses
	G03	Meningitis due to other and unspecified causes
Meningitis fungal	G02.1	Meningitis in mycoses
	G03	Meningitis due to other and unspecified causes
Meningitis histoplasma	G02.1	Meningitis in mycoses
	G03	Meningitis due to other and unspecified causes
Meningitis *listeria*	A32.1	Listerial meningitis and meningoencephalitis
Meningitis toxoplasmal	G05.2 + B58.2	Encephalitis, myelitis, and encephalomyelitis in other infectious and parasitic diseases classified elsewhere + toxoplasma meningoencephalitis

Serious Opportunistic Infection	ICD-10 Code	Category
Meningomyelitis herpes	G04.8	Other encephalitis, myelitis, and encephalomyelitis
	G02.0 + B00.3	Meningitis in viral diseases classified elsewhere + herpesviral meningitis
Methylobacterium infection	A49.8	Other bacterial infections of unspecified site
Miliary pneumonia	A19.0	Acute miliary tuberculosis of a single specified site
	A19.8	Other miliary tuberculosis
Mucocutaneous candidiasis	B37.2	Candidiasis of skin and nail
Mucormycosis	B46.5	Mucormycosis, unspecified
Mycobacterial peritonitis	K67.8 + A31.8	Other disorders of peritoneum in infectious diseases classified elsewhere + other mycobacterial infections
Mycobacterium avium complex immune restoration disease	A31.8	Other mycobacterial infections
Mycobacterium avium complex infection	A31.8	Other mycobacterial infections
Mycobacterium chelonae infection	A31.8	Other mycobacterial infections
Mycobacterium fortuitum infection	A31.8	Other mycobacterial infections
Mycobacterium kansasii infection	A31.8	Other mycobacterial infections
Myocarditis toxoplasmal	B58.8 + I41.2	Toxoplasmosis with other organ involvement + myocarditis in other infectious and parasitic diseases classified elsewhere
Necrotising herpetic retinopathy	H35.8 + B00.5	Other specified retinal disorders + herpesviral ocular disease
Neurocryptococcosis	B45.1	Cerebral cryptococcosis
Neutropenic infection	D70	Agranulocytosis
Neutropenic sepsis	A41.9	Sepsis unspecified
Nocardia sepsis	A43.8 + A41.8	Other forms of nocardiosis + other specified sepsis
Nocardiosis	A43.9	Nocardiosis, unspecified
Oesophageal candidiasis	B37.8	Candidiasis of other sites
Ophthalmic herpes simplex	B00.5	Herpesviral ocular disease
Ophthalmic herpes zoster	B02.3	Zoster ocular disease

Serious Opportunistic Infection	ICD-10 Code	Category
Opportunistic infection	B99	Other and unspecified infectious diseases
Oral candidiasis	B37.0	Candidal stomatitis
Oral fungal infection	B48.8	Other mycoses, not elsewhere classified
Oral hairy leukoplakia	K13.3	Hairy leucoplakia
Oro-pharyngeal aspergillosis	B44.8	Other forms of aspergillosis
	B44.2	Tonsillar aspergillosis
Oropharyngeal candidiasis	B37.0	Candidal stomatitis
	B37.8	Candidiasis of other sites
Oropharyngitis fungal	J02.8+B49	Acute pharyngitis due to other specified organisms + unspecified mycosis
Otitis media fungal	H74.8 + B49	Other specified disorders of middle ear and mastoid + unspecified mycosis
Pancreatitis fungal	K85.8+B49	Other acute pancreatitis + unspecified mycosis
Parvimonas infection	A49.8	Other bacterial infections of unspecified site
Parvimonas micra infection	A49.8	Other bacterial infections of unspecified site
Peliosis hepatis	K76.4	Peliosis hepatis
Penicillium infection	B48.4	Penicillosis
Pericarditis fungal	I32.1 + B49	Pericarditis in other infectious and parasitic diseases classified elsewhere + unspecified mycosis
Pericarditis histoplasma	I32.1 + B39.9	Pericarditis in other infectious and parasitic diseases classified elsewhere + histoplasmosis, unspecified
Phaeohyphomycosis	B48.8	Other specified mycosis
Pneumocystis jirovecii infection	B59 + J17.3	Pneumocystosis + pneumonia in parasitic diseases
Pneumocystis jirovecii pneumonia	B59 + J17.4	Pneumocystosis + pneumonia in parasitic diseases
Pneumonia *cryptococcal*	B45.0	Pulmonary cryptococcosis
Pneumonia cytomegaloviral	B25.0	Cytomegaloviral pneumonitis
Pneumonia herpes viral	J12.8	Other viral pneumonia
Pneumonia toxoplasmal	B58.3	Pulmonary toxoplasmosis
Polyomavirus-associated nephropathy	N16.0 + B33.8	Renal tubulo-interstitial disorders in infectious and parasitic diseases classified elsewhere + other specified viral diseases

Serious Opportunistic Infection	ICD-10 Code	Category
Presumed ocular histoplasmosis syndrome	H32.0 + B39.9	Chorioretinal inflammation in infectious and parasitic diseases classified elsewhere + histoplasmosis, unspecified
Progressive multifocal leukoencephalopathy	A81.2	Progressive multifocal leucoencephalopathy
Progressive vaccinia	B08.0	Other orthopoxvirus infections
Pseudallescheria infection	B48.2	Allescheriasis
Pseudallescheria sepsis	A41.8	Other specified sepsis
Pyelonephritis fungal	N16.0 + B49	Renal tubulo-interstitial disorders in infectious and parasitic diseases classified elsewhere + unspecified mycosis
Respiratory moniliasis	B37.1	Pulmonary candidiasis
Retinitis histoplasma	H30.8 + B39.9	Other chorioretinal inflammations +histoplasma unspecified
Retinitis viral	H30.9 + B34.9	Other chorioretinal inflammations + viral infection, unspecified
Rhodococcus infection	A49.8	Other bacterial infections of unspecified site
Scedosporium infection	B48.8	Other specified mycosis
Sepsis *pasteurella*	A28.0	Pasteurellosis
	A41.5	Sepsis due to other Gram-negative organisms
	A41.4	Sepsis due to anaerobes
	A41.8	Other specified sepsis
Sinusitis *aspergillus*	J01.9 + B44.8	Acute sinusitis, unspecified + other forms of aspergillosis
	J32.9 + B44.8	Chronic sinusitis unspecified + other forms of aspergiliosis
Sinusitis fungal	J01.9 + B49	Acute sinusitis, unspecified + unspecified mycosis
	J32.9 + B49	Chronic sinusitis unspecified + unspecified mycosis
Splenic candidiasis	D73.8 + B37.8	Other disease of spleen + candidiasis of other sites
Splenic infection fungal	D73.9 + B49	Other diseases of spleen + unspecified mycosis
Stomatococcal infection	A49.8	Other bacterial infections of unspecified site
Strongyloidiasis	B78.9	Strongyloidiasis, unspecified
Superinfection mycobacterial	A31.8	Other mycobacterial infections

Serious Opportunistic Infection	ICD-10 Code	Category
Systemic candida	B37.8	Candidiasis of other sites
Systemic mycosis	B49	Unspecified mycosis
Tongue fungal infection	K14.0 + B49	Glossitis + unspecified mycosis
Tonsillitis fungal	J03.8 + B49	Acute tonsillitis due to other specified organisms + unspecified mycosis
Tuberculous endometritis	N74.1	Female tuberculous pelvic inflammatory disease
Upper respiratory fungal infection	J39.8 + B49	Other specified diseases of upper respiratory tract + unspecified mycosis
Varicella zoster gastritis	K29.6 + B01.8	Other gastritis + varicella with other complications
Varicella zoster oesophagitis	K20 + B01.8	Oesophagitis + varicella with other complications
Varicella zoster pneumonia	B01.2 + J17.1	Varicella pneumonia + pneumonia in viral diseases classified elsewhere
Viral myelitis	G04.8	Other encephalitis, myelitis, and encephalomyelitis
	G05.1	Encephalitis, myelitis, and encephalomyelitis in viral diseases classified elsewhere
Viral oesophagitis	K20 + B34.9	Oesophagitis + viral infection, unspecified
Viral sepsis	A41.8	Other specified sepsis
Yersinia sepsis	A41.5	Sepsis due to other Gram-negative organisms
	A20.7	Septicaemic plague

AIDS = Acquired Immunodeficiency Syndrome; HIV = Human Immunodeficiency Virus; ICD-10 = International Classification of Diseases, 10th Revision; JC = John Cunningham

Annex 7. List of Medications Contraindicated with Venetoclax

Strong CYP3A Inhibitors

- Boceprevir
- Clarithromycin
  - Esomeprazole, amoxicillin, and clarithromycin
  - Lansoprazole, amoxicillin, and clarithromycin
  - Lansoprazole, clarithromycin, and tinidazole
  - Omeprazole, amoxicillin, and clarithromycin
  - Pantoprazole, amoxicillin, and clarithromycin
  - Pantoprazole, amoxicillin, clarithromycin, and metronidazole
- Cobicistat
  - Atazanavir, cobicistat
  - Darunavir, cobicistat
  - Emtricitabine, tenofovir alafenamide, darunavir, and cobicistat
  - Emtricitabine, tenofovir alafenamide, elvitegravir, and cobicistat
  - Emtricitabine, tenofovir disoproxil, elvitegravir, and cobicistat
- Conivaptan
- Danaprevir/ritonavir
- Eluitegravir and ritonavir
- Idelalisib
- Indinavir/ritonavir
- Itraconazole
- Ketoconazole
- Lopinavir/ritonavir
- Nefazodone
- Nelfinavir
- Ombitasvir/paritaprevir/ritonavir and/or dasabuvir

- Ombitasvir, paritaprevir, and ritonavir
- Posaconazole
- Ritonavir
- Saquinavir, ritonavir
- Telaprevir
- Tipranavir, ritonavir
- Trolenadomycin
- Voriconazole

Reference:

University of Washington Metabolism and Transport Drug Interaction Database (http://www.druginteractioninfo.org).

[redacted]A useful tool for drug interaction evaluation: the University of Washington Metabolism and Transport Drug Interaction Database. Hum Genomics. 2010;5(1):61-72.

Document Approval

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