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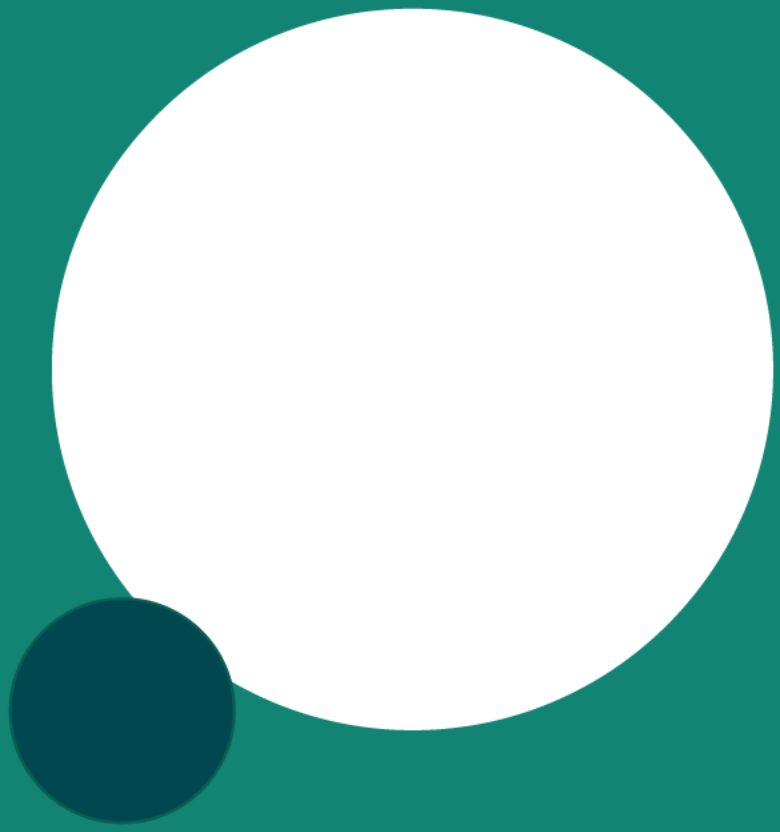

Venetoclax (ABT-199) in Patients with Chronic Lymphocytic Leukemia: Experience Through the Pre-Approval Access Program in European Countries: A Medical Chart Review

Protocol Final V4.0

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Prepared for:

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Contents

Abbreviations

Abbreviation	Full description
AE	Adverse event
BCL-2	B-cell lymphoma-2
BCRi	B-cell-antigen receptor signalling inhibitor
CLL	Chronic lymphocytic leukemia
CRF	Case report form
eCRF	Electronic CRF
EHA	European Hematology Association
EMA	European Medicines Agency
GPP	Good Pharmacoepidemiology Practices
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
MRD	Minimal residual disease
ORR	Overall response rate
OS	Overall survival
PAA	Pre-approval access
PFS	Progression-free survival
TLS	Tumor lysis syndrome
TTP	Time to progression

1. Protocol Synopsis

Title of study:	Venetoclax (ABT-199) in Patients with Chronic Lymphocytic Leukemia: Experience Through the Pre-Approval Access Program in European Countries: A Medical Chart Review
Protocol Number	H17-215
Objectives:	Primary: • The effectiveness of Venetoclax measured as overall response rate (ORR) according to physician assessment at week 36. Secondary: • Overall response rates (ORR) according to physician assessment at 12 months; • Complete response (CR) rates according to physician assessment at 12 months; • Overall survival (OS) at 12 months;; • Time to progression (TTP) at 12 months • Progression free survival (PFS) at 12 months; • Proportion of patients starting treatment in the PAA cohorts and remaining on treatment at week 36; and Adverse events during ramp up and throughout treatment.
Study design:	Retrospective chart review in France, Germany, Netherlands, Sweden and United Kingdom
Target population and study sample:	The target population will be adults who participated in the PAA cohort programs for Venetoclax for the treatment of CLL in the France, Germany, Netherlands, Sweden and United Kingdom and received at least one dose of the treatment. The charts of patients that meet the following eligibility criteria will be included: • Treated with at least one dose of Venetoclax for CLL as part of a PAA treatment within the Venetoclax cohort program (in France, Germany, Netherlands, Sweden and United Kingdom).
Variables	The following data will be collected: • Patient demographics • CLL diagnosis (Criteria, time since diagnosis, etc) • Previous treatments for CLL • Tumor lysis syndrome (TLS) risk prior to initiating treatment with Venetoclax • Venetoclax dosing information and TLS prophylaxis • Treatment outcomes (ORR, CR, OS, PFS, (TTP), Minimal Residual Disease (MRD)
Data sources	Data will be retrospectively extracted from the medical charts of eligible patients.
Study size	The sample size for this study is limited by the extent of the PAA cohort programs for Venetoclax in France, Germany, Netherlands, Sweden and United Kingdom. The target sample for recruitment is 150 patients across all participating countries.

Data analyses	The objective of this retrospective chart review study is descriptive in nature; therefore, no hypothesis testing will be performed. The results of the total study sample will be summarized using descriptive statistics and associated 95% confidence interval; data will be summarized by means, standard deviations, medians, minimums and maximums for continuous variables; and by numbers and percentages for categorical variables. All summarized data will be presented in aggregate, and may be stratified by patient and disease characteristics of interest. Outcomes following Venetoclax treatment will be assessed according to treatment response, TTP, PFS and OS outcomes. Survival will be calculated using Kaplan-Meier survival statistics. The median time to event and rate at 12 months will be calculated together with the 95% confidence intervals. Statistical analyses will be conducted in R.
Sponsor	AbbVie

2. Study Background and Rationale

Venetoclax is a potent, selective inhibitor of B-cell lymphoma (BCL)-2, an anti-apoptotic protein overexpressed by B-cells in chronic lymphocytic leukaemia (CLL) that restores their ability to undergo apoptosis.[1] Venetoclax has been granted conditional marketing authorisation by the European Medicines Agency (EMA) 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; and for the treatment of CLL in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemo immunotherapy and a B-cell receptor pathway inhibitor.[2]

The safety and clinical data supporting this approval is available from Phase 1 and 2 clinical trials in CLL and other hematological indications.

Due to the high unmet need in some patients with relapsed or refractory CLL, Venetoclax was made available in the France, Germany, Netherlands, Sweden and United Kingdomthrough pre-approval access (PAA) programs or compassionate use programs following EMA filing.[3]

Detailed eligibility criteria were specified for the cohort PAA programs, and baseline characteristics were collected to ensure the safe and appropriate use of Venetoclax.[3] The participating physicians were responsible for following the safety reporting guidelines for the PAA cohort programs.

Upon marketing authorization, the PAA cohort programs end according to local regulations and guidelines. At the completion of the PAA cohort programs, all patients continuing to receive Venetoclax transfer to commercial supply and no longer follow the PAA cohort programs guidelines.

The rationale for this retrospective chart review is to obtain additional effectiveness, safety and tolerability and data to complement the early safety data received during the PAA cohort programs. This additional data will provide further understanding regarding the clinical use, treatment management during the Venetoclax ramp up period, treatment duration, effectiveness and tolerability of Venetoclax in a context outside of clinical trials among adult patients with CLL in the presence of 17p deletion or TP53 mutations, or who are unsuitable for or have failed a B-cell receptor pathway inhibitor and for whom there is an unmet medical need.

3. Objectives

The overarching goal of this study is to collect real-world evidence of the effectiveness, safety and tolerability of Venetoclax treatment for CLL from medical charts of patients who received Venetoclax as part of PAA cohort programs in Europe

The primary objective is to describe:

- The effectiveness of Venetoclax measured as overall response rate (ORR) according to physician assessment at week 36

Secondary objectives are to describe:

- ORR and complete response (CR) rates according to physician assessment at 12 months;
- Complete response (CR) rates according to physician assessment at 12 months;
- Overall survival (OS) at 12 months;
- Time to progression (TTP) at 12 months;
- Progression free survival (PFS) at 12 months;
- Proportion of patients starting treatment in the PAA cohorts and remaining on treatment at week 36; and
- Adverse events during ramp up and throughout treatment.

To achieve these objectives, a multi-center retrospective chart review study of patients who started Venetoclax through PAA cohort programs in France, Germany, Netherlands, Sweden and United Kingdomwill be undertaken.

4. Retrospective chart review

4.1. Target Population and Study Sample

The target population will be adults who participated in the PAA cohort programs for Venetoclax for the treatment of CLL in France, Germany, Netherlands, Sweden and United Kingdomand received at least one dose of the treatment. The PAA program commenced in 2016, patients included in this study are at or beyond week 36 at time of initial data collection.

Inclusion Criteria

The charts of patients that meet the following eligibility criteria will be included:

- Treated with at least one dose of Venetoclax for CLL as part of a PAA treatment within the Venetoclax cohort program

Note: Eligible patients for participation in the PAA program included adults with CLL in the presence of 17p deletion or TP53 mutations, or who are unsuitable for or have failed a B-cell receptor pathway inhibitor. and for whom there is an unmet medical need

Exclusion Criteria

No exclusion criteria will be implemented.

4.1.1. Sampling Bias

There is potential for sampling bias to be introduced during site and patient recruitment. The patients are being recruited from a cohort that received treatment with Venetoclax as part of the PAA program; patients from sites that agree to participate in this follow-up study to the PAA cohort program will be included in the study sample. A subset of patients will not be included when sites chose not to participate in the study; therefore, sampling bias may be introduced that will impact the study objectives, particularly objectives aimed at assessing response to treatment and aimed at estimating the number of patients still on treatment at week 36. While sites that decline participation will be asked follow up questions, we anticipate having limited knowledge regarding these patients' use of Venetoclax and the presence of any differences between patients from sites that chose to participate compared to those that did not participate.

4.2. Sample Size

The sample size for this study is limited by the extent of the PAA cohort programs for Venetoclax in France, Germany, Netherlands, Sweden and United Kingdom. Individual centres have treated only a small number of patients within the relevant parameters. The target for recruitment is 150 patients across these countries.

4.3. Study Period

The study accrual process will begin by identifying patients who received Venetoclax treatment as part of a PAA cohort. Due to the low expected number of patients, all eligible patients at a given site will be included in the study sample. Data will be extracted from the charts from prior to first dose of Venetoclax (the state in which the patient met eligibility criteria for inclusion to the Pre-Approval Access cohort program) until 12 months after this first dose, death or loss to-follow up, whichever occurs first. Data will be extracted at up to two different time points: 36 weeks and 12 months post treatment initiation.

4.4. Ethics

Ethics approval will be obtained before the start of data collection according to applicable laws and regulations in each jurisdiction.

This study will be conducted in accordance with the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP).

4.5. Data Collection

4.5.1. Case Report Form

The case report form (CRF) is comprised of two separate forms, for data collection at two points of follow up.

- Form 1: Data collection up to 36 weeks after the first dose of Venetoclax treatment has been received; and
- Form 2: Add-on of data at 12 months after the first dose.

The CRF captures the following data:

	Form 1: Completed at 36 weeks	Form 2: Completed at 12 months
Patient demographics		
Age	√	
Gender	√	
CLL diagnosis		
Time since diagnosis	√	
Stage at diagnosis	√	
Cytogenetics	√	
Previous treatments for CLL		
Time from diagnosis to initial treatment	√	
Prior lines of therapy	√	
• Prior B-cell-antigen receptor signalling inhibitor (BCRi) treatment	√	
Best response achieved with BCRi	√	
Reason for discontinuation of BCRi	√	
Haematopoietic stem cell transplants	√	
Tumor lysis syndrome (TLS) risk prior to initiating treatment with Venetoclax		

	Lymph node involvement;	√	
	Lymphocyte count	√	
	Splenomegaly	√	
	Renal function	√	
	TLS risk status	√	
Venetoclax dosing information and TLS prophylaxis			
	Time on treatment	√	√
	Currently on treatment	√	√
	Hospitalization during dosage ramp-up	√	
	TLS prophylaxis	√	
	Dose reductions	√	√
	Dose interruptions	√	√
	Prolongation of ramp-up	√	
	Maximum dose	√	√
Adverse events (AEs) during treatment*			
	Presence of AEs and SAEs	√	√
	AE type	√	√
	AE time point	√	√
	AE seriousness	√	√
	AE outcome	√	√
	AE causality		
	TLS	√	
Treatment outcomes			
	Treatment response (complete response, complete response with incomplete marrow recovery, partial response, stable disease, progressive disease)	√	√
	Timing of best response	√	√
	Minimal residual disease	√	√
	Venetoclax discontinuation (timing and reason)	√	√
	Time to progression diagnosis (if applicable)	√	√
	Time to death (if applicable).	√	√
	Cause of death and relation to Venetoclax	√	√

*Captured up to 30 days after stopping Venetoclax or when the patient starts another anti-cancer agent, whichever occurs first.

Each CRF will be converted to an Excel® file for data entry. Depending on CRF length, the electronic CRF (eCRF) may be several sheets within a single Excel file. Fields of entry will be, where possible, locked to the required data format. Free text fields will be used only as necessary. In order to collect consistent data, and to assist with data cleaning following data collection, the eCRF will contain a row of dummy data for a sample patient; this will give users entering patient data a template to follow.

4.5.2. Data Extraction

Eligible patient charts will be identified at each site. In jurisdictions where consent is required, living patients or legal representatives of deceased patients will be contacted and provided with the informed consent material, and only charts of patients for whom consent has been obtained will be used in the study.

For eligible patients, data will be retrospectively extracted from the chart capturing data from the time the initiation of Venetoclax (and just before for lab test values) until death, loss to follow up, or 12 months post treatment initiation, whichever occurs first.

Data will be de-identified, with each patient being assigned a subject ID that can only be linked to the patient chart by the site.

Data extraction will be performed by site staff, and the completed CRF will be securely transmitted to ICON. AbbVie will not have access to the source data.

All relevant chart data will be entered into the two Microsoft Excel®-based CRFs.

Each CRF will be completed as eligible patients reach the relevant time point (i.e. 36 and 52 weeks). CRFs for the same patient will be linked through the subject ID.

ICON staff will check data entry for completeness and query sites as necessary to ensure a high data quality.

4.5.3. Secure Data Transfer and Storage

ICON will provide the sites with the CRFs as well as a secure data transfer link through which the completed CRFs can be transmitted to ICON. The completed CRFs will then be stored on ICON's servers, which can only be accessed by authorized staff using a password.

4.5.4. Data Entry Training and Site Management

Before beginning data collection, all sites will receive training in all study protocol and data collection materials. This will include attendance at a group training session via teleconference. ICON staff will be available by email and teleconference to review specific issues and to provide assistance after the initial training session. Sites will also be provided with a training manual detailing the enrolment, data entry and data transfer process.

After the first five charts have been extracted and CRFs transmitted to ICON, the data will be reviewed by the ICON team to determine if any modifications or clarifications are required.

Close-out activities will be performed remotely, via telephone calls to sites. Essential close-out activities include formal communications to sites, query resolution, collection of any study-related materials from sites, and closure of study with the Institutional Review Board (IRB).

4.6. Analysis

A detailed description of the data analysis will be documented in the statistical analysis plan (SAP).

The objective of this retrospective chart review study is descriptive in nature; therefore, no hypothesis testing will be performed. The results of the total study sample will be summarized using descriptive statistics; data will be summarized by means, standard deviations, medians, minimums and maximums for continuous variables; and by numbers and percentages for categorical variables. All summarized data will be presented in aggregate, and may be stratified by patient and disease characteristics of interest (e.g.

age groups, CLL stage). Feasibility of subgroup analysis will be dependent on the number of patients within each subgroup, and any corresponding analysis will be considered exploratory and hypothesis-generating in nature.

Descriptive statistics will be calculated to summarize patient and disease characteristics, treatment patterns and treatment outcomes. Specifically, ramp up management will be described according to the proportion of patients requiring hospitalization during ramp up, the proportion of patients receiving medications to prevent TLS stratified by drug type, and the proportion of patients receiving hydration during ramp up. Venetoclax treatment patterns will be described according to the mean (SD) time on treatment, proportion of patients that had a dose reduction during treatment and the mean (SD) time to reduction, the proportion of patients reaching the pre-specified doses, as well as the proportion of patients discontinuing treatment and reasons for discontinuation.

Outcomes following Venetoclax treatment will be assessed according to ORR, TTP, PFS and OS outcomes. Survival will be calculated using Kaplan-Meier survival statistics. The median time to event and rate at 36 weeks and 12 months will be calculated together with the 95% confidence intervals. Additionally, the proportion of patients on treatment at week 36 will be reported, among those who participated in this follow up study. The proportion of patients experiencing adverse events while receiving venetoclax will be reported including the seriousness and outcome of the AE. Additionally, the proportion of patients experiencing TLS while on treatment will be reported, including the symptoms of TLS and treatments used to treat TLS.

If the data allow, univariate and multivariable regression models will be used to explore and quantify the effects of key patient and disease characteristics on clinical outcomes.

Statistical analyses will be conducted in R.

4.6.1. Missing Data

In accordance with recommended best practices,[4] steps will be taken to minimize the amount of missing data and optimize the integrity of the collected data, by ensuring clarity in the case report form, providing sites with adequate training, ongoing monitoring of entered data, and providing timely communication to site staff who have queries regarding the specifics of data collection. In addition, the case report form will allow for an "unknown" option for all questions, so that if information is missing from a patient's chart this will be made explicit. Data fields which are indicated as "unknown," reflecting missing data in the patient's chart, will be addressed at the analytic stage. All statistics will be restricted to the subset of charts for which the data were available, and the relevant denominator information will be provided in the results tables.

4.6.2. Interim Analyses

An interim analysis will be conducted (

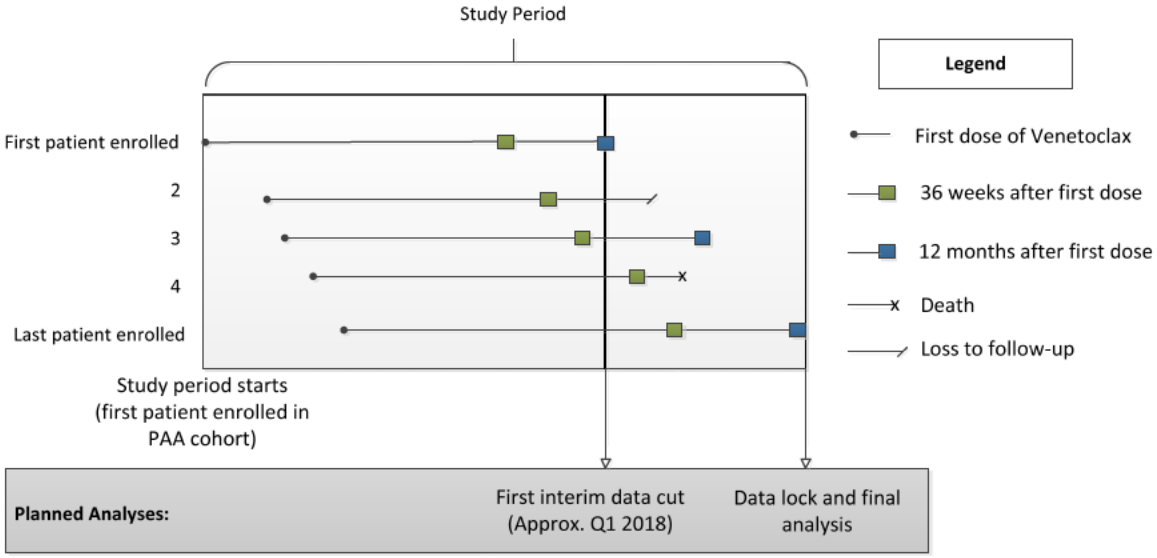

Figure 1). The interim analysis will include all data collected at the time of the interim data cut.

4.6.3. Final Analysis

A final analysis will be conducted when 12 months data has become available for all patients (

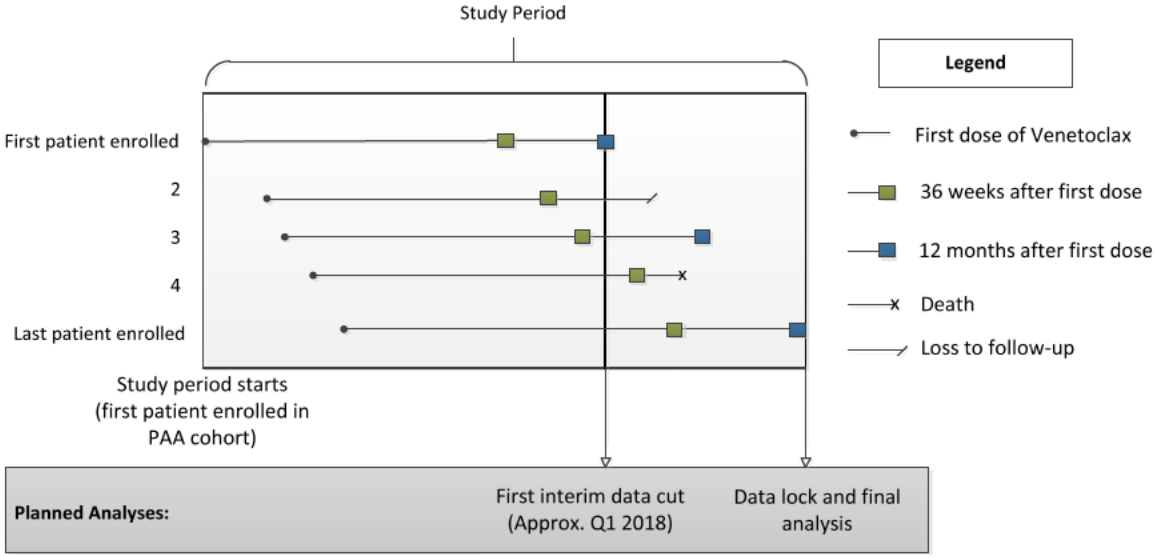

Figure 1). The final analysis will encompass all analyses outlined in the SAP.

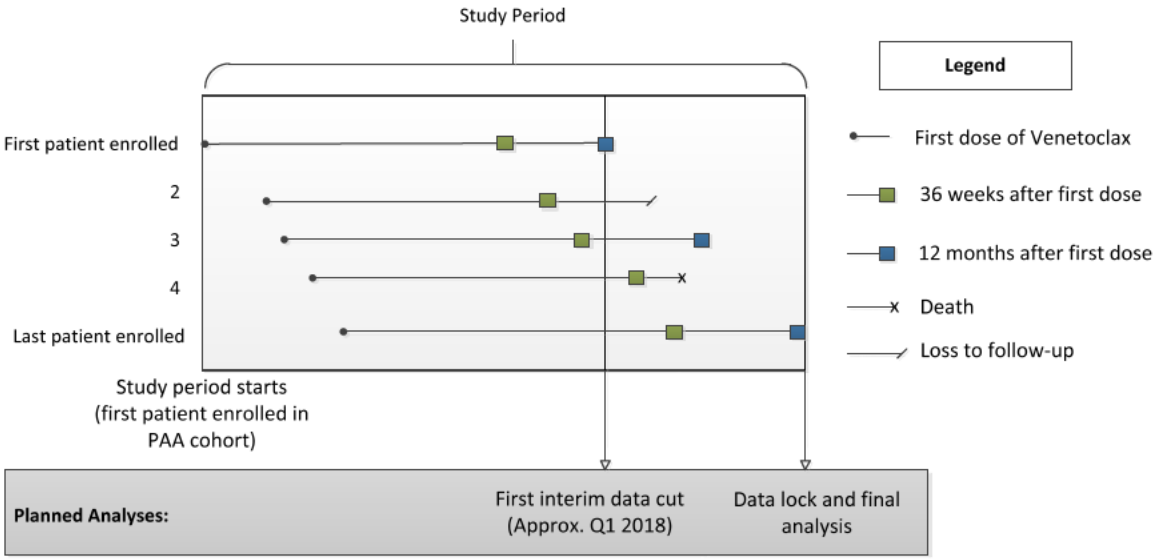

Figure 1. Study period and analysis time points.

4.7. Safety Measures

AEs identified during the chart review will be recorded and summarized in the final study report. AE data will be collected up to 30 days after stopping treatment with Venetoclax, or when the patient initiates another anti-cancer agent, whichever occurs first. These will not require reporting on an individual case basis during the course of the data collection as physicians have already reported during the course of treatment as part of the PAA cohort program.

This study captures and will evaluate secondary data; as such, adverse event data captured as part of this protocol will not be reported as new data to AbbVie pharmacovigilance and is exempt from expedited reporting to Regulatory Agencies as these data have been previously reported during the active period of Pre-Approval Access participation.

5. References

1. Crombie J, Davids MS. Venetoclax for the treatment of patients with chronic lymphocytic leukemia. Future oncology (London, England) 2017.

2. European Medicines Agency. Venclyxto 2016 [Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004106/human_med_002045.jsp&mid=WC0b01ac058001d124.

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4. Wisniewski SR, Leon AC, Otto MW, et al. Prevention of missing data in clinical research studies. Biological psychiatry 2006;**59**(11):997-1000.