4.0 Abstract

Title: Cross-sectional Study Evaluating the Effectiveness of Venetoclax Risk-Minimisation Measures Among Haematologists in Europe

Rationale and Background: Venclyxto (venetoclax), developed by AbbVie and Genentech/Roche, is a first-in-class oral inhibitor of B-cell lymphoma 2 (BCL-2), an anti-apoptotic protein critical to B-cell survival. Venetoclax was initially approved in December 2016 in the European Union (EU) and the United Kingdom (UK) as a monotherapy for the treatment of chronic lymphocytic leukaemia (CLL) in adult patients (European Medicines Agency [EMA], 2016). 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. In 2018, venetoclax was approved in combination with rituximab for adult patients with CLL who have received at least 1 prior therapy and approved in 2020 in combination with obinutuzumab for adult patients with previously untreated CLL. Venetoclax was also approved in combination with a hypomethylating agent for the treatment of adult patients with newly diagnosed acute myeloid leukaemia who were ineligible for intensive chemotherapy in 2021.

Tumour Lysis Syndrome (TLS) has been identified as an important risk for patients with CLL treated with venetoclax. Tumour Lysis Syndrome is a known oncology emergency requiring prompt management of metabolic changes to avoid clinical consequences.

The frequency and severity of TLS is largely mitigated through initiation of venetoclax at a 20-mg dose followed by a dose titration schedule that allows for more controlled killing of tumour cells and gradual debulking of the tumour over the titration period. Prophylaxis measures for TLS include hydration and administration of uric acid reducing agents as well as frequent monitoring of blood chemistries and prompt correction of any abnormalities. More intensive measures may be needed as TLS risk increases.

In May 2021, within the context of a type II variation procedure and at the request of the EMA, the summary of product characteristics (SmPC) was updated and a Direct Healthcare Provider Communication (DHPC) was developed and distributed to increase physicians' awareness and knowledge about risks associated with venetoclax and measures for minimising the risk of TLS. In addition, a patient card was developed and is being distributed to patients to increase awareness and knowledge of the key messages about the risk of TLS associated with venetoclax. AbbVie agreed to evaluate the effectiveness of the DHPC and revised SmPC through the conduct of a physician survey. The current study is being conducted to evaluate the knowledge and use of these materials for the CLL indication due to the risk of TLS in this population.

Research Question and Objectives: The aims of the study are to evaluate physicians' receipt and use of the DHPC, including knowledge among participating haematologists regarding TLS assessment and adherence to the TLS risk-minimisation measures following revisions to the SmPC and dissemination of the DHPC in Europe.

The primary objective is as follows:

- To assess haematologists' knowledge of the following:
  - TLS as a risk of venetoclax treatment for CLL
  - Signs/symptoms of TLS
  - The importance of strict adherence to venetoclax dose titration and TLS risk-minimisation measures as outlined in the SmPC for all patients, including the following:
    - Assessment of patient-specific factors for level of TLS risk, including comorbidities, particularly reduced renal function, tumour burden, and splenomegaly before first dose of venetoclax
    - Administration of prophylactic hydration and antihyperuricemic agents to all patients before first dose of venetoclax
    - Performance of blood chemistry monitoring and tumour burden category assessment
    - Adherence to recommended dose modifications and actions in case of blood chemistry changes or symptoms suggestive of TLS related to venetoclax

The secondary objectives are as follows:

- To ascertain how haematologists receive the DHPC
- To ascertain the number of participating haematologists who did not receive/do not recall receiving the DHPC
- To ascertain the receipt and use of the patient card

Study Design: The study is an observational, cross-sectional survey of knowledge of the risks of TLS for patients with CLL as outlined in the revised SmPC and DHPC for venetoclax among haematologists who have prescribed venetoclax to at least 1 patient with CLL within the past 4 months.

Haematologists will be recruited from an online panel of physicians available for research. An invitation will be sent via email to the selected sample of physicians, inviting them to participate and providing a link to a web-based questionnaire. The questionnaire will begin with screening questions. Those physicians meeting eligibility requirements will review and acknowledge informed consent. Physicians will be asked to complete a one-time questionnaire after providing consent.

Data collection will be initiated in each country several months after the distribution of the DHPC is complete in all countries to allow time for prescribers to have received the DHPC and used the information in their practice and to allow time for study preparation activities.

This study is not designed to assess safety or solicit adverse events (AEs). The survey does not include questions that could potentially identify a safety event or provide free-text fields in which study participants could specify information that may constitute a safety event. However, spontaneous safety events may be communicated by participants during the qualitative cognitive pretesting interviews. The process for AEs reporting will be described further in a brief safety reporting plan.

Population: Countries targeted for approaching physicians for study participation are anticipated to include France, Germany, Spain, Poland, and the UK. Haematologists are eligible to participate if they have prescribed venetoclax to at least 1 patient with CLL within the past 4 months.
Variables: The questionnaire will be based on the revised SmPC Section 4.2 (Posology and Method Of Administration) and 4.4 (Special Warnings and Precautions for Use) and the DHPC available at the time the questionnaire is developed. It will contain closed-ended questions (e.g., multiple choice), with no free-text response fields, eliciting responses measuring physician knowledge of the key information in the revised SmPC and DHPC for venetoclax.
Data Sources: Data will be obtained through self-reported web-based questionnaire responses. Before study implementation, the questionnaire will be tested through cognitive pretest interviews with physicians in each country. The questionnaire will be cognitively tested in local languages to ensure that the introductory material, consent forms, and questionnaire items (question stems and response choices) are culturally appropriate and are easily and correctly understood by physicians similar to those who will participate in the study.
Study Size: The study will target 200 physicians (haematologists) across all countries (approximately 20-50 per country) to allow reasonable precision around estimates of participant knowledge of the safety information regarding TLS.
Data Analysis: The analyses 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. Descriptive tables will be generated for the physicians overall and stratified by country and other identified variables of interest. Analysis tables will include the frequency and percentage of physicians 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). To the extent sample sizes allow, the results for each country will be evaluated and interpreted in the context of the local medical practices and the method and timing of the risk-minimisation measures implementation.
Milestones:
Protocol submission to EMA: Q2 2022 EMA protocol endorsement: To be determined Ethical review as required: Q1 2023 Start of data collection: Q2 2023 End of data collection: Q3 2023 Study progress reports: Annually Registration in the EU PAS Register: Prior to the start of data collection Final report of study results: Q1 2024