FINAL STUDY REPORT OF NON-INTERVENTIONAL POST-AUTHORISATION SAFETY STUDY

PASS Information

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Marketing authorisation holder(s) (MAH):	Kite Pharma EU B.V. Tufsteen 1 2132 NT Hoofddorp The Netherlands
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Joint PASS:	No
Research question and objectives:	The primary study objective was to assess Healthcare Providers' (HCPs) awareness and knowledge of the routine and additional Risk Minimisation Measures (RMMs) addressing the key important identified risks associated with the use of Yescarta and their understanding of the handling and administration of Yescarta. The target population was HCPs from qualified centres in Europe who prescribe, dispense, handle, or administer Yescarta or manage patients experiencing Yescarta-related Adverse Drug Reactions (ADRs) and received training on the additional RMMs. The target groups included HCPs involved in the preparation of Yescarta for administration and patient care.
Country(-ies) of study:	Countries with qualified post marketing centres participated and included Austria, Czech Republic, France, Germany, Italy, the Netherlands, Poland, Spain, Sweden, and the United Kingdom (UK).
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CONFIDENTIAL STATEMENT

1. ABSTRACT

Study KT-EU-471-0116
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Title of Study: Quantitative Testing of Healthcare Provider Knowledge about Yescarta® (axicabtagene ciloleucel) Risk Minimisation Measures

Keywords: Yescarta, risk minimisation measures, cytokine release syndrome, neurologic adverse reactions, healthcare provider survey

Rationale and background: Yescarta, authorised in the European Union (EU) in August 2018, is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after 2 or more lines of systemic therapy. To ensure safe and effective use, Yescarta was authorised with additional Risk Minimisation Measures (RMMs) in the EU. These additional RMMs include educational material targeted for both healthcare providers (HCPs) and patients (patient alert card [PAC]). The primary aim of these additional RMMs is to inform HCPs and patients about important risks associated with Yescarta including cytokine release syndrome (CRS) and serious neurologic adverse reactions, as well as the correct handling and administration of Yescarta. The use of Yescarta is restricted to physicians experienced in the treatment of haematological cancers and that have been trained on the additional RMMs during or after the site qualification process. Another key risk mitigation measure is to ensure that hospitals/clinics treating patients with Yescarta have on-site, immediate access to tocilizumab to manage the risk of CRS.

Research questions and objectives:

The objective of this survey study was to measure the awareness and knowledge of RMMs for Yescarta, as described in the Risk Management Plan (RMP). Specifically, a survey was conducted to measure knowledge and understanding of the key messages in the HCP-directed additional RMMs and the Summary of Product Characteristics (SmPC) for Yescarta, including how to mitigate risk of CRS and neurotoxicity, as well as correct handling and administration of the product to ensure product viability.

The survey:

- Measured the relevant HCPs' knowledge of known important identified risks associated with Yescarta.
- Assessed whether relevant HCPs understood how to identify and treat CRS and serious neurologic adverse reactions.
- Assessed whether the relevant HCPs understood the correct way of handling and administering Yescarta to maintain product viability.
- Assessed whether the relevant HCPs were aware of the PAC, distributed the PAC, and informed patients about the PACs' content.

Setting: The survey was conducted in Austria, Czech Republic, France, Germany, Italy, the Netherlands, Poland, Spain, Sweden, and the United Kingdom (UK).

- **Inclusion Criteria**:
  - HCPs in selected countries who received training on the education materials and prescribed, dispensed, handled, or administered Yescarta, or managed patients experiencing Yescarta-related Adverse Drug Reactions (ADRs).
- **Exclusion Criteria**:
  - HCPs who participated in qualitative pre-testing of the Yescarta survey.
  - HCPs who confirmed they and/or any of their immediate family members worked for Kite Pharma, Inc., Gilead Sciences, Inc., ICON, or the European Medical Agency (EMA).
- **Subgroups:**
  - Country (see list above).
  - HCP specialty: Haematologist/Oncologist, Intensive Care Unit (ICU) Physician, Neurologist, Nurse, Pharmacist, Staff in charge of receipt or handling product.
  - Last time the HCP prescribed, dispensed, handled, administered Yescarta, or treated complications of Yescarta (Less than 1 month ago / 1 to 6 months ago / More than 6 months ago / Don't remember).
  - Number of patients for whom the HCP has prescribed, dispensed, handled, administered Yescarta, or treated complications of Yescarta (None / 1-5 / 6-9 / ≥10).

Study Design: This was a non-interventional, cross-sectional survey of HCPs from 10 European countries who prescribed, dispensed, handled, or administered Yescarta, or managed patients experiencing Yescarta-related ADRs.

Survey data were collected in each local language through self-administered internet-based surveys.

Study size: This survey aimed to collect a minimum of 60 completed HCP surveys (30 HCPs trained regarding the additional RMMs on managing patients experiencing ADRs associated with Yescarta and 30 HCPs trained to understand the correct way of handling and method of administration of Yescarta). A sample size of 60 responders and a target level of HCP awareness for key questions within the survey of 80% allowed the true awareness level to lie within the margin of 67.1% - 92.9%.

Data Sources: The data source for the survey was HCPs who received initial training on the additional RMMs during or after the site qualification process.

Variables collected for analysis: Information on survey administration and eligibility was collected. HCP demographic variables included medical specialty, country, and capacity in which the HCP works and whether they are handling and administering and/or managing patient care and Yescarta-related ADRs.

The primary effectiveness endpoints were the knowledge levels corresponding to the key/essential questions in the survey. Other endpoints were HCPs' knowledge of all other questions on the how to manage the important risks of Yescarta, appropriate handling and administration of Yescarta, and the distribution of all responses to the questions in the survey regarding the key risks of Yescarta, managing the key risks of Yescarta, and appropriate handling and administration of Yescarta.

Data on individual patients treated with Yescarta, or patient-specific outcomes, were not collected.

Statistical methods: Responses to questions for all completed surveys were analysed using descriptive statistics. HCPs' knowledge were evaluated and expressed as number, percentages, and 95% CIs overall, and stratified by subgroups. Survey responses were aggregated and summarised overall in table format. The amount of missing data for each variable was reported. Response rates were reported and characteristics for responders and non-responders were compared based on country. No formal hypothesis testing was conducted, and no adjustments for multiple comparisons were made. An 80% threshold for acceptable level of knowledge for key questions within the survey was used. Key questions within the survey were identified as being essential to measure HCP knowledge of the RMMs.

Results: The primary effectiveness endpoints were the knowledge levels corresponding to 20 key questions covering 5 domains essential to measure HCPs' knowledge of the Yescarta RMMs. CCI [redacted] he knowledge levels for the individual 20 key questions grouped by domain are summarised below:

- Two key questions evaluated HCPs' knowledge of the indication for Yescarta. The majority of HCPs recognized that Yescarta was indicated for the treatment of DLBCL and PMBCL by demonstrating knowledge levels above 80%.
- There were 8 key questions regarding the correct handling, administration, and dispensing of Yescarta and these questions were only applicable for HCPs whose roles were to handle, administer, or dispense Yescarta. For 5 of these 8 questions, knowledge levels met or exceeded the 80% threshold. For 3 out of 8 questions the knowledge levels were below 80%. These 3 questions related to the knowledge about thawing and stability of Yescarta (knowledge that Yescarta should not be thawed at room temperature until there is no visible ice in the infusion bag [knowledge level 66.7%], knowledge that thawing of Yescarta should take approximately 3 to 5 minutes [knowledge level 76.7%], and knowledge that once thawed, Yescarta is not stable at room temperature for up to 10 hours [knowledge level 74.4%]).
- Seven key questions regarding how to identify and treat CRS and serious neurologic adverse reactions were only applicable for HCPs whose roles were to prescribe Yescarta or manage patients who experienced adverse events related to Yescarta. For 4 of these 7 key questions, overall, knowledge levels met or exceeded the 80% threshold. Less than half of HCPs had knowledge that patients were not required to remain in the proximity of the treatment facility for 4 months after the treatment with Yescarta (knowledge level 49.0%). Knowledge that patients who experience Grade 2 or higher neurologic events should be monitored with continuous cardiac telemetry and pulse oximetry was 68.8%. Knowledge of patient restrictions after Yescarta infusion was 70.8%.
- There were 2 key questions regarding the risks associated with the use of Yescarta. These questions were only applicable for HCPs whose roles were to prescribe Yescarta or manage patients who experienced adverse events related to Yescarta. For both questions, knowledge levels exceeded the 80% threshold.
- One question, which was only applicable for HCPs whose roles were to prescribe Yescarta or manage patients who experienced adverse events related to Yescarta, assessed HCPs' awareness of the requirement to provide the PAC to patients. Among HCPs prescribing Yescarta or managing adverse reactions due to Yescarta, 87.8% of HCPs reported providing patients with a copy of the Yescarta PAC.

The results for HCPs' knowledge of all non-key questions on the how to manage the key risks of Yescarta, appropriately handle and administer Yescarta, and inform patients both overall and by country ranged from 32.3% to 100%. Two of these other questions had knowledge levels <50%: knowledge that secondary malignancies are a potential risk (32.3%) and knowledge that that the statement "Patients must be monitored for the first 3 days following the infusion for signs and symptoms of CRS, neurologic adverse reactions, and other toxicities" is not true (32.3%).

Discussion: The measure of success for the primary effectiveness endpoints was that HCPs' knowledge levels for each of the 20 key questions within the survey would be ≥80%. The composite, weighted knowledge level across all 20 key questions was 85.7%, suggesting that overall, HCPs had strong knowledge of the key information about important identified risks associated with Yescarta as well as the knowledge of correct handling and administration of Yescarta.

For 14 of the 20 key questions, the threshold knowledge level was met. For all but 1 of the other 6 key questions, two-thirds or more of HCPs knew the correct information. For the key question where the knowledge level was 49.0%, this was a true/false question "Patients must remain in the proximity of the treatment facility for 4 months after the treatment with Yescarta". The correct answer was false, in that patients should remain in proximity of the treatment facility for 4 weeks, rather than 4 months. However, another 41.7% of HCPs answered this question as "true", which is either a more conservative approach, or, if HCPs were quickly reading the question, this outcome may have been due to simply overlooking the unit of time. Three of the other 6 questions with knowledge levels <80% related to thawing temperature time, and post-thawing stability of Yescarta. This result should be considered in the context of the current guidance for handlers, which is to always have the Kite standard operation procedure (SOP) beside them when performing the thaw, otherwise this level of detail would be challenging to recall for persons who don't handle Yescarta frequently. For 1 of the 2 remaining key questions with a knowledge level <80% (knowledge that Grade 2 or higher neurologic events should be monitored with continuous cardiac telemetry and pulse oximetry), the variability in CAR-T toxicity management practices used among centres may be associated with this survey result.

Few surveys of HCPs have been published regarding practices or opinions on matters surrounding Chimeric Antigen Receptor-T cell (CAR-T) therapies such as Yescarta. Two published studies highlighted the absence of, or the variability in, guidelines related to managed patients receiving CAR-T products. This suggests the possibility that if institutional-level guidelines differ with, or don't have the same details as the Yescarta-specific guidelines, this could have caused some of the lower knowledge levels observed in this survey. This also reinforces the importance of following the Yescarta-specific guidelines, especially for product handling, as the Yescarta-specific instructions are not expected to match more generic CAR-T standard of care guidelines.

A primary limitation of cross-sectional survey studies is selection bias. The impact of selection bias can be minimised through robust outreach to recruit a representative sample. For this survey, the included countries provided a diverse European sample by including countries from various regions of Europe where Yescarta is commercialised. Although the response rate of 11.2% for this Yescarta HCP survey was higher than the pooled response rates reported in the literature, selection bias cannot be excluded.

Conclusion: Results from the study indicate that overall, HCPs' knowledge levels of key information were high in the areas of known important identified risks associated with Yescarta and how to identify and treat CRS and serious neurologic adverse reactions. Furthermore, HCPs' awareness of the PAC and informing patients about the PAC's content was good.

Some knowledge levels were however below the 80% target threshold and were mainly in the domain related to preparation of Yescarta prior to infusion (e.g., thawing procedures). It is not expected that HCPs involved in the management of key risks for Yescarta and not involved in the preparation of Yescarta have a detailed knowledge on the appropriate handling of Yescarta. Furthermore, Gilead/Kite recommends that handlers should have the relevant Kite SOPs beside them when performing the preparation of Yescarta, recognizing this level of detail would be challenging to recall for persons who don't handle Yescarta frequently.

The lower knowledge levels observed for some questions do not negatively impact the safe use of Yescarta and therefore the existing recommendations to minimise these risk are adequate.

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