EU Risk Management Plan for Venetoclax (VENCLYXTO)

AbbVie Inc. (AbbVie)

RMP Version Number: 11.0

Data lock points for this RMP:

Study M19 065: 12 October 2022

AML: 04 January 2020

CLL: 11 February 2021

Date of final sign off: September 2025

Rationale for submitting an updated RMP:

To update pharmacovigilance activities related to TLS and to add that distribution of DHPC in European countries (CLL only) was completed in 2021 and effectiveness evaluation completed in 2025 as per EMA request.

Summary of significant changes in the RMP: A summary of significant changes is included in RMP Annex 8.

Administrative Information on the RMP

Part	Module/Annex	Date last updated for submission (sign-off date)	Version number of RMP when last submitted
Part 1:	Product Overview	April 2022	8.1
Part II:	Safety Specification		
	SI – Epidemiology of the indication and target population(s)	October 2019	5.2
	SII – Non-clinical part of the safety specification	January 2020	5.3
	SIII – Clinical trial exposure	January 2025	10.0
	SIV – Populations not studied in clinical trials	May 2025	10.1
	SV – Post-authorization experience	May 2025	10.1
	SVI – Additional EU requirements for the safety specification	November 2018	3.4
	SVII – Identified and potential risks	August 2025	10.2
	SVIII – Summary of the safety concerns	August 2025	10.2
Part III:	Pharmacovigilance Plan	August 2025	10.2
Part IV:	Plan for Post-authorization Efficacy Studies	July 2024	9.0
Part V:	Risk Minimization Measures	August 2025	10.2
Part VI:	Summary of the RMP	August 2025	10.2
Part VII:	Annexes		
	Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study program	August 2025	10.2
	Annex 3 – Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan	August 2025	10.2
	Annex 4 – Specific adverse drug reaction follow-up forms	August 2025	10.2
	Annex 5 – Protocols for proposed and on-going studies in RMP Part IV	June 2019	5.1
	Annex 6 – Details of proposed additional risk minimization activities	August 2025	10.2
	Annex 7 – Other supporting data	May 2021	8.0
	Annex 8 – Summary of changes to the risk management plan over time	August 2025	10.2

NA = not applicable

Other RMP versions under evaluation:

RMP Version Number: N/A

Submitted on: N/A

Procedure number: N/A

Details of the Currently Approved RMP:

Version number: 10.1

Approved with procedure: EMA/VR/0000246380

Date of approval (opinion date): July 2025

QPPV name: Sina Schader

QPPV signature: The EU QPPV has approved the RMP through an electronic document system per the marketing authorization holder's (MAH) standard operating procedure.

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List of Abbreviations

A	Alemtuzumab
ADD	Average daily dose
ADME	Adsorption, distribution, metabolism, and excretion
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
APL	Acute promyelocytic leukemia
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the plasma concentration-time curve
B	Bendamustine
BCL	B-cell lymphoma
BCR	B-cell receptor
BCRP	Breast cancer resistance protein
BG	Bendamustine and obinutuzumab
BM	Bone marrow
BR	Bendamustine and rituximab
BTK	Bruton's tyrosine kinase
C	Cyclophosphamide
CCDS	Company Core Data Sheet
CCI	Charlson comorbidity index
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum observed plasma concentration
CMQ	Custom MedDRA Query
CNS	Central nervous system
CPRD	Clinical Practice Research Datalink
CR	Complete remission
CrCl	Creatinine clearance
Cri	Complete remission with incomplete blood count recovery

CSR	Clinical Study Report
CT	Computed tomography
CTLS	Clinical tumor lysis syndrome
CYP	Cytochrome P450
DDI	Drug-drug interaction
DHPC	Direct Healthcare Professional Communication
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EPAR	European Public Assessment Report
ESMO	European Society for Medical Oncology
EU	European Union
EU5	European Union Five (France, Germany, Italy, Spain, United Kingdom)
F	Fludarabine
FC	Fludarabine and cyclophosphamide
FCR	Fludarabine, cyclophosphamide, and rituximab
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
G	Obinutuzumab
GClb	Obinutuzumab in combination with chlorambucil
G-CSF	Granulocyte colony stimulating factor
GF	Growth factor
GH	Growth hormone
GI	Gastrointestinal
HBV	Hepatitis B virus
HCP	Healthcare Professional/Provider
HCT	Hematopoietic stem cell transplantation
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HMA	Hypomethylating agent
HRQoL	Health-related quality of life
HSCT	Hematopoietic stem cell transplantation

IARC	International Agency for Research on Cancer
IIS	Investigator-initiated study
IRC	Independent review committee
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
MDS	Myelodysplastic syndrome
MRD	Minimal residual disease
MTD	Maximum tolerated dose
MUGA	Multiple-gated acquisition (scan)
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NOAEL	No-observed-adverse-effect-level
NPM	Nucleophosmin
nPR	Nodular partial response
ORR	Objective response rate or overall response rate
OS	Overall survival
PAA	Pre-Approval Access
PASS	Post Authorization Safety Study
PC	Patient card
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PMOS	Post-Marketing Observational Study
PNB	Patient Named Basis
PND	Post-natal day
PR	Partial remission
PRAC	Pharmacovigilance Risk Assessment Committee
PSUSA	Periodic Safety Update (Report) Single Assessment
PT	Preferred term
PTD	Patient treatment days
PTT	Partial thromboplastin time
PTY	Patient treatment years
PY	Patient-years
QD	Once a day

QLQ	Quality of Life Questionnaire
QTc	Corrected QT interval
R	Rituximab
RMP	Risk Management Plan
RPTD	Recommended Phase 2 dose
R/R	Relapsed/refractory
SEER	Surveillance, Epidemiology, and End Results
SLE	Systemic lupus erythematosus
SLL	Small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TLS	Tumor lysis syndrome
TTNT	Time to next anti-CLL treatment
TTP	Time to tumor progression
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of normal
UK	United Kingdom
US	United States
V + G	Venetoclax in combination with obinutuzumab
V + R	Venetoclax in combination with rituximab
WBC	White blood cell

Part I: Product(s) Overview

Table 1. Product Overview

Active substance(s) (INN or common name)	Venetoclax, ABT-199, GDC-0199
Pharmacotherapeutic group(s) (ATC Code)	L01XX52
Marketing Authorization Holder	AbbVie Deutschland GmbH & Co. KG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Venclyxto
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Not yet assigned
	Summary of mode of action: Venetoclax is a potent, selective, and orally bioavailable small-molecule inhibitor of BCL-2. Venetoclax binds to the BH3-binding groove of BCL-2, thereby liberating proteins like BIM and BAX, which initiate programmed cell death (apoptosis). BCL-2 overexpression contributes to the pathogenesis of various hematologic malignancies and solid tumors, and has been implicated as a resistance factor for certain therapeutic agents.
	Important information about its composition: None
Hyperlink to the Product Information	The SmPC is used for the CLL and AML indications: SmPC

<table>
<tr><td rowspan="2">Indication(s) in the EEA</td><td>Current (CLL):
Venclyxto in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL).
Venclyxto in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.
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, or
• in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.
The indication(s) may differ outside of the EEA.</td></tr>
<tr><td>AML (Combination):
Venclyxto in combination with a hypomethylating agent is indicated for the treatment of adult patients with newly-diagnosed acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy.</td></tr>
<tr><td>Dosage in the EEA</td><td><u>CLL:</u>
<u>Posology</u>
<u>Dose-titration schedule</u>
The starting dose is 20 mg of venetoclax once daily for 7 days. The dose must be gradually increased over a period of 5 weeks up to the daily dose of 400 mg as shown in the table below.
<table>
<tr><th>Week</th><th>Venetoclax Daily Dose</th></tr>
<tr><td>1</td><td>20 mg</td></tr>
<tr><td>2</td><td>50 mg</td></tr>
<tr><td>3</td><td>100 mg</td></tr>
<tr><td>4</td><td>200 mg</td></tr>
<tr><td>≥ 5</td><td>400 mg</td></tr>
</table>
The 5-week dose-titration schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of tumor lysis syndrome (TLS).
<u>Post-titration dose for venetoclax in combination with obinutuzumab</u>
Obinutuzumab administration should start on Cycle 1 Day 1 at 1000 mg (dose may be split as 100 mg and 900 mg on Days 1 and 2). Administer 1000 mg on Days 8 and 15 of Cycle 1 and on Day 1 of each subsequent 28-day cycle, for a total of 6 cycles.
The 5-week venetoclax titration schedule (Table above) should begin on Cycle 1 Day 22 and continue through Cycle 2 Day 28.</td></tr>
</table>

<table>
<tr><td></td><td>After completing the dose titration schedule, the recommended dose of venetoclax is 400 mg once daily from Cycle 3 Day 1 of obinutuzumab to the end of Cycle 12.
Venetoclax should be given in combination with obinutuzumab for 6 cycles, followed by 6 cycles of venetoclax as a single agent.
<u>Post-titration dose for venetoclax in combination with rituximab</u>
The recommended dose of venetoclax in combination with rituximab is 400 mg once daily.
Rituximab should be administered after the patient has completed the dose-titration schedule and has received the recommended daily dose of 400 mg venetoclax for 7 days.
Venetoclax should be taken for 24 months from Cycle 1 Day 1 of rituximab.
<u>Post-titration dose for venetoclax monotherapy</u>
The recommended dose of venetoclax is 400 mg once daily. Treatment should be continued until disease progression or no longer tolerated by the patient.
<u>AML:</u>
The recommended venetoclax dosing schedule (including dose titration) is shown in the table below. Initiate the hypomethylating agent on Day 1.
<table>
<tr><th>Day</th><th>Venetoclax Daily Dose</th></tr>
<tr><td>1</td><td>100 mg</td></tr>
<tr><td>2</td><td>200 mg</td></tr>
<tr><td>3 and beyond</td><td>400 mg</td></tr>
</table>
Venetoclax in combination with a hypomethylating agent should be continued until disease progression or unacceptable toxicity is observed.</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>Venetoclax (10, 50, or 100 mg) is formulated as a film-coated tablet.</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>Yes</td></tr>
</table>

Part II: Safety Specification

Module SI Epidemiology of the Indication(s) and Target Population(s)

Indication

CLL

Venetoclax in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Venetoclax in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.

Venetoclax 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, or
- In the absence of 17p deletion or *TP53* mutation in adult patients who have failed both chemoimmunotherapy and a B cell receptor pathway inhibitor.

The indication(s) may differ outside of the EEA. The epidemiology of CLL is discussed below in common for all indications.

AML

Venclyxto in combination with a hypomethylating agent is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy.

Incidence

CLL:

- CLL is the most common leukemia subtype in adults in Western countries, accounting for approximately 30% of all leukemias. The current World Health Organization classification system recognizes and groups CLL and small lymphocytic lymphoma (SLL) as the same biological entity, with CLL clinically manifesting primarily in bone marrow and peripheral blood, and SLL primarily manifesting in the lymph nodes. The incidence rate of CLL/SLL in EU5 is 7.6 per 100,000 persons with an estimated 23,473 new cases diagnosed in 2017 (Decision Resources Group 2017c).
- 17p deletion or *TP53* mutations in CLL are associated with the most adverse outcomes. In 2010, the incidence rates of relapsed/refractory (R/R) CLL with

17p deletion varied from approximately 0.4 per 100,000 person years in Spain to 0.7 per 100,000 person years in France (CancerMPact 2014).

AML:

- AML is the most common form of acute leukemia in adults (accounting for approximately 25% of all leukemias in adults in the Western world) (Deschler 2006, GLOBOCAN 2012, Klepin 2009).
- The reported incidence rates of AML vary between 1.5 and 5.2 per 100,000 person years across Europe and the US (Schnegg Kaufmann 2018). The estimated 2017 incidence rate of AML in European Union Five (EU5) countries (France, Germany, Italy, Spain, United Kingdom) ranged from 3.12 (Spain) to 5.11 (Italy) per 100,000 persons (Decision Resources Group 2017a) (incidence in mature markets).
- The incidence increases steadily after the age of 40 years, reaching peak values of 15 to 30 per 100,000 at the age of 75 to 80 years (Schnegg Kaufmann 2018).

Prevalence

CLL:

- The 2017 estimated number of prevalent CLL/SLL cases in the EU5 is 148,400 resulting in a prevalence rate of 4.87 per 10,000 persons (Decision Resources Group 2017c).
- Prevalence data on R/R CLL in the EU are not readily available. Based on a survey conducted in March 2017 of 82 physicians who treated a total of 3,514 CLL patients monthly in Western Europe (CancerMPact 2017), 14.7% of patients do not respond to first line therapy (have refractory CLL), 17.4% do not respond to second line therapy, and 24.6% do not respond to third line therapy. Among patients who respond to first line treatment, 17.7% relapse within 1 year, 33.3% relapse between 1 and 5 years, and 21.9% of patients relapse between 5 and 10 years. Only 12.9% of patients remained relapse free within the first 10 years of CLL diagnosis, and this percentage was lower for patients receiving 2 lines of therapy (8.6%) and 3 lines of therapy (5.7%) (CancerMPact 2017).
- While the 17p deletion is found in 5% to 7% of CLL patients in early stages and among patients treated with CLL first line therapy, this high risk chromosomal abnormality is present in 25% to 40% of patients with advanced refractory CLL (Stilgenbauer 2010, Zenz 2008). TP53 mutations have been noted to occur in approximately 8% of CLL patients (Zenz 2010). Approximately 70% to 80% of CLL patients with 17p deletion also have loss of p53 function because of mutation in the remaining *TP53* allele (Zenz 2008). Sole *TP53* mutations in the absence of 17p deletions have been reported to occur in approximately 4% to 5% of patients

(Zenz 2010). The overall prevalence of *TP53* mutations increases with treatment lines from approximately 5% to 10% (first line) to approximately 10% to 40% with advanced refractory CLL (Stilgenbauer 2010, Zenz 2008).

AML:

- The estimated 2017 prevalence rate of AML (excluding acute promyelocytic leukemia [APL]) in EU5 (France, Germany, Italy, Spain, United Kingdom) ranged from 7.56 (Spain) to 10.45 (Italy) per 100,000 persons (Decision Resources Group 2017b) (prevalence in mature markets).
- In the United States (US), the 2017 prevalence rate of AML (excluding APL) was 10.85 per 100,000 persons (Decision Resources Group 2017b) (prevalence in mature markets).

Demographics of the Target Population

CLL:

- The median age at diagnosis is 72 and approximately 70% of patients are older than 65 years of age and only 10% of patients are less than 55 years old (Byrd J 2012, Delgado 2014, Howlader 2012). Patients with CLL are more frequently male than female, and the incidence of disease is higher in Caucasians than in African Americans or Asian/Pacific Islanders (Linet 2007, Redaelli 2004).
- The demographic characteristics of patients with or without 17p deletion or *TP53* mutation are similar to the overall CLL population globally (Baumann 2014, Brown 2014).

AML:

- In Europe, AML is more often diagnosed in males compared with females, with the female to male ratio for newly diagnosed AML cases of 1:1.45 (Sant 2010). In the study of 3,251 AML patients diagnosed in 2012 2014 in Germany and Austria, the median age at diagnosis was 65 years, and was slightly higher in males (66 years) compared with females (64 years) (Nagel 2017).
- In the US, the median age of diagnosis for AML is 68 years (68 and 67 in males and females, respectively), with 57% of the patients diagnosed at 65 years or older; approximately a third are diagnosed over the age of 75 (Howlader N 2018, National Cancer Institute 2018, Noone 2018). Median age at diagnosis is higher among Whites (69 years of age) as compared with African Americans (62 years of age) (Noone 2018). The female to male ratio for newly diagnosed AML cases in the US in 2015 was 1:1.44, and was higher in Whites (1:1.47) than among African Americans (1:1.19)(Noone 2018).

Risk Factors

CLL:

- Patients of older age and male gender are more likely to develop CLL. Besides these factors, risk factors for this disease are largely unknown with only a small percentage of cases attributable to family history (Cramer 2011).

AML:

- Acute myeloid leukemia is associated with older age, previous haematologic disease, genetic disorders, exposure to chemicals or radiation, and prior exposure to some chemotherapies (Table 2).
- Different subtypes of AML may be linked with different predisposing factors. However, for most cases of de novo AML, no specific leukemogenic exposure can be identified as reviewed in: (Deschler 2006).

Table 2. Selected Risk Factors Associated with AML

Genetic Disorders	Down syndrome
	Klinefelter syndrome
	Patau syndrome
	Ataxia telangiectasia
	Shwachman syndrome
	Kostman syndrome
	Neurofibromatosis
	Fanconi anemia
	Li-Fraumeni syndrome
Physical and Chemical Exposures	Benzene
	Drugs such as pipobroman
	Pesticides
	Cigarette smoking
	Embalming fluids
	Herbicides
Radiation Exposure	Nontherapeutic and therapeutic radiation
Chemotherapy	Alkylating agents
	Topoisomerase-II inhibitors
	Anthracyclines
	Taxanes
Previous Haematologic Disease	Myelodysplastic syndrome
	Myeloproliferative neoplasia

Adapted from Deschler 2006.

Main Treatment Options

CLL:

Treatment for CLL is initiated when a patient's disease becomes symptomatic or progressive as defined by the iwCLL updated guidelines for diagnosis and treatment of CLL (Hallek 2008).

For first line CLL patients, treatment options (per ESMO and NCCN Guidelines) include:

- chemoimmunotherapy (fludarabine, cyclophosphamide, and rituximab [FCR]; fludarabine and rituximab [FR]; pentostatin, cyclophosphamide, rituximab; bendamustine and rituximab [BR]),
- ibrutinib (an irreversible inhibitor of Bruton's tyrosine kinase [BTK]).

For patients who are considered inappropriate for fludarabine based regimens due to advanced age and/or comorbidities, treatment options include:

- chlorambucil chemotherapy alone or in combination with anti CD20 antibodies (such as obinutuzumab, ofatumumab, and rituximab),
- ibrutinib.

For patients with relapsed or refractory CLL (R/R CLL), single and multi agent therapies are options. The choice of treatment for patients with R/R CLL is dependent on age, comorbidity, performance status, and *TP53* deletion/mutation status or by time to relapse from start of initial therapy (after 24–36 months or within 24 36 months) in addition to comorbidity, performance status, and *TP53* deletion/mutation status (ESMO and NCCN Guidelines).

The choice of treatments for R/R CLL includes:

- B cell receptor inhibitor such as ibrutinib or idelalisib, with or without rituximab,
- Venetoclax in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy (per NCCN Guideline only),
- chemoimmunotherapy (e.g., BR; FCR; fludarabine + cyclophosphamide [FC], ofatumumab + FC).

A substantial unmet medical need remains for treatments that improve response, maintain remission, provide a more manageable safety profile and achieve long term control of CLL, including those patients harboring the 17p del cytogenetic abnormality and those refractory to or relapsed after initial treatment(s).

AML:

- Standard treatment for newly diagnosed AML in patients who are medically fit consists of remission induction therapy with cytarabine, combined with an anthracycline, usually daunorubicin or idarubicin, followed by consolidation therapy (Döhner 2017, Fey 2013).
- Globally, there exists no single standard of care for older patients with AML who are not candidates for intensive therapy (Döhner 2017). Because the mortality rate associated with induction therapy in patients greater than age 65 years has been shown to be substantially higher than in younger patients, even in the presence of intermediate or favorable risk cytogenetics, many elderly patients are best managed with nonintensive approaches (Appelbaum 2006).
- Low intensity treatment options currently recommended by guidelines for the treatment of AML in patients aged ≥ 60 years based on performance status and

cytogenetics include low dose cytarabine (LDAC) and hypomethylating agents (HMAs) such as azacitidine or decitabine (Döhner 2017, Fey 2013).

- The current treatments for patients with AML who are not candidates for standard induction chemotherapy or hematopoietic stem cell transplantation (HSCT) in the EU include azacitidine, decitabine and LDAC (Döhner 2017, Fey 2013).
- Overall response (complete remission [CR] + complete remission with incomplete blood count recovery [CRi]) rate in a randomized trial was 25.6% and median survival was modest at 7.7 months with decitabine compared with 10.7% and 5.0 months in treatment choice arm consisting of either subcutaneous LDAC (88.5% of patients) or supportive care (11.5% of patients) (Kantarjian 2012).
- The reported overall response (CR + CRi) rate and median overall survival were 27.8% and 10.4 months with azacitidine versus 25.1% and 6.5 months, respectively, with conventional care regimens consisting of best supportive care, LDAC, or intensive chemotherapy (Dombret 2015).
- The relatively poor outcomes associated with currently available treatment options for patients with AML who are ineligible for intensive chemotherapy highlights the need for novel and safe options that offer greater improvements in remission rates and survival.

Natural History of the Indicated Disease/Condition, Including Mortality and Morbidity

CLL:

- The mortality estimates of the total number of CLL deaths in Europe are limited; therefore, survival estimates are also presented. The 5 year mortality rate for Spanish patients diagnosed with CLL between 1995 and 2004 was 24 per 1,000 patient years while the 10 year mortality rate was 41 per 1,000 patient years (Abrisqueta 2009). In Europe, the 5 year relative survival rate of CLL and SLL patients in the Period 2000 2002 was 69.1% (Marcos Gragera 2011).
- Survival of patients with R/R CLL is significantly lower compared to general CLL population, as subjects become increasingly resistant to available therapy. The estimated median overall survival (OS) after R/R CLL is 12 to 16 months (Bazargan 2010, Keating 2002a, Keating 2002b, Wierda 2010) versus 108 months in front line CLL (Döhner 2000).
- CLL patients with a 17p deletion have a significantly increased risk of death compared to those without this deletion (hazard ratio = 8.08; 95% confidence interval: 4.24 15.40), median survival being approximately 10 years in low risk patients and 2 years in high risk patients. The median OS in relapsed CLL patients with 17p deletion is less than 24 months (Döhner 2000). The median survival of patients with p53 mutation is similar (Stilgenbauer 2010).

- Analysis of Flatiron Health database was conducted to assess 1 year survival rates of treated patients with CLL. The analyses involved the following groups:
  - Patients with CLL who received at least 1 prior therapy irrespective of 17p deletion status
  - CLL patients with 17p deletion who failed a B cell receptor pathway inhibitor (BCRi)
  - Patients with CLL who failed both chemoimmunotherapy and a BCRi
  - Among CLL patients who received at least 1 prior line of therapy (n = 999), the 1 year survival estimate was 84% (95% CI: 82% 87%) (see Table 3). The estimated 1 year survival rate among CLL patients with 17p deletion who failed BCRi (ibrutinib, idelalisib) treatment (n = 24) was 84% (95% CI: 69% 100%) (see Table 4). Finally, 1 year survival among patients with CLL who failed both chemoimmunotherapy and a BCRi (n = 199) was 75% (95% CI: 69% 83%) (see Table 5).

Table 3. One-Year Overall Survival Based on Kaplan-Meier Estimator Among CLL Patients with One Prior Line of Therapy

Sample Size (n)	Days	At risk	Events (%)	Survival probability (95% CI)
999	365	583	136 (23%)	0.84 (0.82, 0.87)

CI = confidence interval

Table 4. One-Year Overall Survival Based on Kaplan-Meier Estimator Among CLL Patients with 17p Deletion Who Have Failed a B-Cell Receptor Pathway Inhibitor

Sample Size (n)	Days	At risk	Events (%)	Survival probability (95% CI)
24	365	11	3 (27%)	0.84 (0.69, 1.00)

CI = confidence interval

Table 5. One-Year Overall Survival Based on Kaplan-Meier Estimator Among CLL Patients Who Failed Both Chemoimmunotherapy and a B-Cell Receptor Pathway Inhibitor

Sample Size (n)	Days	At risk	Events (%)	Survival probability (95% CI)
199	365	92	38 (43%)	0.75 (0.69, 0.83)

CI = confidence interval

Important co morbidities:

The prevalence of various comorbid health conditions present at the time of CLL diagnosis are shown in Figure 1. Rheumatological diseases (primarily osteoarthritis, 42% of patients), dyslipidemia (41%) and hypertension (40%) were the three most common comorbid health conditions present at the time of CLL diagnosis. While 548 (48%) patients had no major comorbidities at the time of CLL diagnosis, 394 (34%) had one major comorbidity and 201 (18%) had two or more major comorbidities.

Figure 1. Prevalence of Baseline Comorbid Health Conditions in 1143 CLL Patients

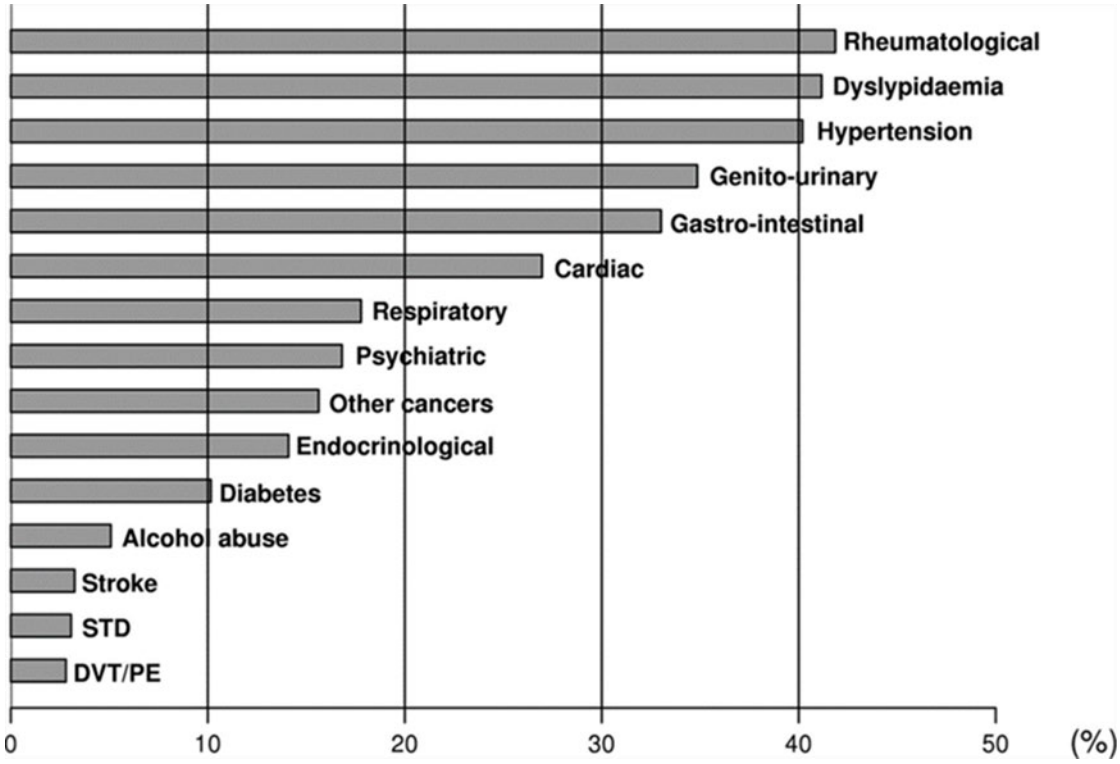

Figure 1 first appeared in a publication by Strati et al.: Relationship between co-morbidities at diagnosis, survival and ultimate cause of death in patients with chronic lymphocytic leukemia (CLL): a prospective cohort study (Strati 2017).

DVT, deep venous thrombosis; PE, pulmonary embolism; STD, sexually transmitted disease. Other cancers did not include non-melanoma skin cancers.

Approximately 70% of patients are older than 65 years of age at the time of CLL diagnosis (Gribben 2010). Thus, comorbidities found in the CLL population are similar to those found in the elderly. A retrospective study was conducted among 2576 patients with a diagnosis of CLL between January 2000 and June 2012 in the UK Clinical Practice Research Datalink (CPRD). Table 6 describes the comorbidities that were reported at baseline (Pfeil 2015).

Table 6. Characteristics of the CLL Study Population in UK Clinical Practice Research Datalink: Comorbidities

Comorbidities[a]	n	Men (%)[b]	Women (%)[b]
None	1529	873 (33.9)	656 (25.5)
Chronic obstructive pulmonary disease	189	136 (5.3)	53 (2.0)
Congestive heart failure	95	64 (2.5)	31 (1.2)
Myocardial infarction	65	46 (1.8)	19 (0.7)
Hypertension	406	221 (8.6)	185 (7.2)
Hypotension	55	37 (1.4)	18 (0.7)
Diabetes	215	127 (4.9)	88 (3.4)
Peripheral vascular disease	82	53 (2.1)	29 (1.1)
Cerebrovascular disease	73	44 (1.7)	29 (1.1)
Renal diseases	392	209 (8.1)	183 (7.1)
Ulcer	187	105 (4.1)	82 (3.2)
Liver disease	8	8 (0.3)	0 (0.0)
Connective tissue disease	3	3 (0.1)	0 (0.0)
Hemiplegia	2	2 (0.0)	0 (0.0)
Dementia	60	28 (1.1)	32 (1.2)
All tumors	7	5 (0.2)	2 (0.0)
Metastatic solid tumor	7	5 (0.2)	2 (0.0)
Lymphoma	86	53 (2.1)	33 (1.3)

a. Comorbidities are arranged by the Charlson comorbidity index (CCI), which consists of 19 comorbid conditions weighted according to the degree to which they predict mortality.

b. The percentages reported are based on the total number of patients (N 2576).

AML:

- The reported relative 5 year survival rate for AML patients is estimated at only 17.0%. The prognosis for patients with AML declines with age: the 5 year relative survival rate in younger adult patients (47.4% for 15 to 49 years) is significantly higher than in older patients (15.4% for 50 to 69 years; and 2.7% for 70 years and over) (Maynadié 2013).

Important co morbidities:

- A clinical study by Lübbert et al (Lübbert 2012) assessed comorbidities' profile among AML patients unfit for induction chemotherapy. Among 225 AML patients,

the most common comorbidities at baseline were infections, cardiovascular diseases, diabetes, and mild hepatic impairment (see Table 7 below).

- Among infections, the most frequently observed were pneumonia/bronchitis (35% of patients requiring antimicrobial treatment), GI infections (16%), fungal infections (16%), and herpes stomatitis (14%) (Lübbert 2012).

Table 7. Prevalence of the Most Frequent Comorbidities (Occurring in > 5% of AML Patients) - Study HCT-CI27 in 225 Evaluable Patients

Comorbidity	n (%)
Infection	51 (22.7)
Cardiac	51 (22.7)
Diabetes mellitus	47 (20.9)
Mild hepatic	46 (10.4)
Prior solid tumor	33 (14.7)
Arrhythmia	26 (11.6)
Moderate pulmonary disease	25 (11.1)
Psychiatric disturbance	19 (8.4%)
Cerebrovascular disease	14 (6.2)

Source: (Lübbert 2012)

Module SII Non-Clinical Part of the Safety Specification

Key Safety Findings (from Non-Clinical Studies)	Relevance to Human Usage
Toxicity	
Repeat-dose toxicity • Neutropenia was not observed in non-clinical studies of mice or dogs. Dose-dependent neutropenia was identified in preclinical studies of human bone marrow cultured ex vivo and rats dosed in vivo.	• In clinical trials, neutropenia was identified as a risk (Section VII.3). Severe neutropenia has been reported; majority are confounded by pre-existing neutropenia, prior multiple therapies and/or disease progression; all were manageable with supportive care.

Key Safety Findings (from Non-Clinical Studies)	Relevance to Human Usage
• In animals, venetoclax reduced lymphocytes and red blood cell hemoglobin in a dose-dependent manner. Both effects were reversible after cessation of dosing with venetoclax, but recovery of lymphocytes was prolonged up to 4 months post treatment. There was no evidence of an increase over the background rate of infections typically found in mice or Beagle dogs, suggesting no immunologic compromise to common laboratory pathogens. Consequently, lymphocyte decreases were considered to be non-adverse up to the highest dosages administered. In non-clinical studies, anemia was adverse only at the highest dosages evaluated, and was notably more severe in rats as compared with that in mice and dogs at similar exposures. • Single cell necrosis in various tissues was identified in dogs, including the gallbladder and exocrine pancreas, with no evidence of disruption of tissue integrity or organ dysfunction; these findings were minimal to mild in magnitude and demonstrated evidence of reversibility in some, but not all, tissues during a 4-week recovery period. • After approximately 3 months of daily dosing in the chronic dog study, a progressive change in hair coat color towards white was observed, due to loss of melanin in the hair. No changes in the quality of the hair coat or skin were observed, nor changes in other pigmented tissues examined (viz., the iris and the pigmented ocular fundus). Reversibility of the hair coat changes has not been assessed.	• Lymphopenia and anemia are both monitorable and reversible. Decreases in lymphocytes are expected based on mechanism of action; no opportunistic infections have been observed in patients as a result of this on target effect. Few serious adverse events of anemia have been reported in clinical trials, all are confounded by pre-existing anemia, prior multiple therapies and/or disease progression; all were manageable with supportive care. • Relevance of single cell necrosis was not established in humans. • No concern of discoloration of hair was noted in study population (mean age 66 years).
Reproductive toxicity • Venetoclax results in testicular toxicity (germ cell depletion) in dogs at all dose levels examined (≥ 5 mg/kg or ≥ 150 mg/day in a 60 kg human) and has not demonstrated reversibility within 4-weeks after dose cessation.	• The findings in dogs suggest there may be a risk of testicular effects by venetoclax in humans, although there are no data in humans from clinical trials, and the actual risk is not known. • However, as the majority of CLL and AML patients are ≥ 65 years of age, this is not likely to be a concern in this elderly population.

Key Safety Findings (from Non-Clinical Studies)	Relevance to Human Usage
• Fertility and early embryonic development studies were conducted in male and female mice. There were no effects of venetoclax on fertility, pregnancy (implantation), ovarian and uterine parameters, male or female reproductive organs, or on female estrus cycling. The no-observed-adverse-effect-level (NOAEL) for males and females was 600 mg/kg/day.	

Key Safety Findings (from Non-Clinical Studies)	Relevance to Human Usage
Developmental toxicity • No evidence of teratogenicity was found in embryofetal development studies in mice with venetoclax or M27 or in rabbits with venetoclax. • Fetal toxicity (post implantation loss and decreased fetal body weights) was observed at the venetoclax high dosage of 150 mg/kg/day in mice; the NOAEL was at the mid dosage of 50 mg/kg/day. There was no embryofetal toxicity in rabbits up to the maximum venetoclax dosage of 300 mg/kg/day (NOAEL), but exposures were low (approximately one-tenth) compared with those in mice. • A pre- and postnatal development study with venetoclax has not been conducted. • Venetoclax was administered (single dose; 150 mg/kg oral) to pregnant rats. Maternal rat systemic exposures (AUC) to venetoclax were approximately 14-times higher than the exposure in humans at the 400 mg dose. Measurable levels of radioactivity in fetal tissues (liver, GI tract) were > 15-fold lower than maternal levels in the same tissues. Venetoclax derived radioactivity was not detected in fetal blood, brain, eye, heart, kidney, lung, muscle or spinal cord. • Venetoclax was also administered (single dose; 150 mg/kg oral) to lactating rats on 8-10 days post parturition. Venetoclax in milk was 1.6 times lower than in plasma. Parent drug (venetoclax) represented the majority of the total drug-related material in milk, with trace levels of three metabolites. • In an embryofetal development study in mice that evaluates embryo and fetal development from implantation and during the period of organogenesis, M27 administered at the maximum feasible dose of 250 mg/kg/day resulted in an increase in post-implantation loss and resorptions. The number of post-implantation loss and resorptions were within historical control range in the M27 group and were below the historical control range in the concurrent control group. The NOAEL was 30 mg/kg/day.	• The risk for teratogenicity or fetal toxicity associated with venetoclax treatment and its major metabolite M27 in humans is not known. • Venetoclax must not be used by females who are pregnant. • Women should avoid becoming pregnant while taking venetoclax and for up 30 days after ending treatment. • Embryofetal toxicity was identified as an important potential risk in humans (see Module SVII). • However, as the majority of CLL and AML patients are ≥ 65 years of age, this is not likely to be a concern in this elderly population. • It is not known whether venetoclax or its metabolites are excreted in human milk. Available data in animals have shown excretion of venetoclax/metabolites in milk. A risk to newborns/infants cannot be excluded. Breast feeding should be discontinued during treatment with venetoclax. • The current/proposed indications for venetoclax do not include adolescents or children (patients < 18 years of age).

Key Safety Findings (from Non-Clinical Studies)	Relevance to Human Usage
Nephrotoxicity • No clinical or anatomic changes have been observed in the kidneys of mice, rats, or dogs up to the highest dosages administered in short or long term toxicology studies.	• No safety signals related to renal effects of venetoclax have been seen in clinical trials
Hepatotoxicity • No clinical or anatomic changes have been observed in the liver of mice up to the highest dosages administered in short term or long term toxicology studies. • Minor, non-adverse effects (increased pigment in Kupffer cells and macrophages in the liver and gall bladder, respectively) were observed in the dog.	• No safety signals related to hepatic effects of venetoclax have been seen in clinical trials
Carcinogenicity • Venetoclax and the M27 major human metabolite were not carcinogenic in a 6-month transgenic (Tg.rasH2) mouse carcinogenicity study at oral doses up to 400 mg/kg/day of venetoclax and at a single dose level of 250 mg/kg/day. AUC exposure margins, relative to clinical AUC at 400 mg/day, were approximately 2-fold for venetoclax and 5.8-fold for M27. • Venetoclax was not mutagenic to bacteria (Ames) in the presence or absence of metabolic activation and was not clastogenic (did not increase the frequency of micronucleated red blood cells) in an in vivo mouse study at doses up to 833 mg/kg. Venetoclax did not induce chromosomal aberrations (human peripheral blood lymphocytes) in the presence or absence of metabolic activation. • No evidence of hyperplastic or neoplastic lesions in chronic toxicity studies in mice (6 months) or dogs (9 months).	• No safety signals related to carcinogenic effects of venetoclax have been seen in clinical trials. However, second primary malignancies is an important potential risk for venetoclax. (see Module SVII). • Based on the results of the preclinical study, carcinogenicity is no longer identified as missing information (see Module SVII).
General Safety Pharmacology	
Cardiovascular • No effects on corrected QT interval (QTc) were observed up to a maximum plasma concentration of 46 µg/mL in dogs.	• Clinical trial data to date suggest no QTc prolongation and/or cardiac dysfunction related to venetoclax administration.
Nervous system/Respiratory System • No neurobehavioral changes or adverse respiratory effects were observed in neuropharmacology studies in mice and rats.	• No adverse central nervous system (CNS) or respiratory effects of venetoclax are anticipated.

Key Safety Findings (from Non-Clinical Studies)	Relevance to Human Usage
Other toxicity-related information or data • M27 is a major human metabolite. Although observed in mice and dogs, M27 is present at much lower levels (0.04- to 0.06-fold), as compared with steady-state levels in humans, and therefore is a disproportionate metabolite. Additionally, M27 shows low in vitro potency (at least 58-fold less than parent) and produced no evidence of in vitro genotoxicity in Ames and chromosome aberration assays. In a 4-week oral toxicity study in mice, M27 had effects similar to venetoclax (decreased lymphocytes and red blood cell mass) but of lesser magnitude, consistent with the low *in vitro* pharmacologic potency of M27 as a Bcl-2 inhibitor.	• There are no anticipated genotoxicity or repeat-dose toxicity risks with the human metabolite M27.
Food effect • Food increased the bioavailability of venetoclax by 3 to 5 fold.	• Venetoclax should be taken with a meal. Taking venetoclax with an empty stomach may result in decreased therapeutic effects. The product information provides guidance on when to take venetoclax in relation to meals.

CLL = chronic lymphocytic leukemia; CNS = central nervous system; NOAEL = no-observed-adverse-effect-level; QTc = corrected QT interval

Non-Clinical Safety Findings that are Included as Safety Concerns

In conclusion, there were no important identified risks from non clinical studies. Embryofetal toxicity has been identified as important potential risks.

Safety Concerns	
Important identified risks	None
Important potential risks	Embryofetal toxicity
Missing information	None

Module SIII Clinical Trial Exposure

Clinical Trial Exposure

Table 8 through Table 11 present venetoclax exposure data from venetoclax clinical studies (monotherapy or combination therapies) conducted in the CLL (R/R and front line) and AML (front line) populations.

A total of 1,503 patients received venetoclax therapy in both the AML and CLL clinical programs.

Venetoclax exposure in CLL

The tables below present venetoclax exposure data from venetoclax clinical studies (monotherapy or combination therapies) conducted in the R/R CLL and front line CLL populations.

Combination therapy:

The pooled data from the combination therapy studies consists of

- 215 patients from Study BO25323 (CLL14) (203 patients from main phase and 12 patients from safety run in phase who received at least one dose of venetoclax)
- 194 patients from Study GO28667/MURANO (venetoclax in combination with rituximab [V + R])
- 198 subjects from
  - M13 365 (V + R)
  - GP28331 (venetoclax + obinutuzumab [G])
  - GO28440 (venetoclax + bendamustine and rituximab [BR]/bendamustine and obinutuzumab [BG])

Descriptions of combination therapy Studies BO25323, GO28667, M13 365, GP28331 and GO28440:

- Study BO25323 (CLL14): open label, multicenter, randomized Phase 3 trial to compare the efficacy and safety of a combined regimen of obinutuzumab and venetoclax versus obinutuzumab and chlorambucil in patients with CLL and coexisting medical conditions. A total of 432 patients were enrolled in the randomized part of the study, and 13 patients were enrolled in the safety run in phase. Patients were assigned in 1:1 ratio to one of the two treatment arms: 216 in the venetoclax and obinutuzumab arm (V + G), and 216 in the obinutuzumab and chlorambucil arm (GClb). The primary objective was to determine efficacy by investigator assessed PFS of a combined regimen of V + G compared with GClb in previously untreated patients with CLL who have coexisting medical conditions. The safety objective of the study was to evaluate the safety of the combination of V + G, compared with GClb, in patients with previously untreated CLL and coexisting medical conditions, focusing on the nature, frequency, and severity of Grade 3 and 4 adverse events and of serious adverse events.

- Study GO28667 (MURANO): open label, Phase 3, multicenter, randomized study in R/R patients with CLL to evaluate the safety and efficacy of V + R compared with BR. A total of 389 patients were randomized (1:1): 194 in the V + R arm and 195 in the BR arm. The duration of therapy was 2 years in the V + R arm and 6 months in the BR arm. The primary endpoint for the study was progression free survival (PFS) (investigator assessed in the EU). Safety endpoints included were adverse events, serious adverse events, adverse events of special interest, and changes in clinical laboratory results in all randomized patients who received at least one dose of study treatment (venetoclax, rituximab, or bendamustine), with patients grouped according to the treatment actually received.
- Study M13 365: open label, Phase 1b, multicenter study evaluating the safety and tolerability of V + R in patients with relapsed CLL or SLL. The study enrolled 49 patients with CLL or SLL. The duration of therapy with V + R was 6 months and then up to 5 years of venetoclax monotherapy. The primary endpoints for the study included safety, MTD and Phase 2 dose finding. Safety evaluations included adverse event monitoring, vital signs, physical examination, lymphocyte enumeration, 12 lead ECG, MUGA/2D echocardiogram, and laboratory assessments.
- Study GP28331: open label, Phase 1b, multicenter, dose finding and safety study of venetoclax administered in combination with obinutuzumab in patients with R/R CLL or previously untreated CLL. A total of 81 patients were enrolled. The primary objective is estimating MTD and evaluating safety and tolerability.
- Study GO28440: open label, Phase 1b, multicenter, dose finding and safety study of venetoclax administered in combination with BR or BG to patients with R/R CLL or previously untreated CLL. A total of 68 patients were enrolled. The primary objective is estimating MTD and evaluating safety and tolerability.

<u>Monotherapy studies:</u>

The data pool from the monotherapy studies consists of

- 401 subjects from
  - M13 982
  - M12 175 [R/R CLL, Arm A]
  - M14 032

These 401 patients from monotherapy studies include 352 patients with R/R CLL who received a daily dose of 400 mg venetoclax, including patients with 17pdel/*TP53* mutation.

The exposure summarized for the pooled studies includes all venetoclax exposure, including the dose titration phase where applicable. The doses of venetoclax received by these subjects ranged from 10 mg to 1200 mg.

Thus, in total, safety data for 1008 patients from clinical studies in CLL will be presented with exposures summarized in the tables below. In addition, 182 subjects have received venetoclax in clinical pharmacology studies, bringing the total number of subjects who have received at least one dose of venetoclax to 1190. Safety in single dose studies are summarized in individual study reports and are not included in this exposure summary.

Venetoclax exposure in AML

Combination therapy:

The pooled data from the combination therapy studies consists of

- 212 total from Study M14 358 (127 patients [venetoclax + azacitidine] and 73 patients [venetoclax + decitabine] and 12 patients [venetoclax + decitabine + posaconazole])
- 283 patients from Study M15 656 (VIALE A) (venetoclax + azacitidine)

Of the 495 AML patients who received combination therapy (listed above), the following received the venetoclax proposed doses:

- 84 patients received venetoclax 400 mg in combination with azacitidine (Study M14 358)
- 31 patients received venetoclax 400 mg in combination with decitabine (Study M14 358)
- 283 patients received venetoclax 400 mg in combination with azacitidine (Study M15 656)

A total of 97 AML patients received other doses (venetoclax 800 mg with azacitidine or decitabine, venetoclax 1200 mg with azacitidine or decitabine, and venetoclax 400 mg with decitabine and posaconazole).

Description of combination therapy Studies M14 358, and M15 656:

- Study M14 358: Phase 1b, open label, non randomized study consisting of two stages. The first stage, a dose escalation stage, evaluated separately the safety and pharmacokinetics (PK) of venetoclax administered orally in combination with azacitidine or decitabine in treatment naïve subjects with AML who were ≥ 60 years of age and who were not eligible for standard induction therapy due to co morbidity or other factors. At a single center, a drug drug interaction sub study evaluated the effect of posaconazole on the PK of venetoclax and safety of

venetoclax when co administered with posaconazole. In the second stage, a dose expansion stage, confirmation of safety and evaluation of preliminary efficacy was performed using two dosing schedules, at two dose levels that were selected based on the safety and efficacy observed during the dose escalation stage. Both decitabine and azacitidine combinations were evaluated in the expansion stage.

- Study M15 656 (VIALE A): Phase 3, double blind, randomized, placebo controlled study to evaluate venetoclax in combination with azacitidine compared to placebo in combination with azacitidine in treatment naïve subjects with AML who are ≥ 18 years of age and not eligible for standard induction therapy due to age or co morbidities. The primary objective of this study is to evaluate if venetoclax in combination with azacitidine improves overall survival (OS) and composite complete remission rate (complete remission + complete remission with incomplete marrow recovery; CR + CRi) compared to placebo in combination with azacitidine in treatment naïve subjects with AML.

Duration of exposure is presented in Table 8.

Table 8. Duration of Exposure in Patients who Received at Least One Dose of Venetoclax in the CLL or AML Clinical Programme (Total)

Duration of Exposure (Months)	CLL		AML		Total	
	n	PY	n	PY	n	PY
All patients (all doses)						
0 – 1	33	1.10	70	3.76	103	4.87
> 1 – 3	53	8.58	77	13.34	130	21.92
> 3 – 6	67	25.34	78	28.38	145	53.72
> 6 – 12	344	281.23	104	71.95	448	353.19
> 12 – 18	123	153.35	57	70.43	180	223.78
> 18 – 24	150	265.82	60	103.76	210	369.58
> 24 – 30	175	380.42	30	65.6	205	446.02
> 30 – 36	35	94.61	8	21.4	43	116.01
> 36	28	104.47	11	38.09	39	142.56
Total (all patients; all doses)	**1008**	**1314.92**	**495**	**416.72**	**1503**	**1731.64**

AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia

Note: Doses for AML include the proposed doses (venetoclax 400 mg with azacitidine [n = 367], venetoclax 400 mg with decitabine [n = 31]) and other doses (venetoclax monotherapy [800 to 1200 mg], venetoclax 800 mg with azacitidine or decitabine, venetoclax 1200 mg with azacitidine or decitabine, venetoclax 400 mg with decitabine and posaconazole).

Note: CLL data pooled from Study GO28667 (MURANO), Study M13-365, Study M13-982, Study M14-032, Study M12-175, Study GO28440, Study GP28331 and Study BO25323 (CLL14). AML data pooled from Study M14-358 (including the 12 patients treated with venetoclax in combination with posaconazole in the DDI cohort), and Study M15-656 (VIALE-A).

PY patient-years

Clinical cut-off dates for CLL:

Study GO28667 (MURANO) 08 May 2017; M13-365 01 July 2016; Study M13-982 10 June 2016; Study M14-032 31 January 2017; M12-175 (Arm A) 10 June 2016; Study GO28440 28 November 2016; Study GP28331 28 November 2016, Study BO25323 (CLL14) 17 August 2018.

Clinical cut-off dates for AML:

Study M14-358 30 August 2019; Study M15-656 (VIALE-A) 04 January 2020.

Exposure by age group is presented in and Table 9.

Table 9. Venetoclax Exposure by Age in Patients who Received at Least One Dose of Venetoclax in the CLL or AML Clinical Programme (Total)

	CLL		AML		Total	
Age Group (years)	**n**	**PY**	**n**	**PY**	**n**	**PY**
All patients (all doses)						
< 65	412	561.71	13	7.93	425	569.64
≥ 65	596	753.21	482	408.8	1078	1162.01
Total	**1008**	**1314.92**	**495**	**416.72**	**1503**	**1731.64**
< 75	827	1093.72	224	184.7	1051	1278.42
≥ 75	181	221.2	271	232.03	452	453.23
Total	**1008**	**1314.92**	**495**	**416.72**	**1503**	**1731.64**

PY patient-years

Note: CLL data pooled from Study GO28667(MURANO), Study M13-365, Study M13-982, Study M14-032, Study M12-175, Study GO28440, Study GP28331 and Study BO25323 (CLL14). AML data pooled from Study M14-358 (including the 12 patients treated with venetoclax in combination with posaconazole in the DDI cohort), and Study M15-656 (VIALE-A).

Clinical cut-off dates for CLL:

Study GO28667 (MURANO) 08 May 2017; Study M13-365 01 July 2016; Study M13-982 10 June 2016; Study M14-032 31 January 2017; Study M12-175 (Arm A) 10 June 2016; Study GO28440 28 November 2016; Study BO25323 (CLL14) 17 Aug 2018

Study GP28331 28 November 2016

Clinical cut-off dates for AML:

Study M14-358 30 August 2019; Study M15-656 (VIALE-A) 04 January 2020.

Exposure by sex is presented in Table 10.

Table 10. Venetoclax Exposure by Sex in Patients who Received at Least One Dose of Venetoclax in the CLL or AML Clinical Programme (Total)

	CLL		AML		Total	
Sex	**n**	**PY**	**n**	**PY**	**n**	**PY**
Male	685	904.91	291	252.25	976	1157.16
Female	323	410.01	204	164.48	527	574.49
Total	**1008**	**1314.92**	**495**	**416.72**	**1503**	**1731.64**

PY patient-years

Note: CLL data pooled from Study GO28667(MURANO), Study M13-365, Study M13-982, Study M14-032, Study M12-175, Study GO28440, Study GP28331 and Study BO25323 (CLL14). AML data pooled from Study M14-358 (including the 12 patients treated with venetoclax in combination with posaconazole in the DDI cohort) and Study M15-656 (VIALE-A).

Clinical cut-off dates for CLL:

Study GO28667 (MURANO) 08 May 2017; Study M13-365 01 July 2016; Study M13-982 10 June 2016; Study M14-032 31 January 2017; Study M12-175 (Arm A) 10 June 2016; Study GO28440 28 November 2016; Study BO25323 (CLL14) 17 Aug 2018.

Study GP28331 28 November 2016

Clinical cut-off dates for AML:

Study M14-358 30 August 2019; and Study M15-656 (VIALE-A) 04 January 2020.

Exposure by race and ethnicity is presented in Table 11.

Table 11. Venetoclax Exposure by Race and Ethnicity in Patients Who Received at Least One Dose of Venetoclax in the CLL or AML Clinical Programme (Total)

	CLL		AML		Total	
	n	**PY**	**n**	**PY**	**n**	**PY**
Race						
White	925	1214.84	397	339.03	1322	1553.86
Black	25	27.44	13	11.92	38	39.36
Asian	10	18.07	69	48.17	79	66.24
Other	20	23.41	7	10.13	27	33.55
Unknown	28	31.16	9	7.47	37	38.63
Total	**1008**	**1314.92**	**495**	**416.72**	**1503**	**1731.64**
Ethnicity						
Hispanic or Latino	47	51.92	29	27.1	76	79.02
Not Hispanic or Latino	894	1197.11	457	381.39	1351	1578.49
Unknown	67	65.89	9	8.24	76	74.13
Total	**1008**	**1314.92**	**495**	**416.72**	**1503**	**1731.64**

PY Patient-years

Note: CLL data pooled from Study GO28667(MURANO), BO25323 (CLL14 [V+G]), Study M13-365, Study M13-982, Study M14-032, Study M12-175, Study GO28440, and Study GP28331. AML data pooled from Study M14-358 (including the 12 patients treated with venetoclax in combination with posaconazole in the DDI cohort), and Study M15-656 (VIALE-A).

Clinical cut-off dates for CLL:

Study GO28667 (MURANO) 08 May 2017; Study M13-365 01 July 2016; Study M13-982 10 June 2016; Study M14-032 31 January 2017; Study M12-175 (Arm A) 10 June 2016; Study GO28440 28 November 2016; Corresponding data from Study BO25323 (CLL14 [V + G]) is not included in this table. Study GP28331 28 November 2016

Clinical cut-off dates for AML: Study M14-358 30 August 2019; Study M15-656 (VIALE-A) 04 January 2020

Module SIV Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Clinical Development Program

CLL-specific

Criterion 1: Subject has undergone an allogeneic stem cell transplant.
Reason for exclusion: Subjects were excluded to avoid bias in the interpretation of safety/efficacy data.
Is it considered to be included as missing information?: No
Rationale: To date, the regimen has no known direct effect on the bone marrow. Since efficacy and safety of the regimen have been determined, these patients may be candidates for treatment. Clinicians will need to determine whether the benefit of treatment outweighs any risks for an individual patient.

Criterion 2: Subject's CLL transformed to Richter's syndrome or prolymphocytic leukemia.
Reason for exclusion: Subjects were excluded to avoid bias in the interpretation of safety/efficacy data.
Is it considered to be included as missing information?: No
Rationale: Richter's is a clinical-pathologic transformation of CLL to an aggressive lymphoma, occurs over time in approximately 15% (5% - 20%) of cases of CLL with the risk being higher in R/R CLL (Sutton 2015). The regimen has no known additional toxicity in the excluded populations based on limited clinical data. Richter's transformation is not part of the currently proposed indication for venetoclax. Clinicians will need to determine whether the benefit of treatment outweighs any risks for an individual patient. Richter's transformation is a potential risk. The frequency of the reported event will be monitored in the clinical trials.

Criterion 3: Subject has active and uncontrolled autoimmune cytopenias despite low-dose corticosteroids.
Reason for exclusion: Determined not to be an appropriate population in which to evaluate a new therapeutic regimen.
Is it considered to be included as missing information?: No
Rationale: Since safety of the regimen has been determined, these subjects may be candidates for treatment. Clinicians will need to determine whether the benefit of treatment outweighs any risks for an individual patient.

Criterion 4: Subject has known allergy to all xanthine oxidase inhibitors and/or rasburicase.
Reason for exclusion: Current TLS measures required rasburicase and/or xanthine oxidase inhibitors (e.g., allopurinol) for patients with a high uric acid level at baseline or in order to manage rapid rising uric acid levels. For patients unable to take rasburicase, alternative uric acid reducing agents were given.
Is it considered to be included as missing information?: No
Rationale: Alternatives to xanthine oxidase inhibitors and rasburicase are available for use in patients with allergies. Clinicians will need to determine whether the benefit of treatment outweighs any risks for an individual patient.

Criterion 5: Subject with an inadequate bone marrow function or not meeting other laboratory criteria at Screening as follows: ANC < 1000/µL (for subjects with an ANC < 1000/µL at Screening and bone marrow heavily infiltrated with underlying disease growth factor support may be administered to achieve the ANC eligibility criteria (≥ 1000/µL) to be eligible for inclusion); Platelets < 30,000/mm^3 Hemoglobin < 8.0 g/dL. Additional laboratory criteria: Subject with inadequate coagulation, renal, and hepatic function, per laboratory reference range: aPTT and PTT > 1.5 × the upper limit of normal (ULN); Calculated creatinine clearance < 50 mL/min using 24-hour creatinine clearance or modified Cockcroft-Gault equation. AST and ALT > 3.0 × ULN of institution's normal range; bilirubin > 1.5 × ULN.
Reason for exclusion: Determined not to be an appropriate population to evaluate a new therapeutic regimen.
Is it considered to be included as missing information?: No
Rationale: Since efficacy and safety of the regimen have been determined, these subjects may be candidates for treatment. Hematological toxicities are manageable by standard supportive care (e.g., growth factors, or blood or platelet transfusion). Patients with renal dysfunction may be at higher risk for TLS, an identified risk for venetoclax during initial 5 weeks of therapy, Section VII.3. Clinicians will need to determine whether the benefit of treatment outweighs risks for an individual patient.

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; HIV = human immunodeficiency virus; aPTT = activated partial thromboplastin time; PTT = partial thromboplastin time; ULN = upper limit of normal

AML-specific

Criterion 1: Subject has received treatment with the following: • hypomethylating agent (HMA) and/or chemo-therapeutic agent for Myelodysplastic syndrome (MDS) • CAR-T cell therapy • Other experimental therapies for AML
Reason for exclusion: Historical studies evaluating monotherapy HMA treatments for AML have excluded subjects who had received these prior therapies (Dombret 2015, Kantarjian 2012). In order to assess the impact of combining venetoclax with an HMA, Study M14-358 also excluded these prior treatments so that the enrolled population is similar to those enrolled to historical studies of HMA monotherapy to reduce bias in the interpretation of the study results. Additionally, in Study M15-656 (VIALE-A), prior HMA was precluded because these therapies were part of the control arms and studies were randomized. Safety follow-up data are also not available for CAR-T cell therapy and other experimental therapies for AML.
Is it considered to be included as missing information?: No
Rationale: Intended use for AML is for newly diagnosed patients so extensive prior treatment is not anticipated. Based on the efficacy and safety results from AML clinical program, there is no evidence to suggest that patients with prior use of HMA should be excluded in real life use. Based on the clinical trial data, safety of patients in combination therapy (V + HMA) is similar to the overall known safety profile of venetoclax.

Criterion 2: Subject has t(8;21), inv(16), t(16;16), t(15;17), or (BCR-ABL1) karyotype abnormalities.
Reason for exclusion: Historical studies evaluating monotherapy HMA treatments for AML have excluded subjects with these karyotype abnormalities. In order to assess the impact of combining venetoclax with an HMA, Study M14-358 also excluded these karyotypes so that the enrolled population is similar to those enrolled in historical studies of HMA monotherapy to reduce bias in the interpretation of the study results.
Is it considered to be included as missing information?: No
Rationale: Subjects with intermediate risk cytogenetics (including normal karyotype) were enrolled and achieved durable remissions. There is no evidence, or clinical hypothesis, that safety of venetoclax would be different in patients with t(8;21), inv(16), t(16;16) abnormalities (favorable cytogenetics) compared to other AML patients. Subjects with t(15;17) and BCR-ABL1 translocations were excluded as acute myeloid leukemias with these two chromosomal abnormalities are treated with specific therapies that are considered standard of care.

Criterion 3: Subject has a white blood cell (WBC) count > 25 × 10^9/L. Note: Hydroxyurea is permitted to meet this criterion.
Reason for exclusion: AML subjects with WBC > 25 × 10^9/L may be at higher risk of TLS; hence they were excluded in the AML studies to minimize the potential risk.
Is it considered to be included as missing information?: No
Rationale: All patients should have white blood cell count < 25 × 10^9/L prior to initiation of venetoclax, and cytoreduction prior to treatment may be required. Additional information on TLS risk assessment, prophylaxis and prevention for AML patients have been provided in the prescribing information. Similarly, TLS risk minimization information has been included in Patient Information Leaflet.

Criterion 4: Subject is a candidate for a bone marrow or stem cell transplant within 12 weeks after study enrollment. Subject has undergone an allogeneic stem cell transplant.
Reason for exclusion: Subjects who are eligible to receive hematopoietic stem cell transplant are eligible for intensive therapy.
Is it considered to be included as missing information?: No
Rationale: Venetoclax with combination therapy was evaluated for use in patients with newly diagnosed AML who are ineligible for intensive therapy and thus are not candidates for hematopoietic stem cell transplant at enrollment.

Both AML and CLL

Criterion 1: Female subject has positive results for pregnancy test.
Reason for exclusion: The impact of venetoclax on pregnancy in humans is unknown. Pregnancy was excluded in all venetoclax clinical trials.
Is it considered to be included as missing information?: No
Rationale: Studies in animals have shown post-implantation loss, resorptions, and decreased body fetal weight but no teratogenicity when administered during organogenesis at tolerated maternal exposures. Pregnancy is unlikely due to the demographics of the CLL population. AML patients also tend to be older. Nonetheless, extreme care should be taken to avoid pregnancy and venetoclax must not be used by females who are, or intend to become, pregnant while on treatment. Embryofetal toxicity is a potential risk; therefore, pregnancy outcomes are monitored to support further characterization of this safety concern.

Criterion 2: Subject is known to be positive for HIV.
Reason for exclusion: Subjects with HIV were excluded from receiving venetoclax due to potential drug-drug interactions (DDIs) between antiretroviral medications and venetoclax, as well as anticipated venetoclax mechanism-based lymphopenia that may potentially increase the risk of opportunistic infections in already immune compromised patient population
Is it considered to be included as missing information?: No
Rationale: HIV infection is not considered a contraindication; therefore, clinicians will need to determine whether the benefit of treatment outweighs any risks for an individual patient and whether dose adjustments may be required due to potential drug interactions.

Criterion 3: Subject received the following treatments prior to the first dose of study drug: **Within 7 days:** Potent CYP3A4 inhibitors (such as fluconazole, ketoconazole, and clarithromycin) (CLL only); Potent CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, or St. John's wort); **Within 28 days:** Steroid therapy for anti-neoplastic intent (CLL only).
Reason for exclusion: Based on in vitro and clinical pharmacology study results, subjects receiving these types of medications (other than steroids) concomitantly with venetoclax were thought to be at risk of experiencing DDIs. In GO28667 (MURANO), strong and moderate CYP3A inhibitors and strong and moderate CYP3A inducers were prohibited during the venetoclax dose-titration phase and used with caution at the designated dose of venetoclax (400 mg). CYP1A2 inhibitors and inducers were prohibited in MURANO because of possible interaction with bendamustine, a CYP1A2 substrate. Patients with AML are at high risk for febrile neutropenia and life threatening fungal infections. Azole antifungal agents, all of which are strong or moderate CYP3A inhibitors, are widely used in these patients for prophylaxis and treatment of invasive fungal infections as standard of care. Taking into consideration the critical need for the use of antifungal prophylaxis, concomitant use of antifungal agents were allowed with appropriate venetoclax dose reductions during the AML studies. Steroids for anti-tumor therapy were excluded in order to isolate the effects of venetoclax.
Is it considered to be included as missing information?: No
Rationale: Selected DDI studies for venetoclax have been completed. Recommendations for use of concomitant medications are included in the SmPC. Strong CYP3A inhibitors are contraindicated during the initial dose-titration phase for CLL patients. In the prescribing information for AML, strong CYP3A4 inhibitors can be administered concomitantly with dose reductions of venetoclax during the 3-day ramp-up schedule and beyond. Clinicians will need to determine whether the benefit of treatment outweighs any risks for an individual patient.

Criterion 4: Patient has consumed grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit within 3 days prior to the first dose of study treatment
Reason for exclusion: Grapefruit products contain strong/moderate CYP3A4 inhibitors.
Is it considered to be included as missing information?: No
Rationale: The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Strong CYP3A inhibitors are contraindicated during the initial ramp-up phase. Moderate CYP3A inhibitors require venetoclax dose reductions. With the variable and inconsistent 'doses' of grapefruit products consumed in the diet, correct venetoclax dose reductions to normalize venetoclax exposure are not possible. Clinicians must determine whether the benefit of treatment outweighs any risks for an individual patient.

Criterion 5: Subject has a cardiovascular disability status of New York Heart Association Class ≥ 2. Class 2 is defined as cardiac disease in which subjects are comfortable at rest but ordinary physical activity, results in fatigue, palpitations, dyspnea or anginal pain.
Reason for exclusion: Determined not to be an appropriate population in which to evaluate a new therapeutic regimen.
Is it considered to be included as missing information?: No
Rationale: To date, evaluations of cardiac function in clinical trials have shown no safety concern. Since safety of the regimen has been determined, these patients may be candidates for treatment. Clinicians will need to determine whether the benefit of treatment outweighs any risks for an individual patient. Patients with cardiac failure may require hospitalization in order to enable more intensive monitoring during rigorous hydration at each step-wise increase in dose in the first 5-week (for CLL patients) or 3-day (for AML patients) ramp-up phase of therapy to reduce the risk of TLS, which is an identified risk for venetoclax during the initial ramp-up phase. Some studies required patients with comorbidities to be enrolled, in which case this exclusion criterion was waived (for example, Study BO25323/CLL14).

Criterion 6: Subject exhibits evidence of other clinically significant uncontrolled condition(s) including: Uncontrolled and/or active systemic infection (viral, bacterial, or fungal). Chronic hepatitis B virus (HBV) or hepatitis C (HCV) requiring treatment.
Reason for exclusion: Determined not to be an appropriate population in which to evaluate a new therapeutic regimen.
Is it considered to be included as missing information?: No
Rationale: Patients should be treated for infections as appropriate prior to initiating venetoclax. Clinicians will need to determine whether the benefit of treatment outweighs many risks for an individual patient.

SIV.2 Limitations to Detect Adverse Reactions in the Clinical Development Program

The clinical development programme is unlikely to detect certain types of adverse reactions, such as those that are rare, caused by long latency, due to cumulative effects or caused by prolonged exposure.

SIV.3 Limitations in Respect to Populations Typically Under Represented in Clinical Development Program

Table 12. Exposure of Special Populations

Type of special population	Exposure (Total number of patients)	Implications
Pregnant or breastfeeding women	In all clinical studies conducted to date with venetoclax in the clinical development programme, pregnant and breastfeeding women were excluded. Women of reproductive potential included in studies were required to use highly effective methods of birth control. Pregnancy, once determined, was a condition for required withdrawal of the subject from the study. Four pregnancies have been reported with venetoclax usage: two in Study GO28667 (MURANO); one in a female patient in the systemic lupus erythematosus (SLE) Study M13-093 who was receiving study treatment with venetoclax; and one in Study GO28440 in a [redacted] year old female patient who was off study treatment. In Study GO28667 (V + R) one pregnancy occurred in the partner of a male patient who was receiving study treatment, and ended in [redacted]; and one in a female patient who had discontinued study treatment after disease progression, and subsequently had [redacted]. The pregnancy in Study M13-093 resulted [redacted]. The pregnancy reported from Study GO28440 was uninterrupted and [redacted]. No pregnancies have been reported to date in AML studies evaluating venetoclax combination therapy.	Studies in mice have shown post-implantation loss and decreased fetal body weight but no teratogenicity when administered during organogenesis at tolerated maternal exposures. Available data in animals have shown excretion of venetoclax/metabolites in milk. Venetoclax must not be used by females who are pregnant. There are no adequate and well-controlled data from the use of venetoclax in pregnant women. It is not known whether venetoclax is excreted in human milk. Breastfeeding should be discontinued during treatment with venetoclax. The median age of AML diagnosis is 68 years. Also, as the majority of CLL patients are > 65 years of age, breastfeeding or pregnancy is unlikely to be a concern in this population. Embryofetal toxicity is a potential risk; as part of routine pharmacovigilance, pregnancy outcomes are monitored and emerging data will inform this safety concern.

Type of special population	Exposure (Total number of patients)	Implications
Patients with hepatic impairment		
Mild hepatic impairment Total bilirubin less than or equal to ULN [1 mg/dL] and AST greater than ULN [40 IU/L], or total bilirubin greater than 1.0 to 1.5 × ULN [> 1 – 1.5 mg/dL] and any AST	269 patients (177 CLL patients and 92 AML patients)	Based on population pharmacokinetic analyses, venetoclax exposures are similar in patients with mild and moderate hepatic impairment and normal hepatic function. No relationship between venetoclax pharmacokinetic parameters and hepatic function has been reported In addition, based on data from 4 healthy female subjects administered a single 200 mg dose of [14C]venetoclax in a mass balance study (Study M13-363), 99.9 ± 5.0% of the administered radioactive dose was recovered in feces, and negligible radioactivity (< 0.1%) was found in urine. About 80% of the administered radioactive dose was excreted in feces as venetoclax metabolites and approximately 20% was excreted as venetoclax. In conclusion, no dose adjustment is recommended in patients with mild or moderate hepatic impairment. Study M15-342 (A Study to Evaluate the Safety and Pharmacokinetics of a Single Dose of Venetoclax in Female Subjects with Mild, Moderate, or Severe Hepatic Impairment) has completed. Study M15-342 was performed in adult females in general good health and nonchildbearing potential. Venetoclax maximum concentration and area under the curve (AUC) exposures in subjects with mild or moderate hepatic impairment were similar to subjects with normal hepatic function. Mean venetoclax AUC exposures in subjects with severe hepatic
Moderate hepatic impairment Total bilirubin greater than 1.5 to 3 × ULN [> 1.5 – 3 mg/dL] and any AST elevation	54 patients (33 CLL patients and 21 AML patients)	
Severe hepatic impairment Total bilirubin greater than 3 × ULN > 3 mg/dL and any AST elevation	8 patients (1 CLL patients, 2 AML patients, 5 patients from Study M15-342)	

Type of special population	Exposure (Total number of patients)	Implications
		impairment were approximately 2.3- to 2.7-fold higher as compared with subjects with normal hepatic function. On the basis of these results, the SmPC and company core data sheet (CCDS) have been updated to recommend a dose adjustment in patients with severe hepatic impairment. Toxicity in patients with severe hepatic impairment is an important potential risk.

Type of special population	Exposure (Total number of patients)	Implications
Patients with renal impairment		
Mild renal impairment (creatinine clearance [CrCl] ≥ 60 and < 90 mL/min),	679 patients (463 CLL patients and 216 AML patients)	The inclusion criteria for venetoclax studies include creatinine clearance ≥ 50 mL/min (CLL) and ≥ 30 mL/min (AML). Among the patients treated in the CLL programme, an increased risk of renal toxicity has not been identified to date. Patients with renal dysfunction may be at higher risk for TLS, an identified risk for venetoclax during the initial 5 weeks of therapy, Section VII.3. When patients for population pharmacokinetics analyses are combined (Studies R&D/15/0256 [505 patients] and GO28667 [report number: 1083048, 182 patients]), and R&D/19/0625 [771 AML patients], venetoclax exposures in patients with mild, moderate, or severe renal impairment were similar to those with normal renal function. In addition, based on data from 4 healthy female subjects administered a single 200 mg dose of [^{14}C]venetoclax in a mass balance study (Study M13-363) after a single oral administration of 200 mg radiolabeled [^{14}C]venetoclax in healthy subjects, > 99.9% of the dose was recovered in feces and < 0.1% of the dose was excreted in urine within 9 days. This indicates that venetoclax is largely eliminated through fecal excretion, with negligible renal excretion. In conclusion, no dose adjustment is recommended in patients with mild, moderate, or severe renal impairment.
Moderate renal impairment (CrCl ≥ 30 and < 60 mL/min)	356 patients (203 CLL patients and 153 AML patients)	
Severe renal impairment (CrCl < 30 mL/min)	6 patients (5 CLL patients and 1 AML patient; please refer to SVII).	

Type of special population	Exposure (Total number of patients)	Implications
End-stage renal disease (CrCl < 15 mL/min) requiring dialysis	6 ESRD patients	The pharmacokinetics of venetoclax have been studied in subjects with end stage renal disease (ESRD) requiring dialysis (Study M19-065). Venetoclax unbound maximum concentration and area under the curve (AUC) exposures in patients with ESRD on a non-dialysis day were comparable to subjects with normal renal function. Moreover, dialysis does not affect the clearance of venetoclax. Therefore, no dose adjustment is needed for patients with ESRD requiring dialysis.
Pediatric patients	CLL is primarily a disease of adults, particularly the elderly; the median age of diagnosis in the European Union (EU) is 72 years and only 10% of patients are less than 55 years old. The median age of diagnosis in the US is 67 years, with 55% of the patients diagnosed at 65 years or older; approximately a third are diagnosed over the age of 75. (Howlader N 2018, National Cancer Institute 2018). AML is primarily a disease of elderly adults. In a study of 3,251 AML patients diagnosed in 2012 to 2014 in Germany and Austria, the median age at diagnosis was 65 years (Nagel 2017). In the US, 57% of the patients diagnosed at 65 years or older; approximately a third are diagnosed over the age of 75, (Howlader N 2018, National Cancer Institute 2018, Noone 2018).	Safety of venetoclax in the pediatric population has not been established in CLL or AML. The current/proposed indications for venetoclax do not include adolescents or children (patients < 18 years of age).
Population with relevant different ethnic origin	Subject populations included patients with a variety of racial backgrounds, but predominantly in Caucasian populations.	CLL occurs more frequently in the western countries, i.e., in Caucasian populations, which were predominant in venetoclax studies (Hallek 2013, Ruchlemer 2013). The incidence of AML is higher in Whites as compared with African-Americans (difference of approximately 20%) (Patel 2012).

Type of special population	Exposure (Total number of patients)	Implications
Elderly	In CLL, among the patients exposed to venetoclax in the clinical trial programme, approximately 40% were ≥ 65 to < 75 years and 16% were ≥ 75 years. Of the patients who had 17p del and received daily doses of 400 mg venetoclax, 40% of patients were ≥ 65 to < 75 years and 18% were ≥ 75 years. In the AML clinical trials approximately 97% (n = 482) of subjects treated with venetoclax were ≥ 65 years. Among these patients, 57% (venetoclax with azacitidine), and 41% (venetoclax with decitabine) were ≥ 75 years old.	For CLL, the differences noted between patients ≥ 65 years and < 65 years of age, and those ≥ 75 years and < 75 years of age, including patients with 17p del, and those who received 400 mg venetoclax daily, were not clinically significant. Based on population pharmacokinetic analyses, age does not have an effect on the pharmacokinetics of venetoclax. Elderly population studied in the AML clinical trials is consistent with AML age distribution of the target population in the real world.

CLL Studies included (Clinical cut-off date): Study GO28667 (MURANO) 08 May 2017; Study M13-365 01 July 2016; Study M13-982 10 June 2016; Study M14-032 31 January 2017; Study M12-175 (Arm A) 10 June 2016; Study GO28440 28 November 2016; Study GP28331 28 November 2016; Study BO25323 (CLL14) 17 August 2018. AML Studies included (Clinical cut-off date): Study M14-358 30 August 2019; Study M15-656 (VIALE-A) 04 January 2020.

Module SV Post-Authorization Experience

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

An estimate of the patients treated with venetoclax was calculated from internal AbbVie sales data. Using the total number of tablets distributed and dividing by the average daily dose (ADD) determined from the product label and medication guidelines, an estimate of the number of patient treatment days (PTD) was obtained. The PTD was further divided by 365.25 to obtain the estimated number of patient treatment years (PTY).

The ADD for venetoclax was based on the product labels for the approved CLL and AML indications and medication guidelines. For CLL, patients were titrated via a 4 week starter pack, starting at 20 mg per day for 1 week, followed by 50 mg per day for 1 week, 100 mg per day for 1 week, and 200 mg per day for 1 week. After the first 4 weeks, patients received 400 mg per day.

For AML, the venetoclax ramp up schedule is shown in the following table.

Dosing Schedule for Ramp-up Phase in Patients with AML

Treatment Day	VENCLEXTA Daily Dose
Day 1	100 mg
Day 2	200 mg
Day 3 and beyond	400 mg

Patient exposure was not available by age, gender or indication. The following table provides the exposure calculation methods by formulation.

Table 13. Venetoclax Patient Exposure Calculated Methods

Venetoclax Patient Exposure Calculation Methods			
	Dose/Duration	**Dose Form (mg)**	**Average Daily Dose (Tablets)**
Starter pack for CLL (Weeks 1 – 4)	20 mg/day for 1 week	10	2
	50 mg/day for 1 week	50	1
	100 mg/day for 1 week	100	1
	200 mg/day for 1 week	100	2
	Total Weeks 1 – 4	1 starter pack = 28 PTD	
Maintenance for CLL (Weeks 5+) or maintenance for AML (Day 4+ in combination with azacitidine or decitabine)	400 mg/day	100	4
Day 1 Ramp-up for AML	100 mg	100	1
Day 2 Ramp-up for AML	200 mg	100	2
Day 3 Ramp-up for AML	400 mg	100	4

AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; PTD = patient treatment days

SV.1.2 Exposure

The estimated cumulative post marketing patient exposure since first approval is [redacted] patient treatment years (PTY) (Table 14). Estimated totals by geographic region are provided in Table 15.

Table 14. Estimated Cumulative Exposure from Venetoclax Marketing Experience: 01 April 2016 through 28 February 2025 from AbbVie Sales

Formulation	Amount Distributed[a]	Average Daily Dose	Patient Treatment Days	Patient Treatment Years
Starter pack (4-week supply)	98,122,557	1 pack = 28 PTD	3,504,377	9,594
10 mg tablets	4,862,812	2 tablets	2,431,406	6,657
50 mg tablets	4,849,445	1 tablet	4,849,445	13,277
100 mg tablets (100 mg dose)	6,743,050	1 tablet	6,743,050	18,461
100 mg tablets (200 mg dose)	12,246,948	2 tablets	6,123,474	16,765
100 mg tablet (400 mg dose)	[redacted]			
100 mg tablets (600 mg dose)	225,612	6 tablets	37,602	103
Total	--	--	[redacted]	

PTD = patient treatment days

a. Total is not calculated as rows represent both starter packs and individual tablets.

Note: Numbers may not sum due to rounding.

Table 15. Estimated Cumulative Post-Authorization Exposure by Geographic Region: 01 April 2016 through 28 February 2025 from AbbVie Sales by Region

Region	Patient Treatment Years
United States	[redacted]
Latin America	12,199
Western Europe / Canada	80,250
JAPAC	41,283
EEME&A	15,864
Total	[redacted]

EEME&A = Eastern Europe, Middle East, and Africa; JAPAC = Japan and Asia Pacific countries

Table 16. Estimated Venetoclax Exposure by EEA Country: 01 April 2016 through 28 February 2025

Country	Patient Treatment Years
Austria	[redacted]
Belgium	
Bulgaria	
Croatia	
Cyprus	
Czech Republic	
Denmark	
Estonia	
Finland	
France	
Germany	
Greece	
Hungary	
Iceland	
Ireland	
Italy	
Latvia	
Lithuania	
Malta	
Netherlands	
Norway	
Poland	
Portugal	
Romania	
Slovakia	
Slovenia	
Spain	
Sweden	
United Kingdom†	
TOTAL	

† UK left the EEA on 31 January 2020.

EEA country in which venetoclax sales were recorded during this time period.

Module SVI Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

There is no anticipated potential for illegal use of venetoclax given its mechanism of action. Based on CNS/neurobehavioral animal studies and in vitro receptor binding studies to identify potential off target effects, no venetoclax CNS/neurobehavioral effects are expected in humans. There have been no reports of venetoclax dependence from any clinical study.

Module SVII Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable; this is an updated EU RMP.

SVII.1.2 Risks and Missing Information Considered Important for Inclusion in the RMP

Important Identified Risks

Identified risk 1: Tumor lysis syndrome
Reason for Inclusion: TLS events ≥ Grade 3 were observed in clinical trials prior marketing authorization of an oral "first-in-class" medication. Gradual titration, TLS prophylaxis and monitoring measures are to be followed when initiating venetoclax to mitigate the risk of TLS
Identified risk 2: Neutropenia
Reason for Inclusion: Neutropenia events ≥ Grade 3 were observed in clinical trials prior marketing authorization of an oral "first-in-class" medication. Regular blood counts are recommended and dose interruptions or reductions are recommended as needed, according to the SmPC.

Important Potential Risks

Potential risk 1: Embryofetal toxicity

Reason for Inclusion: In embryofetal development studies in mice, venetoclax was associated with increased post-implantation loss and decreased fetal body weight at exposures of 1.1 times the human AUC exposure at the recommended dose. No embryofetal toxicity was reported in rabbits, although the total exposures were lower than the ones in mice. The risk of fetal toxicity in humans is unknown. Based on the current data, embryofetal toxicity is considered an important potential risk.

Potential risk 2: Testicular toxicity

Reason for Inclusion: Testicular toxicity (germ cell loss) was observed in general toxicity studies in dogs at exposures of 0.5 to 18 times the human AUC exposure at the recommended dose. Reversibility of this finding has not been demonstrated. Fertility studies were conducted in male mice. There were no effects of venetoclax on male or female reproductive organs. There are no data in humans. Based on the current data, testicular toxicity is considered an important potential risk.

Potential risk 3: Medication error

Reason for Inclusion: The dose of venetoclax must be gradually increased over a period of 5 weeks up to the maximum recommended daily dose of 400 mg to gradually reduce tumor burden (debulk) and decrease the risk of TLS. This dose-titration involves the use of multiple venetoclax strengths of 20 mg, 50 mg, 100 mg and 200 mg in elderly CLL patients.

There is a potential for prescription, dispensing and administration errors which may increase the risk of TLS; thus, medication error is considered an important potential risk.

Potential risk 4: Serious infection

Reason for Inclusion: The majority of patients enrolled in venetoclax clinical trials were heavily pretreated and elderly. The incidence of severe infections (≥ grade 3) in subjects receiving daily dosing of 400 mg venetoclax monotherapy is 17.9% (43/240) with the most common being pneumonia (5.0%) and upper respiratory tract infection (1.3%). There were 2 subjects (0.8%) who experienced fatal infections, both heavily pretreated with multiple risk factors. In absence of randomized data with a control group, serious infection is considered an important potential risk.

Potential risk 5: Richter's transformation

Reason for Inclusion: Richter's transformation occurs over time in approximately 15% (5% – 20%) of cases of CLL with the risk being higher in R/R CLL. Risk factors to develop Richter's transformation are R/R disease 17p del, prior fludarabine based therapy and multiple prior cytotoxic therapies. Almost all patients enrolled in the venetoclax CLL clinical trials were R/R and more than half were 17pdel. The incidence of Richter's transformation from the clinical trial programme in subjects receiving a daily dose of 400 mg venetoclax monotherapy was 7.9% (19/240). In the absence of randomized data with a control group and long term safety data, Richter's transformation is considered an important potential risk.

Potential risk 6: DDI (CYP3A inducers, CYP3A inhibitors)

Reason for Inclusion: In-vitro studies demonstrated that venetoclax is predominantly metabolized by cytochrome P450 CYP3A4. Co-administration of ketoconazole, a strong CYP3A, P-gp, and BCRP inhibitor, have resulted in increased venetoclax C_{max} by 2.3-fold and AUC_{∞} by 6.4-fold. Concomitant use of venetoclax with strong CYP3A inhibitors at initiation and during the dose-titration phase is contraindicated due to increased risk for TLS.

Missing Information

Information 1: Carcinogenicity studies

Reason for Inclusion: Carcinogenicity studies have not been conducted with venetoclax. Venetoclax was not genotoxic in bacterial mutagenicity assay, in vitro chromosome aberration assay and in vivo mouse micronucleus assay. The risk of carcinogenicity on prolonged exposure to venetoclax is unknown.

Data to be Collected Post-Authorization: Adverse events data, including secondary primary malignancies, in Studies GO28667 (MURANO), M14-032, M13-982, M12-175, and P16-562.

Information 2: Safety in severe hepatic impairment

Reason for Inclusion: A study of the pharmacokinetics of venetoclax has not been completed in subjects with severe hepatic impairment. Dosing in severe hepatic impairment is not recommended per SmPC. Based on a population pharmacokinetic analysis venetoclax exposures are similar in subjects with mild and moderate hepatic impairment and normal hepatic function. A trend for increased adverse events was observed in patients with moderate hepatic impairment.

Data to be Collected Post-Authorization: Safety and pharmacokinetics of venetoclax in subjects with various degrees of hepatic impairment in Study M15-342.

Information 3: Safety in severe renal impairment

Reason for Inclusion: The pharmacokinetics of venetoclax has not been studied in subjects with severe renal impairment (CrCl < 30 mL/min) or patients on dialysis and no recommendation is available. Based on population pharmacokinetic analysis venetoclax exposures in subjects with mild or moderate renal impairment are similar to those with normal renal function. Patients with reduced renal function (CrCl < 80 mL/min) may require more intensive prophylaxis and monitoring to reduce the risk of TLS at initiation and during the dose-titration phase.

Data to be Collected Post-Authorization: Routine pharmacovigilance and review of all reports and analysis of ongoing clinical trial data.

Information 4: Safety in long-term exposure (> 12 months)

Reason for Inclusion: Median follow-up for venetoclax in clinical trials is 11.4 months. Venetoclax daily dosing is expected for approximately 2 years or more. There is lack of safety data on the long term exposure to venetoclax > 12 months.

Data to be Collected Post-Authorization: Long-term safety assessed in Studies M14-032, M13-982, M12-175, and P16-562.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Removed Important Identified Risks

Identified risk 1: Neutropenia

Reason for Removal: During EMA procedure PSUSA/00010556/202412, PRAC recommended to remove neutropenia as a risk from the safety concerns. PRAC assessment noted that considering venetoclax was authorised in 2016, and neutropenia is a very common and well-known adverse reaction of a majority of chemotherapeutics, physicians are well aware of the risk, and preventive measures for neutrophil count monitoring are a basic strategy routinely implemented in oncological centres. This risk should be removed from the safety concerns.

Identified risk 2: Serious Infection

Reason for Removal: During EMA procedure PSUSA/00010556/202412, PRAC recommended to remove serious infection as a risk from the safety concerns. PRAC assessment noted that considering venetoclax was authorised in 2016, and serious infection is a very common and well-known adverse reaction of a majority of chemotherapeutics, physicians are well aware of the risk and early identification of infections is a basic strategy routinely implemented in oncological centres. This risk should be removed from the safety concerns.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk 1: Tumor Lysis Syndrome MedDRA terms: TLS SMQ (narrow)
Potential Mechanisms: Primary CLL cells are essentially 'addicted' to BCL-2 for survival and are exquisitely sensitive to Bcl-2 specific inhibitor venetoclax, an on-target pharmacological effect can cause rapid reduction in size of tumor (debulk) and may pose a risk of TLS. TLS can also be a risk in AML, as data from clinical studies demonstrates significant activity to venetoclax, either alone or in combination with an HMA (i.e., azacitidine). In addition, the high proliferative rate in AML can contribute to the risk of TLS.
Evidence Sources and Strength of Evidence: Venetoclax clinical trials and literature. Post-marketing including Investigator Initiated Studies (IIS), Patient Named Basis (PNB)/compassionate use, Post-marketing Observational Studies (PMOS), and other sponsor studies (Pharmacyclics).

Important Identified Risk 1: Tumor Lysis Syndrome
Characterization of the Risk:
Frequency **CLL** *Monotherapy* Among patients for whom the dosing regimen recommended in the SmPC was followed, no events of clinical tumor lysis syndrome (CTLS) were observed; adverse events of TLS (lab changes only) were observed at a rate of 6.1% (4/66). In early dose-finding studies, TLS was observed at a rate of 11.7% (9/77). *In Study GO28667 (V + R)* After 77/389 patients were enrolled in this study, the protocol was amended to incorporate the current TLS prophylaxis and monitoring measures described in the SmPC Section 4.2. In Study GO28667, 6/194 patients (3.1%) in the V + R arm reported AEs of TLS. All events occurred during the venetoclax dose-titration phase and resolved within 2 days. All 6 patients received treatment for the correction of metabolic abnormalities. One patient experienced laboratory TLS due to a medication error. All 6 patients completed the titration period and reached the target dose of 400 mg of venetoclax. No clinical TLS cases were reported in the V + R arm under the current 5-week dose-titration schedule and TLS prophylaxis and monitoring measures. One AE of TLS was reported by the investigator as clinical TLS, characterized by a transient increase in serum creatinine. This AE occurred during the former dose-titration period. 10 patients in the V + R arm experienced at least 2 electrolyte laboratory abnormalities meeting the Howard criteria for laboratory TLS, including 5 of the 6 patients in the V + R arm who reported the AE of TLS. All 10 patients in the V + R arm experienced the event during the venetoclax titration period. All TLS events observed during the study were managed using standard measures for correction of electrolyte abnormalities, lab monitoring, and/or study drug interruptions.
In Study BO25323 (V + G) There were 5 reported AEs of TLS, 3 in the randomized main phase and 2 in the safety run-in phase. Four AEs of TLS occurred following obinutuzumab administration and prior to initiation of venetoclax. All events of TLS were managed per standard of care and resolved. *Post-marketing* A signal for increased severity of TLS was validated in November 2019 based on 3 post-marketing reports of clinical TLS in CLL, including 2 fatal reports and 1 patient requiring hemodialysis, that occurred after a single 20 mg dose of venetoclax, and based on the totality of TLS reports with clinical sequelae or fatal outcome received in the post-marketing setting. A Medical Safety Assessment was performed to evaluate events of TLS received from 11 April 2016 through 04 December 2019 from post-marketing sources. A total of 236 reports of TLS in CLL were reviewed. Seventeen reports described either fatal outcomes or clinical interventions (dialysis/hemofiltration) and provided sufficient information to conclude that these severe consequences were due to TLS. Fifteen of the 17 were reported in Europe. The remaining 219 reports either did not include significant consequences as a result of the event of TLS or did not provide sufficient information for assessment. In the recent February 2021 periodic safety update report (PSUR) (reporting period 05 December 2019 through 04 December 2020), there were 116 initial post-marketing TLS reports in patients with CLL. Of these, 13 reports were from investigator-initiated studies (IIS) and 103 from post marketing sources.

Important Identified Risk 1: Tumor Lysis Syndrome

Three reports listed TLS as the cause of death; 1 additional case reported clinical intervention with dialysis.

Summary of Tumor Lysis Syndrome Adverse Events (V + R)

TLS Event	V + R N = 194
All TLS adverse events	6 (3.1%)
Clinical TLS	1[†]
Laboratory TLS	5
NCI-CTCAE Grade ≥ 3 TLS AE	6
Serious TLS AE	4
TLS AE leading to discontinuation of treatment	0
TLS AE leading to interruption of treatment	4
TLS AE leading to dose reduction	0
TLS AE leading to death	0

† One AE of TLS was reported by the investigator as clinical TLS, characterized by a transient increase in serum creatinine; patient did not satisfy the Howard criteria of laboratory TLS. This AE occurred during the former dose-titration period.

Important Identified Risk 1: Tumor Lysis Syndrome

Summary of Tumor Lysis Syndrome Adverse Events (V + G)

TLS Event	V + G (N = 215)
Number (%) of patients with at least one AE	5 (2.33%)
95% CI for % of patients with at least one AE	(0.76, 5.34)
Total number of AEs	5
Number (%) of patients with at least one AE by worst grade[a]	**5**
Grade 1	0
Grade 2	0
Grade 3	4
Grade 4	1
Grade 5	0
No. of patients with at least one Serious AE	**1 (0.47%)**
Outcome	
No. of Patients with at least one AE resulted in Fatal outcome	0
No. of Patients with at least one AE Recovered/Resolved	5 (2.33%)
No. of Patients with at least one AE with unknown outcome	0

AE = adverse event; No. = number; pts = patients

95% CI for incidence rate was calculated by Clopper Pearson method

[a] = Grades are based on NCI CTCAE.

AML

In the AML trials at the proposed venetoclax doses, TLS can be mitigated in the setting of 3 day ramp-up and TLS prophylaxis measures.

Study M14-358

Venetoclax 400 mg + Decitabine

No events of laboratory or clinical TLS were reported among patients treated with venetoclax 400 mg in combination with decitabine.

Study M15-656

Venetoclax 400 mg + Azacitidine

Three patients (1.1%, 3/283) in the venetoclax 400 mg QD with azacitidine arm experienced laboratory TLS, leading to dose reduction or interruption. One of these patients experienced clinical TLS, two of these patients experienced laboratory TLS. No patients experienced TLS events that led to discontinuation of venetoclax.

Placebo + Azacitidine

One patient (0.7%, 1/144) in the placebo with azacitidine arm experienced laboratory TLS, leading to dose reduction or interruption. No patient experienced clinical TLS. No patient experienced TLS that led to discontinuation of study drug.

Important Identified Risk 1: Tumor Lysis Syndrome

Seriousness/outcomes

CLL

Monotherapy

Following the dosing regimen recommended in the SmPC, TLS was observed at a rate of 6.1% (4/66). No clinical TLS was reported. All 4 events were laboratory TLS; recovered with hydration and correction of metabolic changes, none required dialysis or intensive care. All patients were able to complete titration to the 400 mg dose; there were no discontinuations of study drug due to TLS.

In early dose-finding studies, prior to the initiation of revisions to the dosing regimen and TLS monitoring/prophylaxis measures, 5/77 clinical TLS were reported, which included 2 fatal events of TLS and 3 events with renal failure, one requiring dialysis.

Study GO28667 (V + R)

4/194 patients (2.1%) experienced a serious AE of TLS, of whom one patient had clinical TLS during the former dose-titration period.

Study BO25323 (V + G)

1/215 patients (0.47%) experienced a serious AE of TLS. This event occurred prior to venetoclax administration.

Post-marketing

Of the 17 reports received between 11 April 2016 and 04 December 2019 that provided sufficient information to conclude that the fatal outcome or relevant clinical interventions (dialysis/hemofiltration) were due to TLS, 13 described fatal outcomes with TLS reported as a cause of death. Four reports describing clinical TLS requiring dialysis/hemofiltration reported outcomes as resolved or resolving at the time of the analysis.

In the recent February 2021 periodic safety update report (PSUR) (reporting period 05 December 2019 through 04 December 2020), there were 116 initial post-marketing TLS reports in patients with CLL.

Three reports listed TLS as the cause of death; 1 additional case reported clinical intervention with dialysis.

AML

Study M14-358

Venetoclax 400 mg + Decitabine

There were no serious events of laboratory or clinical TLS at the proposed venetoclax dose of 400 mg in combination with decitabine.

Study M15-656

Venetoclax 400 mg + Azacitidine

Two patients (0.7%, 2/283) reported a serious AE of laboratory TLS (Grade ≥ 3) in the venetoclax 400 mg with azacitidine arm.

Placebo + Azacitidine

One patient (0.7%, 1/144) reported a serious AE of laboratory TLS (Grade ≥ 3) in the placebo with azacitidine arm. No patients had a serious AE of laboratory TLS that resulted in death.

Important Identified Risk 1: Tumor Lysis Syndrome
Severity and nature of risk **CLL** *Monotherapy* Following the dosing regimen recommended in the SmPC, no clinical TLS have been observed (0/66); 0 had grade > 3 events. In early dose-finding studies, 5/77 clinical TLS events were observed; 3 had grade > 3 events.
In Study GO28667(V + R) All 6/194 patients (3.1%) experienced TLS ≥ Grade 3. One patient had serious Grade 4 clinical TLS (during the former dose-titration period, characterized by a transient increase in serum creatinine (122 μmol/L [normal: 80 μmol/L]). *In Study BO25323 (V + G)* In all, 5/215 patients (2.33%) experienced TLS ≥ Grade 3 (one event occurred after initiation of venetoclax treatment). *Post-marketing* A Medical Safety Assessment was performed to evaluate events of TLS received from 11 April 2016 through 04 December 2019 from post-marketing sources. A total of 236 reports of TLS were reviewed. Seventeen reports provided sufficient information to conclude that the fatal outcomes (n = 13) or clinical interventions (n = 4; dialysis/hemofiltration) were due to TLS. Fifteen of the 17 were reported in Europe. • 219 reports either did not include significant consequences as a result of the event of TLS or did not provide sufficient information for assessment. Of the 17 reports that provided sufficient information to conclude that the fatal outcome or relevant clinical interventions (dialysis/hemofiltration) were due to TLS, the relationship to TLS risk assessment was: • High risk in 3 patients (2 fatal, 1 clinical intervention) • Medium risk in 6 patients (4 fatal, 2 clinical intervention) • Low risk in 1 patient (fatal) • Not reported in 7 patients (6 fatal, 1 clinical intervention) Of these 17 reports, relationship to dose at time of onset was: • 400 mg (n = 1, fatal) • 100 mg (n = 6) (4 fatal, 2 clinical intervention) • 50 mg (n = 1, fatal) • 20 mg (n = 8), (6 fatal, 2 clinical intervention) • 1 case not reported (fatal) Of note, 5 patients experienced TLS after a single dose of 20 mg (3 fatal, 2 clinical intervention). Information regarding adherence to TLS prophylaxis and monitoring as well as patient-specific risk factors was reported inconsistently. Upon review of the relevant data, the validated signal of increased severity of TLS was confirmed.

Important Identified Risk 1: Tumor Lysis Syndrome
In the recent February 2021 PSUR (reporting period 05 December 2019 through 04 December 2020), there were 116 initial post-marketing TLS reports in patients with CLL. Thirteen cases were from IIS, of which none reported a fatality with TLS as the cause of death. Of the remaining 103 cases, 3 reports listed TLS as the cause of death; 1 additional case reported clinical intervention with dialysis. **AML** *Study M14-358* *Venetoclax 400 mg + Decitabine* No patients reported a Grade ≥ 3 AE of laboratory or clinical TLS at the proposed venetoclax dose of 400 mg in combination with decitabine. *Study M15-656* *Venetoclax 400 mg + Azacitidine* The AEs of laboratory TLS experienced by 2 patients (0.7%, 2/283) in the venetoclax 400 mg QD with azacitidine arm were Grade ≥ 3. No patients experienced TLS AEs that resulted in death. *Placebo + Azacitidine* The AE of laboratory TLS experienced by 1 patient (0.7%, 1/144) in the placebo with azacitidine arm was Grade ≥ 3. No patients experienced TLS AEs that resulted in death.
Risk Factors and Risk Groups: The risk is higher among patients who have high tumor burden. Also, patients with renal dysfunction or splenomegaly may be at added risk. These risk factors are not unique to venetoclax. They are consistent with that reported in literature, e.g., patients with bulky disease (including elevated white blood cell [WBC] count in patients with CLL), renal dysfunction, and baseline elevations in uric acid are at higher risk (Blum 2011). In a study involving 772 chemotherapy treated patients with AML, factors significantly associated with increased risk of clinical and laboratory TLS included elevated WBC (≥ 25×10^9/L), uric acid (> 7.5 mg/dL), lactate dehydrogenase (≥ 1 × ULN) and creatinine (> 1.4 mg/dL) (Montesinos 2008).
Preventability: **CLL** The frequency and severity of TLS is largely mitigated through initiation of venetoclax at 20 mg dose followed by a dose titration schedule that allows for more controlled killing of cells and gradual debulking of the tumor over the titration period. Prophylaxis measures for TLS include hydration, administration of uric-acid reducing agents, frequent monitoring of blood chemistries and prompt correction of any abnormalities. More intensive measures may be needed as TLS risk increases. A patient card will be provided as additional risk minimization measures for TLS (refer to Part V Section V.2 – Additional Risk Minimization Measures for details). Updated recommendations regarding TLS will be provided in the SmPC in sections 4.2 and 4.4.

Important Identified Risk 1: Tumor Lysis Syndrome
AML TLS is a risk for any highly effective treatment for patients with acute leukemias, including AML. All patients in the AML clinical trials were required to have a white blood cell count < 25 × 10^9/L prior to initiation of venetoclax. Additionally, all patients received prophylactic measures including adequate hydration and anti-hyperuricemic agents prior to initiation of first dose and during the 3-day venetoclax ramp-up phase; blood chemistries were closely monitored during the ramp-up period.
Impact on the Risk-Benefit Balance of the Product: TLS is a known oncology emergency requiring prompt management of metabolic changes to avoid clinical consequences. Tumor lysis syndrome could lead to clinically important consequences such as: renal impairment, cardiac arrhythmias, seizures (and their consequences) or death. Detailed information and guidance to mitigate the risk (including dose titration schedule, TLS prophylaxis and monitoring measures) is provided in the SmPC and the risk-benefit balance is favorable.
Public Health Impact: The potential impact to public health is anticipated to be low for both CLL and AML patients.

Important Potential Risk 1: Embryofetal Toxicity
MedDRA: IUE (In utero exposure) CMQ
Potential Mechanisms: The pro-apoptotic mechanism of action for venetoclax is consistent with anticipated embryotoxicity. The wide distribution of sBcl-2 in the developing embryo (pre- and post-implantation) suggests that many immature cells require a death repressor protein, and pharmacological perturbation of these anti-apoptotic proteins (with drugs such as venetoclax), can alter embryo development. This is evidenced by studies that have demonstrated that knockout or knock down of Bcl-2 family proteins can adversely affect embryo growth and development (Boumela 2011, LeBrun 1993, Novack 1994).
Evidence Sources and Strength of Evidence: Non-clinical studies
Characterization of the Risk: No evidence of teratogenicity was found in embryofetal development studies in mice with venetoclax or M27 or in rabbits with venetoclax. Fetal toxicity (post implantation loss and decreased fetal body weights) was observed at the high venetoclax dosage of 150 mg/kg/day in mice (maternal exposures approximately 1.2 times the human AUC exposure at a 400 mg/day dose). There was no embryofetal toxicity in rabbits up to the maximum venetoclax dosage of 300 mg/kg/day (NOAEL), but exposures were low (maternal exposures approximately 0.2 times the human AUC exposure at 400 mg/day) compared with those in mice. A pre- and postnatal development study with venetoclax has not been conducted.

Important Potential Risk 1: Embryofetal Toxicity
In an embryofetal development study in mice, M27 administered at the maximum feasible dose of 250 mg/kg/day (9-times the human M27 exposure at the venetoclax MRHD of 400 mg/day) resulted in an increase in post-implantation loss and resorptions. The number of post-implantation loss and resorptions were within historical control range in the M27 group and were below the historical control range in the concurrent control group. The NOAEL was 30 mg/kg/day.
The risk for teratogenicity or fetal toxicity associated with venetoclax treatment in humans is not known.
Risk Factors and Risk Groups: Women of childbearing potential are at risk.
Preventability: Women of childbearing potential are advised to avoid pregnancy when receiving venetoclax. Women of childbearing potential must use a highly effective method of contraception while taking venetoclax.
Impact on the Risk-Benefit Balance of the Product: As the majority of CLL patients are ≥ 65 years of age, embryofetal toxicity is not likely to be a concern in this elderly population. Patients with AML are also typically elderly. In addition, venetoclax is not recommended during pregnancy and in women of childbearing potential not using highly effective contraception. The risk-benefit balance is favorable.
Public Health Impact: Low

Important Potential Risk 2: Medication Error
Medication Error SMQ (broad)
Potential Mechanisms: **CLL** Potential errors could occur in the prescribing, dispensing, and administration of venetoclax especially during the gradual dose increase over a period of 5 weeks up to the recommended daily dose of 400 mg. **AML** Medication errors including prescribing, dispensing or administration of venetoclax may occur during the 3-day ramp-up phase with a starting dose of 100 mg or at the recommended daily dose.
Evidence Sources and Strength of Evidence: Clinical trials and human factor studies.
Characterization of the Risk: At the time when an application was submitted for Marketing Authorisation Approval for venetoclax monotherapy in CLL, there had been no adverse events reported describing a medication error in either the dose titration period or at daily dosing. During clinical trials, dosing was captured, and instances of incorrect dosing were identified e.g., a patient taking a lower or higher dose than prescribed. Of the medication errors that were reported during venetoclax monotherapy clinical trials, no clear pattern was noted based on the known safety profile of venetoclax (i.e., TLS, neutropenia, or infection).

Important Potential Risk 2: Medication Error

Reports of accidental ingestion of venetoclax in two children of 2 separate patients have been reported in the overall venetoclax clinical programme. It was confirmed that in one report the child did not swallow the tablet. In the second case, the child initially was noted to have high sodium levels that normalized; no other adverse events were reported for this child.

No new safety findings regarding medication error have emerged from the venetoclax CLL clinical programme. One patient in Study GO28667 (MURANO [V + R]) received a first dose of 100 mg rather than 20 mg in error and experienced an associated AE of TLS.

No safety signals related to medication errors have been identified from the venetoclax AML programme.

Medication error is considered a potential risk and is a focus of postmarketing surveillance activities.

The SmPC provides guidance on missed doses.

Risk Factors and Risk Groups:

CLL:

Risk groups include elderly CLL patients. Risk factors include venetoclax having three different tablet strengths, use during the current 5-week titration period.

AML:

Risk groups include elderly AML patients. Risk factors include venetoclax dose ramp-up over 3 days, during which 100-mg tablets are used (multiple tablets to be administered).

Preventability:

CLL

Venetoclax is to be initiated following a step-wise increase dosing regimen, administered orally once daily at a dose of 400 mg until disease progression or unacceptable toxicity. Commercial packaging and product labeling were originally designed to help minimize dosing errors, specifically for the initial 4 weeks (the former dose-titration period).

Each venetoclax film-coated tablet contains 10, 50, or 100 mg of venetoclax. The starting dose of venetoclax is 20 mg once daily. The dose must be gradually increased over a period of 5 weeks up to the maximum recommended daily dose of 400 mg as shown in the table below, in order to reduce the risk of TLS.

Week	Venetoclax Daily Dose
1	20 mg
2	50 mg
3	100 mg
4	200 mg
≥ 5	400 mg

Important Potential Risk 2: Medication Error

To facilitate patient adherence and reduce medication errors with the dosing regimen (a step-wise increase in dose), for the first 4 weeks of treatment up to the stage when the patient starts on 400 mg once daily, patients who do not require hospitalization are dispensed 7 daily dose blisters in one carton. In the EU, each carton is dispensed weekly to the patient during the first 4 weeks of the dose titration, thereby minimizing the potential for dosing errors by the patient. In some non-EU markets where a care model is available to support its use, a '4-week starting pack' is dispensed.

Venetoclax tablets are presently supplied in daily-dose blisters enclosed by an outer carton. The different tablet strengths are differentiated by color. For Week 1, the daily dose comprises two 10-mg tablets. For Week 2, the daily dose comprises one 50-mg tablet. For the Week 3 and Week 4 dose regimens, each daily dose comprises of one (Week 3) or two (Week 4) 100-mg tablets in daily dose blisters.

Treatment is dispensed monthly for patients who have reached the dose of 400 mg (four 100-mg tablets) once daily.

Commercial packaging and related information have been designed to reduce medication errors.

AML

Venetoclax will be administered following a daily ramp-up schedule in combination with a hypomethylating agent until disease progression or unacceptable toxicity. The venetoclax dosing is initiated as a 3-day ramp-up schedule starting dose of 100 mg as shown below.

To minimize medication errors, venetoclax tablets will be provided as a single 100 mg strength and dispensed to the patients.

Dosing Schedule for Ramp-up Phase in Patients with AML

Day	Venetoclax Daily Dose
1	100 mg
2	200 mg
3 and beyond	400 mg

Impact on the Risk-Benefit Balance of the Product:

Packaging design, different tablet shapes, and risk communication messages for venetoclax have been validated by human factors testing to minimize medication errors to residual risk level, it is therefore anticipated that errors by patients and healthcare providers will have minimum impact on the product risk-benefit balance. The risk-benefit balance is favorable.

Public Health Impact:

Low

Important Potential Risk 3: Richter's transformation (for CLL only) MedDRA terms: *In Study GO28667 (V + R) or other venetoclax CTs* Search criteria: Individual reports of Richter's syndrome retrieved from the listing of Patients with Disease Transformation in Study GO28667 (MURANO) and Study BO25323 (CLL14).
Potential Mechanisms: Unknown
Evidence Sources and Strength of Evidence: Venetoclax clinical trials and literature.
Characterization of the Risk: Frequency *Monotherapy* The incidence of Richter's transformation in patients receiving a daily dose of 400 mg venetoclax monotherapy is 7.9% (19/240). *In Study GO28667 (V + R)* A total of 6/194 patients (3.1%) in Study GO28667 (MURANO [V + R]) and 5/188 patients (2.7%) in the BR arm developed Richter's transformation of CLL. *In Study BO25323 (V + G)* Overall, 1 patient (0.5%) in the GClb arm and 2 patients (0.9%) in the V+G arm developed Richter's transformation of CLL.
Seriousness/outcomes *Monotherapy* The majority of events of Richter's transformation were serious and reported as disease progression resulting in discontinuation of venetoclax. *In Study GO28667 (V + R)* In Study GO28667 (MURANO [V + R]), 5 patients developed transformation of CLL to diffuse large B-cell lymphoma (DLBCL) and 1 patient developed transformation of CLL to Hodgkin's disease. In the BR arm, transformation of CLL to DLBCL was observed in 3 patients. One patient developed non B-cell lymphoma and 1 patient experienced Richter's transformation; no further details were provided.

Important Potential Risk 3: Richter's transformation (for CLL only)
Severity and nature of risk As Richter's transformation is a form of disease progression, it may result in death.
Risk Factors and Risk Groups: Risk factors include R/R disease, 17p del, multiple prior cytotoxic therapies, prior fludarabine-based therapy.
Preventability: None
Impact on the Risk-Benefit Balance of the Product: Richter's transformation is a form of disease progression of the preexisting CLL. It is a clinico-pathological condition indicating the transformation of CLL into an aggressive lymphoma with a severe outcome. The risk-benefit balance of venetoclax for the individual patient remains favorable.
Public Health Impact: Public health impact is expected to be minimal, as Richter's transformation is an aggressive progression of the disease being treated (CLL) in the target population. Additionally, data from Study GO28667 (MURANO) and BO25323 supports similar rates of Richter's transformation between the V + R and standard of therapy (BR) arms; and GClb arm and V + G arm respectively. Richter's transformation occurs in approximately 15% (5% – 20%) of all cases of CLL (Sutton 2015).

Important Potential Risk 4: Second primary malignancy
Search criteria: **CLL and AML** Second primary malignancies were identified by the SMQ search "malignant tumors" (narrow) and "myelodysplastic syndromes" (narrow).
Potential Mechanisms: Unknown
Evidence Sources and Strength of Evidence: Published literature and venetoclax clinical trial data
Characterization of the Risk: **CLL** Frequency *Monotherapy* The rate of second primary malignancies in subjects receiving daily dosing of 400 mg venetoclax monotherapy was 13.2% (39/296). *In Study GO28667 (V + R)* A total of 21/194 patients [10.8%] in the V + R arm in comparison to 13/188 patients [6.9%] in the BR arm developed second primary malignancies. In Study BO25323 (V + G)

Important Potential Risk 4: Second primary malignancy

Rates of second primary malignancies were comparable in the GClb arm and the VEN + G arm (10.3% vs. 13.7%).

Summary of Treatment-Emergent AEs – Second Primary Malignancies AEs (V + G)

	CLL (CLL14) (N = 215)
Number (%) of patients with at least one AE	29 (13.5%)
95% CI for % of patients with at least one AE	(9.22, 18.79)
Total number of AEs	35
Number (%) of patients with at least one AE by worst grade[a]	**29 (13.5%)**
Grade 1	2 (0.93%)
Grade 2	12 (5.58%)
Grade 3	8 (3.72%)
Grade 4	4 (1.86%)
Grade 5	2 (0.93%)

No. of patients with at least one Serious AE	**14 (6.51%)**
Outcome	
No. of Patients with at least one AE resulted in Fatal outcome	2 (0.93%)
No. of Patients with at least one AE Recovered/Resolved	17 (7.91%)
No. of Patients with at least one AE with unknown outcome	0

AE = adverse event; No. = number; pts = patients

95% CI for incidence rate was calculated by Clopper Pearson method

[a] = Grades are based on NCI CTCAE.

Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.

AML

It should be noted that adverse events identified for Second Primary Malignancy: "Malignant Tumours" SMQ Narrow and "Myelodysplastic Syndromes" SMQ Narrow may identify manifestations or progression of AML. These SMQs were not used in Study M14-358.

M15-656

Venetoclax 400 mg + Azacitidine

Of the 283 patients treated with 400 mg venetoclax in combination with azacitidine, 3.9% (11/283) experienced events in either malignant tumours SMQ or myelodysplastic syndromes SMQ. Basal cell carcinoma and squamous cell carcinoma of the skin each occurred in more than 1 patient.

Placebo + Azacitidine

Of the 144 patients treated with placebo in combination with azacitidine, 1.4% (2/144) experienced events in either malignant tumours SMQ or myelodysplastic syndromes SMQ. Malignant melanoma and renal cancer were occurred in 1 patient each.

Important Potential Risk 4: Second primary malignancy
Seriousness/outcomes **CLL** *Monotherapy* The majority of events of second primary malignancy observed following venetoclax monotherapy were nonserious; 5.4% (19/352) of subjects receiving daily dosing of 400 mg venetoclax had serious events. One subject experienced an event with a fatal outcome. This subject, a [redacted]-year-old [redacted] died of plasma cell myeloma which the investigator attributed to the subject's compromised immune system. *In Study GO28667 (V + R)* A total of 13/194 patients (6.7%) reported serious events of second primary malignancy on the V + R arm in comparison to 9/188 (4.8%) reported on the BR arm. One patient on the V + R arm had the fatal event of colorectal cancer while 4 patients on the BR arm had the fatal event of second primary malignancies (malignant lung neoplasm [2], AML [1], lymphoma [1]). **AML** *Study M15-656* *Venetoclax 400 mg + Azacitidine* Of the 283 patients treated with 400 mg venetoclax in combination with azacitidine, 1.1% (3/283) experienced Grade ≥ 3 events in either malignant tumours SMQ or myelodysplastic syndromes SMQ which were also categorized as serious adverse events. Adenocarcinoma gastric, chloroma, and erythroleukemia occurred in 1 patient each. *Placebo + Azacitidine* Of the 144 patients treated with placebo in combination with azacitidine, 1.4% (2/144) experienced Grade ≥ 3 events in either malignant tumours SMQ or myelodysplastic syndromes SMQ, which were also categorized as serious adverse events. Malignant melanoma and renal cancer occurred in 1 patient each.
Severity and nature of risk Second primary malignancy may result in death.
Risk Factors and Risk Groups: **CLL** Risk factors include patients with CLL, CLL R/R disease, multiple prior cytotoxic therapies, prior fludarabine-based therapy. **AML** AML is associated with older age, previous hematologic disease, some genetic disorders with cancer predisposition syndromes, and/or exposure to chemicals or radiation, and prior exposure to some chemotherapies for prior malignancies.
Preventability: None

Important Potential Risk 4: Second primary malignancy
Impact on the Risk-Benefit Balance of the Product: Patients with CLL (both 1L and R/R) are at risk of developing second primary malignancies due to underlying immune impairment and increased risk associated with advanced age. In the R/R population, prior treatment with cancer therapies is also known to be associated with an increased risk of secondary malignancies, including myelodysplasia. In AML, impact on the risk-benefit is minimal, due to low reported frequency of second malignancy and aggressiveness of AML. The risk-benefit balance of venetoclax for the individual patient remains favorable.
Public Health Impact: Public health impact is expected to be low as patients with CLL are at risk of developing second primary malignancies due to underlying immune impairment and prior chemotherapy exposure. In AML, public health impact is minimal due to low reported frequency and aggressiveness of AML.

Important Potential Risk 5: Toxicity in Patients with Severe Hepatic Impairment
Search criteria: No individual AE criteria were used. All AEs reported in patients with severe hepatic impairment were evaluated for consistency against what is already known for venetoclax.
Potential Mechanisms: Patients with severe hepatic impairment may have higher venetoclax concentrations due to reduced hepatic elimination. Mean venetoclax AUC exposures in subjects with severe hepatic impairment were approximately 2.7-fold higher compared to subjects with normal hepatic function.
Evidence Sources and Strength of Evidence: Venetoclax clinical trial data
Characterization of the Risk: **CLL** *Monotherapy* None of the 240 patients treated in venetoclax CLL monotherapy studies had severe hepatic impairment. *In Study GO28667 (V + R)* None of the patients treated with V + R in Study GO28667 had severe hepatic impairment. *In Study M15-342* Of 5 subjects with severe hepatic impairment who received single doses of 50mg venetoclax in Study M15-342, 1 of these 5 subjects experienced an adverse event (PT of headache).

Important Potential Risk 5: Toxicity in Patients with Severe Hepatic Impairment
AML *Study M14-358* *Venetoclax 400 mg + Decitabine* None of the subjects treated with 400 mg venetoclax in combination with decitabine had severe hepatic impairment. *Study M15-656* *Venetoclax + Azacitidine* Two patients treated with venetoclax had severe hepatic impairment at baseline. No adverse events of TLS were reported for either subject.
Seriousness/outcomes **CLL** *Monotherapy* None of the 240 patients treated in venetoclax CLL monotherapy studies had severe hepatic impairment. *In Study GO28667 (V + R)* None of the patients treated with V + R in Study GO28667 had severe hepatic impairment. *In Study M15-342* The event of headache that was experienced by a subject with severe hepatic impairment was non-serious and resolved. **AML** *Study M14-358* *Venetoclax 400 mg + Decitabine* None of the subjects treated with 400 mg venetoclax in combination with decitabine had severe hepatic impairment. *Study M15-656* *Venetoclax 400 mg + Azacitidine* Two patients treated with venetoclax had severe hepatic impairment at baseline. No serious adverse events of TLS were reported for either subject. Severity and nature of risk **CLL** In clinical trials with venetoclax, one Grade 2 event of headache was experienced by a subject with severe hepatic impairment. **AML** In clinical trials with venetoclax, 2 subjects had severe hepatic impairment at baseline. No serious adverse events of TLS were reported for either subject.
Risk Factors and Risk Groups: Patients with severe hepatic impairment are at risk.

Important Potential Risk 5: Toxicity in Patients with Severe Hepatic Impairment
Preventability: The SmPC has been revised to include statement that in patients with severe hepatic impairment, there is reduction of at least 50% in the dose of venetoclax throughout treatment and close monitoring for signs of toxicity.
Impact on the Risk-Benefit Balance of the Product: CLL patients with severe hepatic impairment are expected to benefit from efficacy of venetoclax including higher response rates and MRD negativity, the increased AUC exposures in these patients will be mitigated with a dose reduction of venetoclax, thus reducing potential for safety risks. The risk-benefit profile in these patients is favorable. AML patients with severe hepatic impairment are expected to benefit from the efficacy of venetoclax, including improved survival and/or response rates. The increased AUC exposures in these patients will be mitigated with a dose reduction of venetoclax. The risk-benefit profile in these patients is favorable.
Public Health Impact: Public health impact is expected to be minimal as the prevalence of hepatic impairment in the general population is low, and hepatic failure due to infiltration of lymphoma or leukemia is uncommon.

SVII.3.2 Presentation of the Missing Information

Missing information 1: Safety in long-term exposure (> 12 months) (for CLL only)
Evidence source: Limited data are available on long-term exposure (> 12 months) (for CLL only).
Anticipated risk needs to be further characterized: CLL The long-term safety (> 12 months) of venetoclax will be monitored through ongoing prospective observational cohort study (Study P16-562) as well as routine pharmacovigilance activities.

Module SVIII Summary of the Safety Concerns

Table 17. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Tumor lysis syndrome
Important potential risks	Embryofetal toxicity Medication error Richter's transformation (for CLL only) Second primary malignancy Toxicity in patients with severe hepatic impairment
Missing information	Safety in long-term exposure (> 12 months) (for CLL only)

Part III: Pharmacovigilance Plan (Including Post-Authorization Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection

Specific follow-up questionnaires for pregnancies to address embryofetal toxicity (CLL and AML):

The pregnancy questionnaire is part of routine pharmacovigilance follow up processes, which includes use of pharmacovigilance questionnaires for follow up of missing information. The questionnaire includes routine follow up questions regarding the mother's current and past pregnancy history, medical history, and current medications. Through routine pharmacovigilance follow up processes, two attempts will be made to gather additional information using the pregnancy questionnaire for spontaneous reports of pregnancies. In addition, a further questionnaire will be sent to obtain information regarding the pregnancy outcome.

III.2 Additional Pharmacovigilance Activities

CLL

Study P16-562 summary

Study Short Name and Title:

Study P16 562: Prospective observational study to assess the long term safety profile of venetoclax in a Swedish cohort of Chronic Lymphocytic Leukaemia (CLL) patients

Rationale and Study Objectives:

CLL constitutes the most common type of leukemia, with an incidence of 3 8 cases per 100,000 inhabitants per year in Europe (Redaelli 2004, Sant 2010)

CLL is a 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. Study P16 562 aims to characterize the long term safety of venetoclax in CLL patients treated under real world care. Sweden was chosen for this study, given the possibility of linking at an individual patient level highly granular Electronic Medical Records (EMR) data from hematology clinics to data from national health registries.

The study primary objective is to characterize the long term safety of venetoclax, including determining the incidence in CLL patients exposed to venetoclax of select adverse events.

Safety concerns addressed include:

Safety in long term exposure (> 12 months) of venetoclax.

Select list of adverse events:

- Second primary malignancies
- Richter's transformation (DLBCL, HL)
- Opportunistic serious infections
- Autoimmune hematological event
  - Other autoimmune hemolytic anemia
  - Idiopathic thrombocytopenic purpura
- Tumor Lysis syndrome

Study Design:

Prospective cohort study over an 8 year period, running from Q1 2018 to Q1 2026 and including 1) a national patient cohort based on data from national and population based health registers in Sweden, and 2) a sub cohort based on patient level data from selected hematology clinic EMRs in Sweden and cross linked with national register data.

Study Population:

Patients diagnosed with CLL prior to the prospective study period and who are still alive at the start of the prospective study (Q1 2018), as well as incident cases of CLL who are diagnosed during the prospective study period (2018 onwards). Cohort 1 will include CLL patients

identified in the Swedish Cancer Registry, while Cohort 2 (sub cohort of Cohort 1) will include CLL patients identified in the EMRs under the study period.

Milestones:

Interim analyses are planned every second year over a study period of 8 years.

The final clinical study report is planned in Q2 2026.

Study M16-185 summary

Study Short Name and Title:

A Study to Assess the Effect of Venetoclax on the Pharmacokinetics of Ethinyl estradiol/Levonorgestrel in Female Patients with Hematologic Malignancies

Rationale and Study Objectives:

The primary objective of this study is to investigate the effect of venetoclax on the pharmacokinetics of ethinyl estradiol/levonorgestrel.

Safety concerns addressed include:

Use in patients who require oral contraceptives

Study design:

Open label, multicenter, Phase I study

Study populations:

Up to 12 female subjects with hematological malignancies.

Milestones:

Study is ongoing, final CSR is planned for Q1 2028.

Study P22-905 summary

Study Short Name and Title:

Cross sectional Study Evaluating the Effectiveness of the Venetoclax Patient Card Among Adult Patients in Europe

Rationale and Study Objectives:

To evaluate patients' receipt and use of the venetoclax patient card (PC) and to assess their knowledge of the contents of the PC, including TLS symptoms, patient actions to minimize TLS, and patient actions if TLS symptoms occur.

Safety concern addressed includes:

Tumor lysis syndrome (TLS)

Study design:

This study is a cross sectional survey of knowledge of the risks and safe use of venetoclax as outlined in the PC among adult patients who have recently received venetoclax for treatment of CLL per standard of care. Patients will be identified through a diverse selection of medical practices representing hematologists who prescribe venetoclax across at least 5 European countries. Patients initiating venetoclax for the treatment of CLL in the past 8 weeks will be targeted for participation in the study. Patients will be identified and recruited through clinical sites. The study will target 200 patients with CLL across all countries (approximately 30 50 per country) to allow reasonable precision around estimates of participant knowledge of the safety information regarding TLS. Analyses included in the final study report will be descriptive in nature and will include distributions of the responses to all of the individual questions and, if appropriate, summary measures across logical groupings of questions. Analysis tables will include the frequency and percentage of patients who select each response to each individual question. Results from this study will be reviewed qualitatively to identify patterns suggesting that the educational activities have been successful (e.g., yielding consistently high percentages of correct responses across all questions), not successful (e.g., yielding consistently low percentages of correct responses), or partially successful (e.g., yielding high percentages for most responses and low percentages for selected responses).

Study populations:

Adult patients who have recently received venetoclax for treatment of CLL per usual care, in selected European countries.

Milestones:

Study updates will be provided annually via post approval measure until study is completed. This final clinical study report will be submitted Q4 2026.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 18. On-Going and Planned Additional Pharmacovigilance Activities

Study Name Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
CLL				
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				

Study Name Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				

Study P16-562
Prospective Observational Cohort Study to Assess the Long Term Safety of Venetoclax in the Swedish Cohort of Chronic Lymphocytic Leukaemia Patients
 	
Ongoing
	To characterize long term safety of venetoclax including determining the incidence of select adverse events in CLL patients exposed to venetoclax.	Safety in long-term exposure (> 12 months) of venetoclax
		
		<u>Select list of adverse events:</u>
		• Second primary malignancies
		• Richter's transformation (DLBCL, HL)
		• Opportunistic serious infections
		• Autoimmune hematological event
		  ○ Other autoimmune hemolytic anemia
		  ○ Idiopathic thrombocytopenic purpura
		• Tumor Lysis syndrome
			Interim CSR
			
			Final report
				Every second year over a study period of 8 years
				
				Planned Q2 2026

Study Name Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study M16-185 A Study to Assess the Effect of Venetoclax on the Pharmacokinetics of Ethinyl estradiol/Levonorgestrel in Female Patients with Hematologic Malignancies Ongoing	Open-label study to assess the effect of venetoclax on the pharmacokinetics of oral contraceptives in hematologic malignancy patients	Use in patients who require oral contraceptives	Final CSR	Planned Q1 2028
Study P22-905 Cross-sectional Study Evaluating the Effectiveness of the Venetoclax Patient Card Among Adult Patients in Europe Ongoing	Evaluate patients' receipt and use of the venetoclax PC and to assess their knowledge of the contents of the PC, including TLS symptoms, patient actions to minimize TLS, and patient actions if TLS symptoms occur.	Tumor lysis syndrome	Study updates Final report	Annually via post-approval measure until study completion Q4 2026

Part IV: Plans for Post-Authorization Efficacy Studies

Not applicable.

Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimisation Plan

V.1 Routine Risk Minimizations Measures

Table 19. Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities

Tumor Lysis Syndrome (TLS)	<u>Routine Risk Communication:</u>
	• Posology and method of administration:
	  ○ SmPC section 4.2 - 5–week dose titration and prevention of TLS (CLL),
	  ○ SmPC section 4.2 – 3-day dose titration schedule for azacitidine or decitabine prevention of TLS (AML)
	• SmPC section 4.4 - Special warnings and precautions for use, including risk factors to identify patients at greater risk of TLS (CLL and AML).
	• SmPC section 4.3 and section 4.5 - Interaction with other medicinal products and other forms of interaction; information on contraindicated drugs during titration phase due to increased risk of TLS (CLL and AML)
	• SmPC section 4.8 - Undesirable effects, including summary description of TLS observed in clinical development of venetoclax (CLL and AML)
	• PIL section 2 – prevention of TLS (CLL and AML)
	• PIL section 3 – dose-titration of venetoclax and preventative measures for TLS (CLL and AML)
	• PIL section 4 – symptoms of TLS (CLL and AML)
	<u>Routine risk minimization activities recommending specific clinical measures for TLS:</u>
	• The 5-week dose-titration schedule for CLL patients to minimize the risk of TLS is included in section 4.2 of the SmPC
	• A 3-day dose-titration schedule for azacitidine or decitabine for AML patients for the prevention of TLS included in section 4.2 of the SmPC

Safety Concern	Routine Risk Minimization Activities
	• Preventative measures of TLS are included in SmPC section 4.2 (CLL and AML) • Pre-dose assessment of blood chemistries and for patients at risk monitoring of blood chemistries post dose are included in SmPC section 4.2 (CLL and AML) • Identification of patients at risk of TLS is included in SmPC section 4.4 (CLL and AML) • During initiation and dose titration, dose modifications for use with moderate CYP3A inhibitors for CLL and moderate and strong CYP3A inhibitors for AML are included in SmPC section 4.2 (CLL and AML) <u>Other routine risk minimization measures:</u> • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Pack size and Package leaflet
Embryofetal Toxicity	<u>Routine Risk Communication:</u> • SmPC – section 4.4, includes information for women of childbearing potential (CLL and AML) • SmPC – section 4.6, includes information on contraception methods in women of childbearing potential and on potential harm to the fetus (CLL and AML) • SmPC – section 5.3, includes preclinical information on embryofetal toxicity in animal studies (CLL and AML) • PIL section 2, information on pregnancy and use of effective contraception methods for women of childbearing potential (CLL and AML) <u>Routine risk minimization activities recommending specific clinical measures for embryofetal toxicity:</u> • Avoidance of pregnancy while on venetoclax and use of highly effective contraceptive methods recommended in SmPC section 4.6. (CLL and AML) <u>Other routine risk minimization measures:</u> • Prescription only medicine • Use of treatment should be initiated and supervised by specialist • Package leaflet

Safety Concern	Routine Risk Minimization Activities
Medication Error	Routine Risk Communication: • SmPC section 3 – the shape and color of venetoclax tablets, distinct for each strength (10 mg, 50 mg and 100 mg), are provided (CLL) • SmPC Section 4.2 – the 5-week dose titration schedule, dose by week is described (CLL) • SmPC section 4.2 - dose titration schedule for 3 days with azacitidine or decitabine (AML) • SmPC section 6.5 –includes the nature and contents of container for each venetoclax dose strength (10 mg, 50 mg, and 100 mg) (CLL) • PIL section 3 - Description of how to take venetoclax during the 5-week titration. (CLL) • PIL section 3 – Description of how to take venetoclax during the 3 day schedule titration (AML) • PIL section 6 – includes what each strength of Venclyxto looks like and the amount in each pack (CLL) Routine risk minimization activities recommending specific clinical measures for medication errors: None Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • In CLL, each carton will be dispensed weekly to the patient during the first 4 weeks of the dose titration • In AML, only 100 mg tablets will be dispensed to minimize medication errors • Labeling and packaging layout (immediate and outer packaging) has been designed to minimize medication errors • Pack size and package leaflet
Richter's Transformation (CLL)	Routine Risk Communication: None Routine risk minimization activities recommending specific clinical measures for Richter's transformation: None Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist

Safety Concern	Routine Risk Minimization Activities
Second primary malignancy	Routine Risk Communication: None (CLL and AML) Routine risk minimization activities recommending specific clinical measures for second primary malignancy: None (CLL and AML) Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists
Toxicity in patients with severe hepatic impairment	Routine Risk Communication: • SmPC section 4.2 - Posology and method of administration includes a dose adjustment in patients with severe hepatic impairment (CLL and AML) • SmPC section 5.2 - Includes information on hepatic impairment PK study results (CLL and AML) • PIL section 2 - Includes information on potential dose reduction in subjects with severe hepatic impairment (CLL and AML) Routine risk minimization activities recommending specific clinical measures for Toxicity in Severe Hepatic Impairment: • Recommendation for dose reduction of at least 50% throughout treatment for patients with severe hepatic impairment. These patients should be closely monitored for signs of toxicity as is included in SmPC section 4.2 (CLL and AML) Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist • Package leaflet
Safety in Long-term Exposure (>12 Months) (CLL)	Routine Risk Communication: None Routine risk minimization activities recommending specific clinical measures for safety in long term exposure: None Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists

V.2 Additional Risk Minimization Measures

Additional Risk Minimization (Tumor Lysis Syndrome in CLL Patients):

Tumor Lysis Syndrome is a known risk for venetoclax. Updated safety information is being provided in the SmPC. An additional risk minimization measure consisting of educational material targeted to patients is being implemented in European countries.

Patient-Directed Measure – Patient Card

Objectives:

- To increase patient understanding and awareness of the risk of TLS, patient behaviors to minimize this risk, and TLS symptoms to prompt patient actions including to seek immediate medical attention in case of their occurrence.
- To remind patients of the need to carry the card at all times as a communication aid to treating HCPs.

Rationale for the Additional Risk Minimization Activity:

After implementation of the current prophylaxis and monitoring measures, events of TLS with severe consequences and fatal outcome have been reported in the post marketing setting in CLL patients. Following a validated signal on increased severity of TLS associated with venetoclax, the SmPC was updated to provide detailed safety information and minimization measures.

The patient card was considered necessary to communicate to patients the risk of TLS, patient behaviors to minimize this risk, and describe TLS symptoms to prompt patient actions including to seek immediate medical attention in case of their occurrence.

Implementation Plan (including Target Audience and Planned Distribution Path):

- The patient card is available in print or electronically. Depending on local regulations or competent authority guidance in European countries, the printed material is disseminated to hematologists in European countries who then distribute the patient card to their respective patients who are prescribed venetoclax. If applicable, the printed material has information on how to request additional patient cards or access to the same information in electronic format.
- Depending on local regulations or competent authority guidance in the European countries, the patient card is available on the local competent authority website, AbbVie Care website, and/or the venetoclax specific website available in the local countries.

Plans to Evaluate the Effectiveness of the Interventions and Criteria for Success:

Study P22 905: Effectiveness evaluation of the additional risk minimization program will be performed using a Category 3 PASS Cross sectional survey study to evaluate effectiveness of the patient card.

The objectives of the patient survey are to evaluate patient receipt and use of the patient card and their understanding and awareness of the contents of the patient card related to the risk of

TLS, patient behaviors to minimize this risk, and TLS symptoms to prompt patient actions including to seek immediate medical attention in case of their occurrence.

This cross sectional, multi country survey study will collect information on patient demographics, disease history, treatment with venetoclax, receipt of patient card, patient understanding and awareness of the content of the patient card, and patient behaviors and actions resulting from receipt of the patient card.

Removal of Additional Risk Minimization Activity: DHPC

Rationale for the removal:

Distribution of the DHPC in EU countries was completed in June 2021. As an evaluation of the effectiveness of the DHPC as an additional risk minimization measure, Study P22 907 met its objectives to evaluate physicians' receipt and use of the DHPC, including knowledge among participating haematologists regarding potential TLS risk of venetoclax in the treatment of patients with CLL and TLS assessment and adherence to the TLS risk minimisation measures following revisions to the SmPC and dissemination of the DHPC to physicians in select EU countries and the UK. While the overall physicians' reported receipt of the DHPC was low (47%), the relatively high level of knowledge among physicians also suggests that the key safety information is available and is used by treating physicians. With the completion of Study P22 907 (Procedure No. EMA/VR/0000245044), the effectiveness evaluation of the DHPC has been completed. As no further action or evaluation regarding the DHPC was recommended, the DHPC as additional risk minimization has been removed.

V.3 Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table 20. Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Tumor lysis syndrome (TLS)	Routine risk minimization measures: Posology and method of administration, including prophylactic measures for TLS, are described in section 4.2 of the SmPC (CLL and AML). Warnings and precautions for TLS are listed in section 4.4 of the SmPC (CLL and AML). Interaction with other medicinal products is described in section 4.5 of the SmPC (CLL and AML). TLS is described in section 4.8 of the SmPC (CLL and AML).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: Study P22-905: Cross-sectional survey study to evaluate effectiveness of the patient card (CLL only)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Packaging design and language to facilitate adherence to the dose-titration schedule • Pack size and package leaflet Additional risk minimization measures: • Distribution of DHPC in European countries (CLL only) (activity completed in 2021 and effectiveness evaluation completed in 2025) • Distribution of a patient card in European countries (CLL only)	
Embryofetal toxicity	Routine risk minimization measures: Language concerning embryofetal toxicity is included in section 4.6 and section 5.3 of the SmPC (CLL and AML). Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Package leaflet Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Questionnaire for pregnancies (CLL and AML) Additional pharmacovigilance activities: None
Medication error	Routine risk minimization measures: Posology and method of administration are described in section 4.2 of the SmPC (CLL and AML). Description of contents of venetoclax container, including dose strength, shape and color of tablets, in section 3 and section 6.5 of SmPC (CLL). Language concerning overdose is included in section 4.9 of the SmPC (CLL and AML). Other routine risk minimization measures: • Prescription only medicine	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• Use of treatment should be initiated and supervised by specialists • In CLL, each carton will be dispensed weekly to the patient during the first 4 weeks of the dose titration • In AML, only 100 mg tablets will be dispensed to minimize medication errors • Labeling and packaging layout (immediate and outer packaging) has been designed to minimize medication errors • Pack size and package leaflet Additional risk minimization measures: None	
Richter's transformation (for CLL only)	Routine risk minimization measures: None Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional Pharmacovigilance: None
Second primary malignancy	Routine risk minimization measures: None Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional Pharmacovigilance Activities: Study P16-562.

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Toxicity in Patients with severe hepatic impairment	Routine risk minimization measures: Posology and method of administration of dose adjustments in patients with severe hepatic impairment are described in section 4.2 of the SmPC (CLL and AML). PK study results pertaining to hepatic impairment are described in section 5.2 of the SmPC (CLL and AML). Other routine risk minimization measures: • Prescription only medication • Use of treatment should be initiated and supervised by specialist • Package leaflet Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Safety in long-term exposure (> 12 months) (for CLL only)	Routine risk minimization measures: Median duration of treatment is included in section 5.1 of the SmPC (CLL) Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional Pharmacovigilance Activities for CLL indication: Study P16-562

Part VI Summary of the Risk Management Plan

Summary of risk management plan for Venclyxto (venetoclax)

This is a summary of the risk management plan (RMP) for Venclyxto. The RMP details important risks of Venclyxto, how these risks can be minimized, and how more information will be obtained about Venclyxto's risks and uncertainties (missing information).

Venclyxto's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Venclyxto should be used.

This summary of the RMP for Venclyxto should be read in the context of all this information, including the assessment report of the evaluation and its plain language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Venclyxto's RMP.

I. The Medicine and What it Is Used For

Venclyxto is authorized for the treatment of

CLL:

- Patients with previously untreated CLL in combination with obinutuzumab.
- CLL in combination with rituximab in adult patients who have received at least one prior therapy.
- 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; or
- 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.
- (See SmPC for the full indication)

AML

- Adult patients with newly diagnosed AML in combination with a hypomethylating agent who are ineligible for intensive chemotherapy.

It contains venetoclax as the active substance and it is given by mouth.

Further information about the evaluation of Venclyxto's benefits can be found in Venclyxto's EPAR, including in its plain language summary, available on the EMA website, under the medicine's webpage.

[https://www.ema.europa.eu/en/documents/product information/venclyxto epar product information en.pdf].

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Venclyxto, together with measures to minimize such risks and the proposed studies for learning more about Venclyxto's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorized pack size the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Venclyxto is not yet available, it is listed under "missing information" below.

II.A List of Important Risks and Missing Information

Important risks of Venclyxto are risks that need risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Venclyxto. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	• Tumor lysis syndrome
Important potential risks	• Embryofetal toxicity • Medication error • Richter's transformation (for CLL only) • Second primary malignancy • Toxicity in patients with severe hepatic impairment
Missing information	• Safety in long-term exposure (> 12 months) (for CLL only)

II.B Summary of Important Risks

The SmPC was used for the CLL and AML indications. Only major differences between the CLL and AML risk minimization measures are pointed out in the table below. Otherwise, only sections of the SmPC are presented.

Important identified risk: Tumor lysis syndrome	
Evidence for linking the risk to the medicine	Because CLL cells are essentially 'addicted' to BCL-2 for survival and are exquisitely sensitive to venetoclax, an on-target pharmacological effect can cause rapid reduction in size of tumor (debulk) and may pose a risk of TLS. TLS could also be a risk in AML, as primary AML cells have also been shown in preclinical studies to be highly sensitive to venetoclax, either alone or in combination with azacitidine.
Risk factors and risk groups	The risk is more among subjects who have high tumor burden. Also, subjects with renal dysfunction or splenomegaly may be at added risk. These risk factors are not unique to venetoclax. They are consistent with that reported in literature, e.g., patients with bulky disease (including elevated white blood cell [WBC] count in patients with CLL), renal dysfunction, and baseline elevations in uric acid are at higher risk (Blum 2011). In a study involving 772 chemotherapy treated patients with AML, factors significantly associated with increased risk of clinical and laboratory TLS included elevated WBC (≥ 25 - 75 × 10^9/L), uric acid (> 7.5 mg/dL), lactate dehydrogenase (≥ 1 - 4 × ULN) and creatinine (> 1.4 mg/dL) (Montesinos 2008).
Risk minimization measures	Routine risk minimization measures: Posology and method of administration, including prophylactic measures for TLS, are described in section 4.2 of the SmPC (CLL and AML). Warnings and precautions for TLS are listed in section 4.4 of the SmPC (CLL and AML). Interaction with other medicinal products is described in section 4.5 of the SmPC (CLL and AML). TLS is described in section 4.8 of the SmPC (CLL and AML). Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Packaging design and language to facilitate adherence to the dose titration schedule • Pack size and package leaflet Additional risk minimization measures: • Distribution of DHPC in European countries (CLL only) (activity completed in 2021 and effectiveness evaluation completed in 2025). • Distribution of patient card in European countries (CLL only)

Additional pharmacovigilance activities	Additional pharmacovigilance activities Study P22-905: Cross-sectional survey study to evaluate effectiveness of the patient card (CLL only).

Important potential risk: Embryofetal toxicity	
Evidence for linking the risk to the medicine	The pro-apoptotic mechanism of action for venetoclax is consistent with anticipated embryotoxicity. The wide distribution of Bcl-2 in the developing embryo (pre- and post-implantation) suggests that many immature cells require a death repressor protein, and pharmacological perturbation of these anti-apoptotic proteins (with drugs such as venetoclax), can alter embryo development. This is evidenced by studies that have demonstrated that knockout or knock down of Bcl-2 family proteins can adversely affect embryo growth and development (Boumela 2011, LeBrun 1993, Novack 1994).
Risk factors and risk groups	Women of childbearing potential
Risk minimization measures	Routine risk minimization measures: Language concerning embryofetal toxicity is included in section 4.6 and section 5.3 of the SmPC (CLL and AML). Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Package leaflet

Important potential risk: Medication error	
Evidence for linking the risk to the medicine	CLL Potential intentional errors in the prescribing, dispensing, and administration of venetoclax especially during the gradual dose increase over a period of 5 weeks up to the recommended daily dose of 400 mg. AML Medication errors including prescribing, dispensing or administration of venetoclax may occur during the 3-day ramp-up phase with a starting dose of 100 mg or at the recommended daily dose
Risk factors and risk groups	CLL: Risk groups include elderly CLL patients. Risk factors include venetoclax having three different tablet strengths and use during the 5-week dose-titration period. AML: Risk groups include elderly AML patients. Risk factors include venetoclax dose ramp-up over 3 days, during which 100-mg tablets are used (multiple tablets to be administered).
Risk minimization measures	Routine risk minimization measures: Posology and method of administration are described in section 4.2 of the SmPC (CLL and AML). Description of contents of venetoclax container, including dose strength, shape and color of tablets, in section 3 and section 6.5 of SmPC (CLL). Language concerning overdose is included in section 4.9 of the SmPC (CLL and AML). Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • In CLL, each carton will be dispensed weekly to the patient during the first 4 weeks of the dose titration • In AML, only 100 mg tablets will be dispensed to minimize medication errors • Labeling and packaging layout (immediate and outer packaging) has been designed to minimize medication errors • Pack size and package leaflet

Important potential risk: Richter's transformation (for CLL only)	
Evidence for linking the risk to the medicine	Unknown
Risk factors and risk groups	Risk factors include R/R CLL disease, 17p del, multiple prior cytotoxic therapies, prior fludarabine-based therapy.
Risk minimization measures	Routine risk minimization measures: None Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist

Important potential risk: Second primary malignancy	
Evidence for linking the risk to the medicine	Unknown
Risk factors and risk groups	CLL patients with R/R disease, multiple prior cytotoxic therapies, prior fludarabine-based therapy
Risk minimization measures	Routine risk minimization measures: None Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialist
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CLL only Study P16-562

Important potential risk: Toxicity in patients with severe hepatic impairment	
Evidence for linking the risk to the medicine	Patients with severe hepatic impairment may have higher venetoclax systemic exposures due to reduced hepatic elimination.
Risk factors and risk groups	Patients with severe hepatic impairment are at risk
Risk minimization measures	Routine risk minimization measures: Posology and method of administration including dose modification, included in section 4.2 of the SmPC (CLL and AML). PK study results pertaining to hepatic impairment are included in section 5.2 of the SmPC (CLL and AML). Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists • Package leaflet

Missing information: Safety in long-term exposure (> 12 months) (for CLL only)	
Risk minimization measures	Routine risk minimization measures: Median duration of treatment is included in section 5.1 of the SmPC Other routine risk minimization measures: • Prescription only medicine • Use of treatment should be initiated and supervised by specialists
Additional pharmacovigilance activities	Additional pharmacovigilance activities: CLL: Study P16-562 See Section II.C of this summary for an overview of the post-authorization development plan.

II.C Post-Authorization Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorization

Not applicable.

II.C.2 Other Studies in Post-Authorization Development Plan

CLL

Study short name: Study P16-562

This is a prospective observational cohort study to assess the safety of venetoclax in the Swedish cohort of CLL patients.

Purpose of this study: to assess the long term safety of venetoclax using a prospective cohort containing both venetoclax exposed and non exposed patients.

Study short name: Study M16-185

This is a clinical drug drug interaction study with an oral contraceptive.

Purpose of study: to assess the effect of venetoclax on the pharmacokinetics of oral contraceptives in patients with a hematologic malignancy.

Study short name: Study P22-905

This is a cross sectional, multi country survey study.

Purpose of this study: To evaluate patients' receipt and use of the venetoclax PC and to assess their knowledge of the contents of the PC, including TLS symptoms, patient actions to minimize TLS, and patient actions if TLS symptoms occur.

Part VII: Annexes

Annex 1	EudraVigilance Interface
Annex 2	Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program
Annex 3	Protocols for Proposed, On-Going and Completed Studies in the Pharmacovigilance Plan
Annex 4	Specific Adverse Drug Reaction Follow-Up Forms
Annex 5	Protocols for Proposed and On-Going Studies in RMP Part IV
Annex 6	Details of Proposed Additional Risk Minimization Activities (If Applicable)
Annex 7	Other Supporting Data (Including Referenced Material)
Annex 8	Summary of Changes to the Risk Management Plan Over Time

Annex 4. Specific Adverse Drug Reaction Follow-Up Forms

Follow-up forms included:

Questionnaire for Pregnancies v10

We are requesting more information regarding the pregnancy that you or your patient experienced *to help us ensure the safety of our medications for all individuals using them. If additional information is required, we will follow up at several timepoints for further information*

Patient Information mother ☐ **Reference Numbers**

Name: Initials: Patient ID: AER #

Address: City, State: Postal code: Affiliate Ref #

Email:

Height: _____ cm ☐ in ☐ Weight: _____ kg ☐ lb ☐ Race/Ethnicity: Other reference #:

Sex: M ☐ F ☐ Date of Birth:_____/_____/_____ (d/m/y) Pregnancy weight gain: Age group^:

Age at Time of Event:

^ Age groups: ☐ pediatric/Adolescent (10 years to 17 years), ☐ Adult (18 years to 64 years)

Maternal health complications during pregnancy/within 2 weeks after the pregnancy	Event Onset (d/m/y)	Event End (d/m/y)	Event Criteria[1]	Was this caused by an AbbVie medication[2]?	Outcome[3]

Select one of the following to answer the questions designated with numbers 1-3.

1. Event Criteria: Serious (Death, Hospitalization, Prolonged Hospitalization, Congenital anomaly, Life-threatening, Medically Important, Persistent or Significant Disability) or Non-serious
2. Causality: Reasonable Possibility, No Reasonable Possibility, Non-Assessable
3. Outcome: Death, Recovered, Not recovered, Recovering, Worsened, Unknown, or Recovered with Sequela (provide Sequela if available)

Pregnancy Information:

Last menstrual period date	Estimated due date	Method of pregnancy confirmation	Pregnancy ongoing Yes ☐ No ☐	Delivery date	Single or twin/multiple pregnancy
Delivery method (e.g. normal spontaneous vaginal delivery, scheduled/unplanned c-section)	Was Assisted Reproductive Technology used (ie; IVF, intrauterine insemination, etc) If YES, please specify:				
Please provide gestational age at the time of AbbVie drug exposure and method of determining gestational age, and duration of exposure:					

Did you use /Was the patient using a form of birth control at the time of becoming pregnant? Yes ☐ No ☐. If yes, please list the type of birth control used:

Did you/the mother experience any complications during pregnancy, delivery or post-partum (e.g. hypertensive disorder, eclampsia, diabetes of pregnancy, HELLP syndrome)? Yes ☐ No ☐ If yes, describe and give start/stop dates:

Did you/the mother experience any infections during pregnancy (e.g. CMV, Toxoplasma, Rubella, oral or genital herpes, or other)? Yes ☐ No ☐ If yes, describe and give start/stop dates:

Did you/the mother receive any anesthetic/sedation/medication during the pregnancy or delivery? Yes ☐ No ☐ If yes, please provide details:

Were any diagnostic or genetic test or labs done during the pregnancy (e.g. amnio, CVS, ultrasound) Yes ☐ No ☐ If yes, please provide details and if any fetal defects were found:

Pregnancy outcome

Live birth	Yes ☐ No ☐	**If yes, please continue in section Infant Status and skip the below**

Stillbirth	Yes ☐ No ☐	Date of event (m/d/y):	Gestational age at time of event (weeks):
Miscarriage	Yes ☐ No ☐	Date of event (m/d/y):	Gestational age at time of event (weeks):
Elective Abortion (ended early)	Yes ☐ No ☐	If yes, please indicate reason **below**:	Gestational age at time of event (weeks):
Ectopic Pregnancy	Yes ☐ No ☐	Date of diagnosis (m/d/y):	Gestational age at time of event (weeks):

If a miscarriage, stillbirth or elective abortion occurred, were any Fetal defect(s) found? Yes ☐ No ☐ Specify:	Chromosomal analysis performed or Other ☐ Specify:
Any Maternal Medical History, include previous pregnancy and results (eg live birth, stillbirth, miscarriage, elective abortion, ectopic pregnancy) family history, genetic or familial abnormalities:	

Infant Status:

Current Infant age	Date of delivery (m/d/y)	Birth weight ☐ lb oz ☐ kg	Birth Length cm ☐ in ☐
Male ☐ Female ☐	Gestational age at delivery:	Apgar score 1 5 min:	Birth Head circumference cm ☐in ☐
Did the baby have any birth defects? Yes ☐ No ☐ If Yes, please describe:			
Has the baby been growing appropriately (height, weight, head circumference) since birth? Yes ☐ No ☐ If No, please describe:			
Has the baby met the expected developmental milestones since birth? Yes ☐ No ☐ If No, please describe:			
Has the baby been breastfed? Yes ☐ No ☐, if yes please describe duration and if ongoing:			

Did the baby have any infections after birth: Yes ☐ No ☐ If Yes, please describe:

Bacteria ☐ Virus ☐ Fungus ☐ Parasite ☐ Unknown ☐ Other ☐

Please provide start and end dates:

Describe:

Was the baby hospitalized for any infections: Yes ☐ No ☐ If Yes, describe which one and provide dates of hospitalization:

Has the baby had any other illness or medical condition: Yes ☐ No ☐ If Yes, please describe:

Please provide onset and end dates:

Was the Baby hospitalized for any illness or medical condition: Yes ☐ No ☐ If Yes, describe which one and provide dates of hospitalization:

Has the baby needed any treatments/interventions: Yes ☐ No ☐ If Yes, please describe:

Was the Baby hospitalized for these treatments: Yes ☐ No ☐ If Yes, please describe provide dates of hospitalization:

Has the baby received any medications/supplements/vitamins: Yes ☐ No ☐ If Yes, please describe which:

Has the baby received any vaccinations: Yes ☐ No ☐ If Yes, please describe which:

Medication List, Laboratory Tests & Diagnostic Test Results

For convenience you may print this information from your electronic medical record (EMR) and include with this form or hand write in tables on page 3.

Instructions to print from EMR

- Include active medication List at time of patient event. Write the start/end date or indication of patient medications if not included in EMR print out.
- Include laboratory tests and diagnostic tests for the 3-day period surrounding the event or most currently available.

Medications *(active at time of event) (C), Past (P), and Treatment information (T). Include herbal, over the counter medications, vaccines/recreational drugs and supplements Including details of other drugs taken within 6 months or during pregnancy:*

Mother ☐ **Father** ☐

Name	Dose	Form	Frequency	Route	Start Date (d/m/y)	End Date (d/m/y)	Indication	If medication stopped, did event abate? *If yes, provide date*
					___/___/_____	___/___/_____		
					___/___/_____	___/___/_____		
					___/___/_____	___/___/_____		
					___/___/_____	___/___/_____		

AbbVie Medication Lot Number:	Expiration Date: ____/_____/_____(d/m/y)	*If unable to provide lot number,* indicate reason below:

Discarded ☐ Not Accessible to Physician ☐ Not on Patient's File ☐ Didn't Receive in Original Package ☐ Not Legible on Package ☐

If AbbVie/Pharmacyclics product was discontinued, was it restarted? Date Dose

Medical History prior to current pregnancy in the mother or biological father

Tobacco Use	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	Form/Amount/Start/Stop Dates:
Alcohol Use	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	Amount/Start/Stop Dates:
Recreational Drug Use	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	Amount/Start/Stop Dates:
Bone Marrow or Solid Organ Transplant	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	If yes, please specify
Immunodeficiency	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	If yes, please specify
HIV/AIDs	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	
Neurological disorder (ex. Multiple Sclerosis)	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	If yes, please specify:
Syphilis/ Toxoplasmosis/CMV	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	If yes, please specify:
Cancer	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	If yes, please specify:

Bone or skeletal disease (dwarfism)	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	If yes, please specify:
Cleft lip/palate	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	If yes, please specify:
Cystic fibrosis	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	If yes, please specify:
Down syndrome	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	If yes, please specify:
Muscular dystrophy	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	If yes, please specify:
Neural tube defect (spina bifida, anencephaly)	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	If yes, please specify:
Neurofibromatosis	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	If yes, please specify:
Other chromosome abnormality	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	If yes, please specify:
Other nerve/muscle disorder	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	If yes, please specify:
Polycystic kidney disease	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	If yes, please specify:
Sickle cell disease	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	If yes, please specify:
Tay Sachs/Canavan disease	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	If yes, please specify:
Thalassemia	Yes ☐ No ☐ Unknown ☐	Mother ☐ Father ☐	If yes, please specify:
Gonorrhea/Chlamydia	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
Diabetes	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
RH negative treatment	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
Hypertension	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
Asthma/TB	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
Heart Disease/Murmur	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
Infertility	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
Lupus/Rheumatoid	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
Arthritis/Sjorgens	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
Uterine anomaly	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
Kidney disease	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
Diethylstilbestrol (DES) exposure	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
Recurrent urinary tract infections/Pyelonephritis/stones	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
Herpes	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify
Epilepsy/seizures	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
Psychiatric Disorder/Anxiety/Depression/Bipolar	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
Liver Disease/Hepatitis A,B,C	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:

Blood clots/DVT/Pulmonary Embolus	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
Bleeding Disorder (Von Willebrand's/Hemophilia)	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
Hypothyroid/Hyperthyroid	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
Folate deficiency	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
Obesity	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
Breast cancer	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
Ovarian cancer	Yes ☐ No ☐ Unknown ☐	Mother only	If yes, please specify:
Other pertinent family medical history: Mother ☐ Father ☐			

Did maternal death occur? Yes ☐ No ☐

Date of Death (d/m/y)	Autopsy: Yes ☐ No ☐ Unknown ☐	Autopsy Date (d/m/y):
Autopsy Results:	Cause of Death:	
Was Death Certificate Obtained: Yes ☐ No ☐ Unknown ☐		

Contact Information

Does reporter agree to have HCP/MD contacted? Yes ☐ No ☐ Not Applicable ☐

Physician/HCP Name/Specialty:
Address:
Email:
City, State: Postal code:
Phone Number:

Person completing form *if different from Physician/HCP*

Name:
Address:
Email:
City, State: Postal code:
Phone Number:

Supplemental Tables (if needed)

Laboratory & Diagnostic Results *Include laboratory tests and diagnostic tests for the 3-day period surrounding the event or most currently available.*

Laboratory test	Date (d/m/y)	Result (include units of measure)	Reference Range
	___/___/_____		

Diagnostic test	Date (d/m/y)	Results (key findings). *If desired attach results. Include reference ranges:*
	___/___/_____	

	___/___/_____		
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Annex 6. Details of Proposed Additional Risk Minimizations Activities (If Applicable)

An additional risk minimization measure for Tumor Lysis Syndrome in CLL patients consists of an educational material targeted to patients, which will be implemented in European countries.

Key messages of the additional risk minimization measure:

Patient Card that contains the following:

- Contact details of the venetoclax prescriber and patient.
- Instruction to patients on how to minimize TLS risk.
- List of TLS symptoms to prompt patient actions including to seek immediate medical attention in case of their occurrence.
- Instructions that the patient should carry the patient card at all times and to share it with HCPs involved in their care (i.e., emergency room HCPs, etc.).
- Information for the HCPs treating the patient that venetoclax treatment is associated with the risk of TLS.

Annex 7. Other Supporting Data (Including Referenced Material)

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