NI PASS PROTOCOL (PRIMARY DATA COLLECTION)

TITLE:	**EVALUATION OF THE EFFECTIVENESS OF THE ADDITIONAL RISK MINIMISATION MEASURES FOR GLOFITAMAB: A PASS SURVEY AMONG HEALTHCARE PROFESSIONALS IN EUROPEAN COUNTRIES**
PROTOCOL NUMBER:	BO44309
VERSION NUMBER:	3.0
AUTHOR:	[redacted] Senior Clinical Scientist F. Hoffmann-La Roche Ltd | Product Development Oncology-Hematology [redacted] [redacted]* Safety Director, Clinical Safety, Roche Product Ltd Product Development Safety, Clinical Safety Community [redacted] [redacted] Associate Principal IQVIA, Real-World Evidence Solutions, [redacted]
HMA-EMA CATALOGUE OF RW STUDIES NUMBER:	To be registered
STUDIED MEDICINAL PRODUCT:	Columvi™/ Glofitamab
DATE FINAL:	See electronic date stamp below
*The safety strategy of this document has been aligned by [redacted] with the Glofitamab Safety Strategy Leader [redacted].	

FINAL PROTOCOL APPROVAL

ACTIVE SUBSTANCE:	ATC Code: L01FX28 Generic Name: Glofitamab
PRODUCT REFERENCE NUMBER:	Not applicable
PROCEDURE NUMBER:	EMEA/H/C/005751
JOINT PASS:	No
RESEARCH QUESTION AND OBJECTIVES:	The aim of this study is to evaluate, through a self-reported survey, the effectiveness of the additional Risk Minimisation Measures (aRMMs) included in the Risk Management Plan (RMP) for Glofitamab in terms of key process indicators. In this study key process indicators encompass prescribers' awareness of the Educational Materials (EMs), knowledge/comprehension of important identified risk (Tumour flare) and adherence with respect to the safety messages in the Health Care Professional (HCP) brochure. The primary objectives are: 1. To assess prescribers' awareness of the Glofitamab EMs by estimating the proportion of prescribers who acknowledge having received the EMs and read the HCP brochure. 2. To assess prescribers' knowledge of the risk of Tumour flare (TF) that may occur with Glofitamab use and on the specific guidance for risk minimisation measures for TF, as described in the HCP brochure, by estimating the proportion of prescribers with correct responses to the risk knowledge questions. 3. To assess prescribers' adherence with respect to the aRMMs by estimating the proportion of prescribers whose responses to the practice-related questions are consistent with the guidance provided in the HCP brochure.
COUNTRIES OF STUDY POPULATION:	11 European countries: Austria, Belgium, Bulgaria, Croatia, France, Germany, Greece, Italy, Portugal, Norway, Sweden
MARKETING AUTHORISATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany
MAH CONTACT PERSON:	[redacted], Senior Clinical Scientist

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Events
aRMMs	additional Risk Minimisation Measures
ASCT	Autologous Stem Cell Transplantation
CAR T- cell	Chimeric Antigen Receptor T-cell
CI	Confidence Interval
CR	Complete Response
CRS	Cytokine Release Syndrome
DLBCL	Diffuse Large B-cell Lymphoma
EDC	Electronic Data Capture
EEA	European Economic Area
EMA	European Medicines Agency
EMs	Educational Materials
EU	European Union
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EphMRA	European Pharmaceutical Marketing Research Association
GemOx	Gemcitabine and Oxaliplatin
GVP	Good Pharmacovigilance Practices
HCP	Health Care Professional
HMA	Heads of Medicine Agencies
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
MAH	Marketing Authorisation Holder
NHL	Non-Hodgkin's Lymphoma
NI	Non-interventional
PASS	Post-Authorisation Safety Study
Pola-R-CHP	Polatuzumab Vedotin-Rituximab- Cyclophosphamide, Doxorubicin, Prednisolone
PRAC	Pharmacovigilance Risk Assessment Committee
R-CHOP	Rituximab- Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone
RMP	Risk Management Plan
R/R	Relapsed or Refractory
TF	Tumour Flare
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SmPC	Summary of Product Characteristics
SOPs	Standard Operating Procedures
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
US	United States

2. RESPONSIBLE PARTIES

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3. SYNOPSIS

TITLE:	**EVALUATION OF THE EFFECTIVENESS OF THE ADDITIONAL RISK MINIMISATION MEASURES FOR GLOFITAMAB: A PASS SURVEY AMONG HEALTHCARE PROFESSIONALS IN EUROPEAN COUNTRIES**
PROTOCOL NUMBER:	BO44309
VERSION NUMBER:	3.0
DATE OF SYNOPSIS:	27 October 2025
HMA-EMA CATALOGUE OF RW STUDIES NUMBER:	To be registered
STUDIED MEDICINAL PRODUCT:	Columvi™ / Glofitamab
SCIENTIFIC RESPONSIBLE	[redacted], Safety Strategy Leader
MAIN AUTHOR:	[redacted], Clinical Safety Director
PHASE:	IV, non-interventional study
INDICATION:	CD20-positive B-cell non-Hodgkin lymphomas, including diffuse large B-cell lymphoma and follicular lymphoma, and other blood cancers
MARKETING AUTHORISATION HOLDER:	Roche Registration GmbH Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany

Rationale and Background

Non-Hodgkin's lymphoma (NHL) is the most common haematological malignancy disease worldwide. The most frequent sub-type of NHL is Diffuse large B-cell lymphoma (DLBCL) representing 30% of the cases.

For over two decades, the combination of the monoclonal antibody rituximab with a regimen of 4 drugs (cyclophosphamide, doxorubicin, vincristine, and prednisolone) (R-CHOP) has been the standard first-line treatment for DLBCL. Since 2021, Pola-R-CHP, a regimen that substitutes vincristine with polatuzumab vedotin, has emerged as a new first-line option. However, more than 40% of patients with DLBCL either relapse or are refractory to the first-line treatment. Most patients with DLBCL that were relapsed or refractory (R/R) on first-line are ineligible for the second-line treatment, i.e., chemoimmunotherapy followed by consolidative autologous stem cell transplantation (ASCT). Moreover, from those who received a second-line treatment, 45% will proceed to a third-line treatment.

Bispecific antibodies are the emerging third-line or later (3L+) treatment for patients with R/R DLBCL. Glofitamab is an IgG1 fully humanised anti-CD20xCD3 bispecific

monoclonal antibody with a '2:1' structure. This dual targeting structure activates and redirects T-cells to engage and eliminate target B-cells by realising cytotoxic proteins into the B-cells.

Data from a phase I/II clinical trial (NP30179) demonstrated that Glofitamab monotherapy is able to induce durable complete response (CR) when administered intravenously for a fixed treatment duration of maximum 12 cycles to patients with R/R DLBCL who had received at least two prior therapies. In the global phase III STARGLO open-label trial (GO41944), Glofitamab in combination with gemcitabine and oxaliplatin (GemOx) demonstrated durable efficacy in patients with R/R DLBCL ineligible for ASCT who have received at least one prior therapy.

Glofitamab was well tolerated by patients, with an overall favourable safety profile. Cytokine release syndrome (CRS) was the most common adverse event (AE) occurring in 67.6% of patients treated with Glofitamab monotherapy and in 44.2% of those receiving Glofitamab with GemOx, with most cases being grade 1 or 2. Additionally, immune effector cell-associated neurotoxicity syndrome (ICANS), was observed in 4.8% of patients treated with monotherapy and in 2.3% of those on the combination regimen, with most cases being grade 1 or 2.

Another reported AE was Tumour flare (TF), which occurred in 11.7% of patients in Glofitamab monotherapy (all grades) and in 1% (grade $\geqslant$ 2) of those patients in Glofitamab in combination with GemOx. Depending on the size and location of the tumour, TF may result in effects on surrounding structures that can compromise organ function. Despite potential severe clinical consequences when TF occurs, this phenomenon is poorly understood, misinterpreted as disease progression, and poorly recognised by HCPs. Therefore, there is a need to increase HCP awareness of TF, as early identification and treatment of TF is critical.

On 7 July 2023, Glofitamab (Columvi™) monotherapy received from the European Medicines Agency (EMA) a conditional marketing authorisation valid throughout the European Union (EU) to treat adults with DLBCL whose cancer has returned (relapsed) or stopped responding (refractory) after at least two previous treatments. More recently in April 2025, EMA expanded the authorisation of Glofitamab for use in combination with GemOx, as a second-line treatment in patients with earlier R/R DLBCL who are ineligible for ASCT. The Marketing Authorisation Holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed Risk Management Plan (RMP).

Additional risk minimisation measures (aRMMs) were required to manage the important identified risks of CRS, ICANS and TF associated with the use of Glofitamab. The proposed aRMMs include Educational Materials (EMs) in the format of a Patient Card for patients (for the important identified risk of CRS and ICANS) and a Health Care Professional（HCP) brochure for prescribers (for the important identified risk of TF).

This study focuses on the important identified risk of TF for Glofitamab and its aRMMs, in the form of an HCP brochure. The HCP brochure is intended to educate and increase HCP awareness and understanding of the key signs and symptoms of TF so that HCPs can identify and manage the risks in a timely and appropriate manner.

Therefore, the study aims to evaluate the effectiveness of the HCP brochure on physicians prescribing Glofitamab to ensure that prescribers are able to recognise early signs and symptoms of TF and provide appropriate management.

To fulfil a Category III Post-Authorisation Safety Study (PASS), the MAH proposed a non-interventional (NI) PASS through an HCP survey as detailed in the RMP for Glofitamab, to evaluate the effectiveness of the aRMMs. The survey will assess awareness, knowledge, and adherence of Glofitamab prescribers to the aRMMs plan.

Research Question and Objectives

The study aims to evaluate, through a self-reported survey, the effectiveness of the aRMMs included in the RMP for Glofitamab in terms of key process indicators. In this study key process indicators encompass prescribers' awareness of the EMs, knowledge/comprehension of the important identified risk of TF and adherence with respect to the safety messages in the HCP brochure.

The primary objectives are:

1. To assess prescribers' awareness of the Glofitamab EMs by estimating the proportion of prescribers who acknowledge having received the EMs and read the HCP brochure.
2. To assess prescribers' knowledge of the risk of TF that may occur with Glofitamab use and on the specific guidance for risk minimisation measures for TF, as described in the HCP brochure, by estimating the proportion of prescribers with correct responses to the risk knowledge questions.
3. To assess prescribers' adherence with respect to the aRMMs by estimating the proportion of prescribers whose responses to the practice-related questions are consistent with the guidance provided in the HCP brochure.

The secondary objective is:

1. To assess whether the prescribers self-reported the HCP brochure as useful for their clinical practice.

Study Design

This study will use primary data collection via a web-based questionnaire of HCPs (oncologists/haematologists/haematologist-oncologists/others, in countries where applicable only) who have prescribed Glofitamab. The self-reported survey will be an anonymous, cross-sectional, multinational, conducted in 11 countries within the European Economic Area (EEA).

Description of Study

The survey will assess prescribers' awareness, knowledge and adherence to the aRMMs for Glofitamab. The HCP survey shall be conducted using a staggered approach, depending on the Glofitamab implementation of the updated EMs per country. The data collection is expected to start in Q2 2026 to allow enough time in each country for the implementation of the local aRMMs for at least 12 months. Fieldwork/data collection is planned for a 6-month period, consisting of 3 months of active data collection in each country with the possibility of extending for an additional 3 months if the target sample size is not achieved.

Studied Medicinal Product

Glofitamab (Columvi™) is an antineoplastic agent presented in 2.5 mg and 10 mg concentrate solution for infusion into a vein. The product regimen lasts 4 hours for the first 2 cycles and 2 hours for subsequent infusions, depending on the side effects. Each cycle lasts 21 days and the medicine is given for up to 12 cycles or until the disease gets worse or side effects become unacceptable.

Population

HCPs from geographically dispersed countries within the EEA (Austria, Belgium, Bulgaria, Croatia, France, Germany, Greece, Italy, Portugal, Norway, and Sweden) where Glofitamab is approved and reimbursed will be targeted for participating to this survey.

The study population will be restricted to physicians (oncologists/haematologists/haematologist-oncologists/others) who meet the following inclusion criteria for study entry:

- Having prescribed Glofitamab to patients with R/R DLBCL in routine clinical practice, i.e., outside of the context of a clinical trial/ post-approval programmes/ compassionate use programmes at least once in the last 12 months prior taking the survey. Therefore, HCPs who have prescribed Glofitamab exclusively in the context of clinical trials, i.e., who have no experience in prescribing the drug in clinical practice, will not be included in the study.
- Willing to participate in the survey.

Physicians who meet any of the following exclusion criteria will be excluded from study entry:

- Inactive and retired prescribers.
- Those who are not involved in patient treatment (e.g., insurance prescribers).
- Those who declare having a conflict of interest with the survey (i.e., prescribers employed by regulatory bodies, Roche, IQVIA, etc).

Variables

Variables related to participation in the study:

- Response to study invitation: non-response, acceptance, refusal
- Response to screening questions
- Response to questionnaire: partially complete, complete
- Country of practice

Variables related to prescriber's characteristics:

- Practice information: primary specialty, duration of practice in primary specialty
- Involvement as investigator in clinical trials regarding Glofitamab
- Past experience with Glofitamab: number of patients treated, time since last prescription

Variables related to the prescriber's awareness of the Glofitamab EMs:

- Receipt of Glofitamab EMs (HCP brochure, Patient Card) (yes, no, I do not remember)
- Access to Glofitamab EMs from other sources (hospital's website, Roche's website, National Regulatory Agency website, others, no)
- Reading Glofitamab HCP brochure (yes, no)

Variables related to the prescriber's knowledge/comprehension of the risk of TF associated with the use of Glofitamab:

- Knowledge/comprehension of TF (true and false statements)
- Knowledge/comprehension of risk of TF associated with the use of Glofitamab (true and false statements)
- Knowledge/comprehension of the specific guidance for minimising the risk of TF, as described in the HCP brochure (tick boxes)

Variables related to the prescriber's adherence to the safety measures in the HCP brochure:

- Distribution of the Patient Card to patients receiving Glofitamab (yes, no)
- Counselling of patients to carry the Patient Card (yes, no)
- Inform patients on the risk of CRS and ICANS associated with use of Glofitamab (yes, no)
- Inform patients to seek medical attention immediately if they have any CRS symptom and ICANS symptom (yes, no)
- Evaluate the lymphoma distribution to anticipate the potential spectrum of clinical manifestations of TF (yes, no)

Variables related to the usefulness of Glofitamab HCP brochure:

- Use of the HCP brochure as a source to gain awareness and knowledge of TF (yes, no)
- Use of other source to gain awareness and knowledge of TF (Summary of Product Characteristics (SmPC), Columvi™/Glofitamab website, guidelines, scientific literature, scientific conference materials, internet, others, no)

Data Sources

The survey represents primary data collection from Glofitamab prescribers conducted through a web-based questionnaire. Answers will be submitted anonymously and collected using a secure electronic data capture system that will be used to create the dataset for analysis.

The OneKey™ database will be used to identify and recruit oncologists/haematologists/haematologist-oncologists/others in the selected countries. The OneKey™ is a large and comprehensive worldwide database of HCPs.

Study Size/Determination of Sample Size

In this study 120 HCPs will be surveyed across 11 countries within the EEA, which will allow a margin of error of 7.2% with a 95% confidence interval (CI) to detect a proportion of interest of 80%. Assuming a participation rate of 5%, at least 2400 HCPs will be invited to complete the questionnaire to achieve the sample size. However, as the

universe of Glofitamab prescribers in each country is unknown, at the time of the survey, the sample size may need to be adjusted.

For each selected country, the survey sample will include HCPs identified from OneKey™ lists. The potential contactable respondents will be randomly selected and a pragmatic split by country will be implemented to ensure that a sufficient size of participants is allocated in the smaller countries.

Data Analysis

All the analyses will be descriptive, and no comparative analysis will be reported. The statistical results will be presented by prescribers' specialty and per country (if possible, given the number of respondents), and overall.

Continuous variables will be described by their mean, standard deviation, and median, first quartile (Q1), third quartile (Q3), minimum and maximum. Categorical variables will be described as the total number and relative percentage per category. CI of 95% will be evaluated, when applicable. The analysis of participation rate will be conducted reporting response rate, partial response rate and refusal rate. The analysis of questionnaires will be conducted using completed questionnaires submitted by the participants. Specifically, the proportions of answers among participants will be evaluated by reporting the frequency of each option provided by the participants. Success of the aRMMs for HCPs is defined as an 80% threshold based on the percentage of prescribers classified as aware of, knowledgeable about and/or adherent to the aRMMs. Overall results will be presented both unweighted (results obtained from raw data) and weighted. A weight variable will be applied to each statistical unit (i.e., the HCPs) during the results calculation to correct any over- or under-sampling that may have occurred for a country. This weight variable will indicate how many unit(s) of the population of interest an observation will count in a statistical procedure. Its value will change per country.

Milestones

Start Date of Study:

The study is planned to start by Q2 2026, which is the period of the implementation of data collection of the HCP survey.

End of Study

The study is planned to end by Q4 2026, which is the last period of data collection of the HCP survey.

Length of Study

This study will last 6 months with a fieldwork comprising an initial 3 month of data collection in each country, with a possible extension of 3 additional months.

The final study report is planned for submission to EMA in Q4 2027.

4. PROTOCOL AMENDMENTS AND UPDATES

Any protocol amendments will be prepared by the Marketing Authorisation Holder (MAH) or designee.

Protocol amendments will be submitted to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from regulatory authorities (as locally required) before implementation of any changes, except for changes that involve logistical or administrative aspects only (e.g., change in contact information).

The amendments/updates to version 2.0 of the study protocol dated 05 July 2024, approved by the Pharmacovigilance Risk Assessment Committee (PRAC), are summarised in the table below.

Protocol version (date)	Section of the protocol	Amendment or update	Reason
V3.0 (27 October 2025)	• Title page • 3. Synopsis	• Changed registry website name from EU PAS to HMA-EMA Catalogue. • MAH contact person update.	Administrative changes
V3.0 (27 October 2025)	• 3. Synopsis • 6.1 Study rationale • 6.2 Study Background • 8.3.2 Variables from questions in the HCP questionnaire • 8.7.4.2 Assessment of success • Appendix 2 • Appendix 3 (Question 13 and 14)	• References to ICANS were added throughout the protocol to reflect its inclusion as an additional important identified risk for Glofitamab. • A sentence, summarising study results related to the occurrence of ICANS in patients treated with Glofitamab, was added to provide context in the background section. • ICANS was incorporated into two questions (13 and 14) assessing adherence to the information provided in the HCP brochure.	The inclusion of ICANS as an additional important identified risk for Glofitamab, based on the PRAC recommendation dated 11 July 2024, led to updates in the EMs* and impact relevant sections of the protocol and questionnaire. *The Patient Card was updated to include information on ICANS, its symptoms, and warning for the treating physician. The HCP brochure was revised accordingly to reflect the new content in the Patient Card and to mention ICANS as an important identified risk associated to Glofitamab.
V3.0 (27 October 2025)	• 3 Synopsis • 5. Milestones	• The study milestones have shifted, with the start of data collection moved from 2025 to 2026, and	Updates to the EMs to include ICANS affected study timelines. This is because data collection

Protocol version (date)	Section of the protocol	Amendment or update	Reason
	• 8.1.1 Overview of the study design • Figure 1 • 8.4.2 Collection of Data • Table 1 • 8.7.6 Interim/Final Analysis and Timing of Analysis	the final study report rescheduled from 2026 to 2027. • The reimbursement dates and distribution periods for EMs were updated based on the most recent information available for each country.	should start within 12-18 months following the implementation of the local aRMMs, i.e., distribution of the Glofitamab updated EMs in each country.
V3.0 (27 October 2025)	• 3 Synopsis • 6.1 Study rationale • 6.2 Study Background	Updated information has been added to the study rationale and background.	• Updated information has been added to reflect: - A new first-line regimen has emerged for DLBCL. - Recent approval (2025) of Glofitamab in combination with other cancer drugs (GemOx). - Update the rates of CRS and ICANS for Glofitamab monotherapy and Glofitamab with GemOx.
V3.0 (27 October 2025)	• Title page • 3 Synopsis • 8.1.1 Overview of the study design • Figure 1 • 8.2 Setting • 8.2.1 Countries • 8.4.2 Collection of Data • Table 1 • Table 4	• The list of countries was updated to remove Spain and add France and Portugal, increasing the total from 10 to 11 countries. • The study title has been revised to remove the reference to the number of countries.	The list of countries was revised based on the most current information regarding reimbursement timelines and distribution of EMs. Spain was removed due to the absence of reimbursement expectations at the time of this protocol amendment and was replaced by Portugal and France, where EMs have already been distributed.
V3.0 (27 October 2025)	• Synopsis • 8.1.1 Overview of the study design	Data collection will now occur in a single continuous phase rather than two separate waves (3 months each). The study fieldwork duration	This change was made because the EMs have been currently distributed within a similar timeframe across

Protocol version (date)	Section of the protocol	Amendment or update	Reason
	• Figure 1 • 8.4.2 Collection of Data	remains at 6 months—comprising 3 months of active data collection per country and an additional 3 months if the target sample size is not reached.	participating countries, removing the need for a wave-based data collection approach.
V3.0 (27 October 2025)	• Synopsis • 8.5 Study Size • Table 2 • Table 3	• Table 2 has been updated with corrected values based on the sample size formula, and a new row reflecting an 80% proportion of interest has been added. • A new column reflecting an 80% proportion of interest has been added in Table 3.	Discrepancies were identified in the values presented in Table 2, which did not align with the sample size formula. To ensure consistency the values were updated accordingly. Data for the 80% proportion of interest was added to both tables to enhance completeness.
V3.0 (27 October 2025)	• All sections • 12 References • Appendix 3	• Stylistic and formatting updates • SmPC reference has been updated • The instructions for Question 6 were revised to ensure accurate logic to the follow-up Question 6a.	To be aligned with the content that has changed in the protocol.

CRS=Cytokine Release Syndrome; EM=Educational Materials; GemOx=Gemcitabine and Oxaliplatin; HCP=Health Care Professional; ICANS=Immune Effector Cell-Associated Neurotoxicity Syndrome; PRAC=Pharmacovigilance Risk Assessment Committee; SmPC=Summary of Product Characteristics

5. MILESTONES

Study milestones are given in the following table.

Milestone	Planned Date
Registration of protocol in the HMA-EMA Catalogue of real-world data sources and studies	After endorsement of the protocol and before start of data collection
Start of data collection	Q2 2026
End of data collection	Q4 2026
Final report of study results	Q4 2027
Registration of the results in the HMA-EMA Catalogue of real-world data sources and studies	After approval of the final report

HMA=Heads of Medicine Agencies; EMA=European Medicines Agency

6. RATIONALE AND BACKGROUND

6.1 STUDY RATIONALE

Non-Hodgkin's lymphoma (NHL) is the most common haematological malignancy disease worldwide with more than 30 subtypes (Padala and Kallam 2023). In 2020, the estimates accounts for 72,035 new cases of NHL in Western Europe and 73,652 in the United States (US) (Kanas et al. 2022). Worldwide, the NHL incidence is 5,4 cases and 2,6 deaths per 100,000 population (GLOCAN 2020). The most frequent sub-type of NHL is Diffuse large B-cell lymphoma (DLBCL) representing 30% of the cases (Perry et al. 2016). The patients median age at DLBCL diagnosis is around 64 years (Perry et al. 2016) and accompanying the ageing population growth the 10-year prevalence of DLBCL is projected to increase by 7% in the European Union (EU) and 11% in the US (Kanas et al. 2022).

The disease, DLBCL, is characterised by a clonal proliferation of a germinal or post-germinal malignant B-cell (Susanibar-Adaniya and Barta 2021). Typically, patients have the DLBCL diagnosis at advanced stages (stages III or IV) with the presence of a rapidly growing mass or enlarging lymph nodes in a nodal or extra nodal site (Padala and Kallam 2023).

For over two decades, the combination of the monoclonal antibody rituximab with a regimen of 4 drugs (cyclophosphamide, doxorubicin, vincristine, and prednisone) (R-CHOP) has been the standard first-line treatment for DLBCL (Brusamolino 2009). Since 2021, Pola-R-CHP, a regimen that substitutes vincristine in R-CHOP with polatuzumab vedotin, has emerged as a new first-line treatment option. However, more than 40% of patients with DLBCL either relapse or are refractory to the first-line treatment (Karlin and Coiffier 2013), and recent data suggest that Pola-R-CHP does not significantly reduce the proportion of patients who develop primary refractory disease or experience early relapse compared to R-CHOP (Bock and Epperla 2025). Most patients with DLBCL that were relapsed or refractory (R/R) on first-line are ineligible for the second-line treatment, i.e., chemoimmunotherapy followed by consolidative autologous stem cell transplantation (ASCT) (Sawalha 2021). Moreover, from those who received a second-line treatment, 45% will proceed to a third-line treatment (Halwani et al. 2019).

Nonetheless, around 47% of eligible patients for third-line or later therapies (3L+) in the EU and 44% in the US did not initiate treatment (Kanas et al. 2022).

Until recently, the chimeric antigen receptor T-cell (CAR T-cell) product was the only third-line treatment choice for patients with DLBCL who are chemoresistant, ineligible for ASCT or whose disease progresses or relapses after ASCT. However, due to significant toxicities with serious adverse effects its use is limited for unfit patients with comorbidities and for those patients with very aggressive disease that does not allow them to wait for the CAR T-cell product manufacturing (Sawalha 2021). Also, only 40% of the patients are expected to achieve complete response (CR) with CAR T-cell treatment (Schuster et al. 2019; 2021).

Bispecific antibodies are the emerging third-line or later (3L+) treatment for patients with R/R DLBCL (Sawalha 2021). Glofitamab is an IgG1 fully humanised anti-CD20xCD3 bispecific monoclonal antibody with a '2:1' structure, i.e., 2 binding sites for CD20 on B-cells and one site for CD3 on T-cells. This dual targeting structure activates and redirects T-cells to engage and eliminate target B-cells by releasing cytotoxic proteins into the B-cells (Bacac et al. 2018; Sawalha 2021).

A robust clinical development programme for Glofitamab is ongoing, investigating the molecule as a monotherapy and in combination with other medicines, for the treatment of people with CD20-positive B-cell NHL, including DLBCL and follicular lymphoma, and other blood cancers.

Glofitamab monotherapy begins in a step-up dosing schedule (2.5 mg cycle 1 day 8 and 10 mg cycle 1 day 15), leading to the recommended dose of 30 mg (cycle 2 and later ones). In the first 2 cycles, the infusion takes 4 hours and for the following cycles 2 hours. Each cycle lasts 21 days, and treatment is given for up to 12 cycles or until the patient discontinuation due to progressive worsening disease or occurrence of serious adverse effect (EMA 2025a; Roche 2025). In the combination regimen, Glofitamab is administered with gemcitabine and oxaliplatin (GemOx) at cycles 1-8 and as monotherapy at cycles 9-12. For more information on Glofitamab, please refer to the most recent version of the Summary of Product Characteristics (SmPC) (Roche 2025).

Data from a phase I/II clinical trial (NP30179) demonstrated that Glofitamab monotherapy is able to induce durable CR when administered intravenously for a fixed treatment duration of maximum 12 cycles to patients with R/R DLBCL who had received at least two prior therapies. At a median follow-up of 12.6 months, 39% of patients (61/155) achieved a CR and 52% (80/155) had an overall response rate. Responses were achieved early, with a median time of 42 days to the first CR (Dickinson et al. 2022). In the global phase III STARGLO open-label trial (GO41944), Glofitamab in combination with GemOx demonstrated durable efficacy in patients with R/R DLBCL ineligible for ASCT who have received at least one prior therapy. With 2-year follow-up, the CR rate was 58.5%, and the median progression-free survival was 13.8 months (Abramson et al. 2024).

Glofitamab was well tolerated by patients, with an overall favourable safety profile. In patients treated with Glofitamab monotherapy (n=145), cytokine release syndrome (CRS) was the most common adverse event (AE) occurring in 67.6% of patients. CRS events were generally low grade (50.3% grade 1 and 13.1% grade 2), had a predictable time of onset and occurred mostly at initial doses. Incidence of grade ≥3 CRS was low (4.2%), with no grade 5 events. Additionally, immune effector cell-associated neurotoxicity syndrome (ICANS), were observed in 7 patients (4.8%), the majority were grade 1 or 2 and considered unrelated to Glofitamab study treatment (EMA 2025b;

Roche 2025). In patients treated with Glofitamab in combination with GemOx, CSR occurred in 44.2% patients (76/172), most were low grade (31.4% grade 1 and 10.5% grade 2), and no grade 4 or fatal events were observed. ICANS events were reported in 2.3% patients (4/172); most were grade 1 or 2 (2% patients), with one patient with a grade 3 event (delirium) (EMA 2025b; Roche 2025).

Another reported AE was Tumour flare (TF), which occurred in 11.7% of patients in Glofitamab monotherapy (all grades), with no life-threatening or fatal cases (Dickinson et al. 2022; Roche 2025) and in 1% (grade $\geqslant$ 2) of those patients in Glofitamab in combination with GemOx (Abramson et al. 2024). TF is characterised by volumetric enlargement of tumour sites, usually during the early cycles of treatment, mimicking disease progression (Taleb, 2019). Depending on the size and location of the tumour, TF may result in effects on surrounding structures that can compromise organ function, such as dyspnoea due to airway compression, pleural or pericardial effusion, and haemorrhage or perforation if major blood vessels or highly vascularised areas are involved.

TF occurrence has been frequently associated with haematologic malignancies, and with the use of immunomodulatory agents and immune checkpoint inhibitors (Taleb, 2019). The influx of immune cells into tumour sites in response to Glofitamab treatment may lead to TF. Life-threatening or fatal cases associated with TF have been reported as rare (Taleb, 2019). Despite potential severe clinical consequences when TF occurs, this phenomenon is poorly understood, misinterpreted as disease progression, and poorly recognised by HCPs. Therefore, there is a need to increase HCP awareness of TF, as early identification and treatment of TF is critical.

CRS, ICANS and TF were considered important identified risks associated with the use of Glofitamab that require additional risk minimisation measures (aRMMs). Therefore, aRMMs in the form of Educational Materials (EMs) have been proposed in the EU Risk Management Plan (RMP) for Glofitamab. The proposed aRMMs include EMs in the format of a Patient Card for patients (for the important identified risk of CRS and ICANS) and a Health Care Professional (HCP) brochure for prescribers (for the important identified risk of TF). The aim of the HCP brochure is to increase the likelihood of early recognition of TF and to reduce the impact of TF in patients treated with Glofitamab.

6.2 STUDY BACKGROUND

On 7 July 2023, Glofitamab (Columvi™) monotherapy received from the European Medicines Agency (EMA) a conditional marketing authorisation valid throughout the EU to treat adults with DLBCL whose cancer has returned (relapsed) or stopped responding (refractory) after at least two previous treatments, establishing its use as a third-line treatment (EMA 2025a). More recently in April 2025, EMA expanded the authorisation of Glofitamab for use in combination with GemOx, as a second-line treatment in patients with earlier R/R DLBCL who are ineligible for ASCT. The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP.

The aRMMs were required to manage the important identified risks of CRS, ICANS and TF associated with the use of Glofitamab in addition to the product labelling. This study focuses on the important identified risk of TF for Glofitamab and its aRMMs, in the form of an HCP brochure. The HCP brochure is intended to educate and increase HCP awareness and understanding of the key signs and symptoms of TF so that HCPs can identify and manage the risks in a timely and appropriate manner.

Therefore, the study aims to evaluate the effectiveness of the HCP brochure on physicians prescribing Glofitamab to ensure that prescribers are able to recognise early signs and symptoms of TF and provide appropriate management. To fulfil a Category III Post-Authorisation Safety Study (PASS) study, the MAH proposed a non-interventional (NI) PASS through an HCP survey as detailed in the EU RMP for Glofitamab, to evaluate the effectiveness of the aRMMs. The survey will assess awareness, knowledge, and adherence of Glofitamab prescribers to the aRMMs plan.

7. RESEARCH QUESTION AND OBJECTIVES

7.1 RESEARCH QUESTION

The study aims to evaluate, through a self-reported survey, the effectiveness of the aRMMs included in the RMP for Glofitamab in terms of key process indicators. In this study key process indicators encompass prescribers' awareness of the EMs, knowledge/comprehension of the important identified risk of TF and self-reported adherence with respect to the safety messages in the HCP brochure.

7.2 OBJECTIVES

The primary objectives are:

1. To assess prescribers' awareness of the Glofitamab EMs by estimating the proportion of prescribers who acknowledge having received the EMs and read the HCP brochure.
2. To assess prescribers' knowledge of the risk of TF that may occur with Glofitamab use and on the specific guidance for risk minimisation measures for TF, as described in the HCP brochure, by estimating the proportion of prescribers with correct responses to the risk knowledge questions.
3. To assess prescribers' adherence with respect to the aRMMs by estimating the proportion of prescribers whose responses to the practice-related questions are consistent with the guidance provided in the HCP brochure.

The secondary objective is:

1. To assess whether the prescribers self-reported the HCP brochure as useful for their clinical practice.

8. RESEARCH METHODS

8.1 STUDY DESIGN

This study will use primary data collection via web-based questionnaire of HCPs (oncologists/haematologists/haematologist-oncologists/others, in countries where applicable only) who have prescribed Glofitamab. The self-reported survey will be an anonymous, cross-sectional, multinational, conducted in countries within the European Economic Area (EEA).

8.1.1 Overview of Study Design

The survey will assess prescribers' awareness, knowledge and adherence to the aRMMs for Glofitamab. The study is planned to be conducted in 11 countries within the EEA.

The survey shall be conducted using a staggered approach, depending on the Glofitamab implementation of the EMs per country. In each country, potential participants will be identified using the HCP lists from the proprietary OneKey™ by IQVIA. The data collection is expected to start in Q2 2026 to enable implementation of the local aRMMs, i.e., distribution of the updated EMs for Glofitamab, for at least 12 months in each country before initiating the study. The self-reported survey will be conducted in a web-based format with multiple-choice and closed-ended questions as appropriate. Fieldwork/data collection is planned for a 6-month period, consisting of 3 months of active data collection in each country with the possibility of extending for an additional 3 months if the target sample size is not achieved.

Start Date of Study:

The study is planned to start by Q2 2026, which is the period of the implementation of data collection of the HCP survey.

End of Study:

The study is planned to end by Q4 2026, which is the last period of data collection of the HCP survey.

Length of Study:

This study will last approximately 6 months with a fieldwork comprising an initial 3 months of data collection in each country, with a possible extension of 3 additional months. The final study report is planned for submission to EMA in Q4 2027.

An overview of the study design is provided in Figure 1.

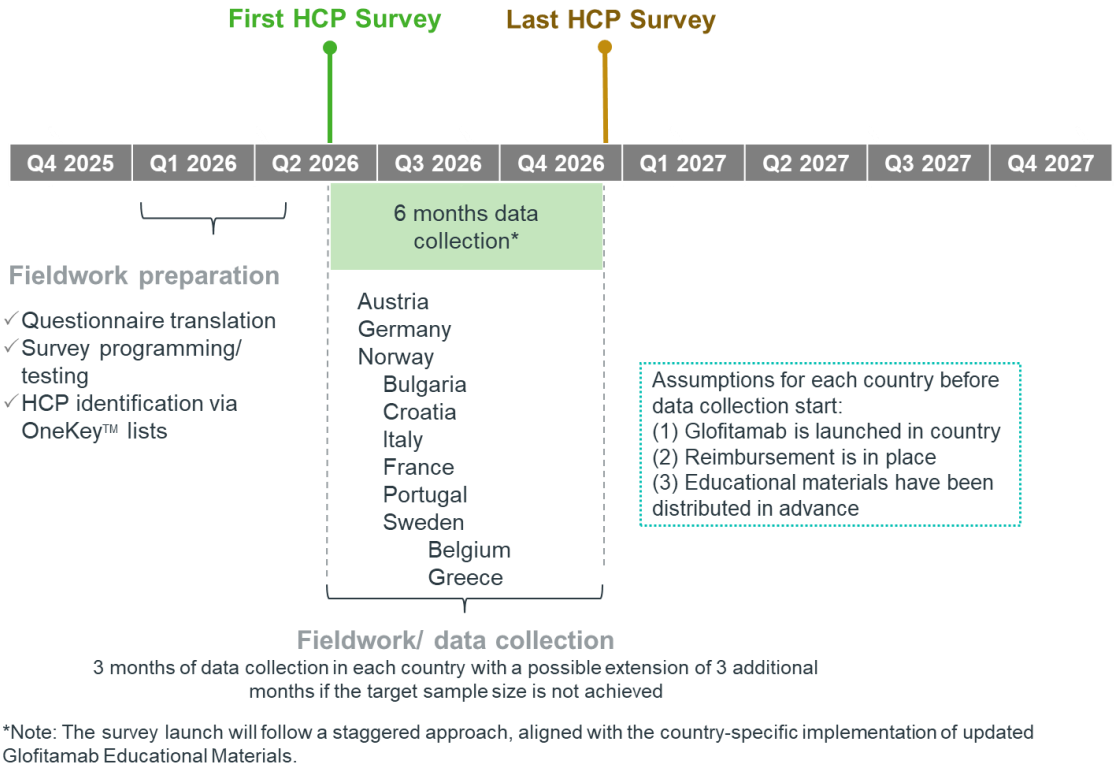

Figure 1: Study design overview

8.1.2 Rationale for Study Design

According to the guidelines on Good Pharmacovigilance Practices (GVP) Module V, VIII, and XVI, effectiveness of aRMMs should be assessed (EMA 2017a; 2017b; 2017c). The effectiveness of the aRMMs for Glofitamab will be assessed using a self-reported survey to prescribers to evaluate their awareness of the EMs, knowledge of identified important risks (TF) and self-reported adherence to the safety messages in the HCP brochure. To minimise selection bias, a comprehensive database of registered HCPs, OneKey™, will be used to randomly select potential participants to complete the survey.

8.2 SETTING

The survey will be conducted among HCPs who prescribed Glofitamab in inpatient and/or outpatient settings in 11 countries within the EEA. The survey will start within at least 12 months following the implementation of the local aRMMs as per European guideline on GVP, Module XVI (Rev 3) (EMA 2017c).

8.2.1 Countries

Target countries selected for the conduct of the survey must be representative of the European population among which Glofitamab is marketed. Countries from different parts of the EEA have been chosen in such a way that countries with different sizes, cultures, and healthcare systems are represented. In total, 11 European countries have been suggested: Austria, Belgium, Bulgaria, Croatia, France, Germany, Greece, Italy, Portugal, Norway, and Sweden. The target countries included in this study reflect the PRAC recommendations for the inclusion of Eastern European markets.

The selected countries will be included based on the current information on Glofitamab reimbursement and launch plans (more information on Section 8.4.2 and Table 1). If reimbursement is not available in any specific country during data collection period, another country with similar geographical location might replace it, if possible. Also, additional countries may be included or substituted the ones stated above if there is slow uptake of Glofitamab in the market.

8.2.2 Study Population

HCPs from geographically dispersed countries within the EEA where Glofitamab is approved and reimbursed will be targeted for participating to this survey. In each country, potential participants will be identified according to their specialty and will be randomly selected, according to the procedure described in Section 8.2.3.

The study population will be restricted to physicians (oncologists/haematologists/haematologist-oncologists/others) who meet the following inclusion criteria for study entry:

- Having prescribed Glofitamab to patients with R/R DLBCL in routine clinical practice, i.e., outside of the context of a clinical trial/ post-approval programmes/ compassionate use programmes, at least once in the last 12 months prior taking the survey. Therefore, HCPs who have prescribed Glofitamab exclusively in the context of clinical trials, i.e., who have no experience in prescribing the drug in clinical practice, will not be included in the study.
- Willing to participate in the survey.

Physicians who meet any of the following exclusion criteria will be excluded from study entry:

- Inactive and retired prescribers (when documented information is available to identify them).
- Those who are not involved in patient treatment (e.g., insurance prescribers).
- Those who declare having a conflict of interest with the survey (i.e., prescribers employed by regulatory bodies, MAH, IQVIA, etc).

8.2.3 Recruitment Procedure

In each country, all physician specialties (oncologist or haematologist or haematologist-oncologist) who are targeted to receive Glofitamab EMs under local authority agreements will be identified using OneKey™. OneKey™ is a large and comprehensive worldwide database of HCPs. More information about OneKey™ is provided in Section 8.4.1.

Potential participants will be randomly selected and contacted on an ongoing basis by country. Randomisation will be handled automatically and performed in batches using regional distribution weights to ensure geographic representativeness of physicians in the sample. HCPs will be mainly invited to participate in the study by email and followed up by phone call if applicable. The invitation email includes an overview of the study with a unique link to access the online survey. HCPs who will accept to participate, will answer screening questions in the first part of the survey to confirm their eligibility to participate in the study (eligibility criteria described in Section 8.2.2).

Potential participants will be considered unreachable if they have been contacted between 3 to 5 times without an answer. While IQVIA will make the best efforts to ensure randomisation of the sample, care will be taken in order not to re-contact HCPs who have not provided any response for other surveys in the last 5 years.

The data collection will be deemed accomplished when the target sample size is achieved or if all potential participants have been contacted 3 to 5 times, whichever happens first. If the HCPs list has been exhausted in any particular country, the recruitment in this country will be prematurely ended and a strategy will be determined to adjust the sample size with associated weighting.

8.2.4 Dosage, Administration, and Compliance of Studied Product(s)

Not applicable.

8.2.5 Concomitant Medication and Treatment

No information on concomitant medication and treatment will be collected.

8.3 VARIABLES

8.3.1 Variables From the Survey Platform

The survey platform tracks the status of the HCPs throughout the survey (from invitation to questionnaire completion). Therefore, the following variables will be retrieved by the platform.

Variables related to participation:

• Response to study invitation

- non-response (HCPs that neither refused nor accepted the study invitation).
- acceptance (HCPs that accepted the invitation regardless of their eligibility and completion).
- refusal (HCPs that explicitly refused the invitation).

• Response to screening section

- HCPs that accepted the invitation who either did not start completing the screener or did not answer all the screening questions.
- non-eligibles after screening questions.
- eligibles after screening questions that did not start completing the questionnaire.

• Response to questionnaire

- partially complete (prescribers that start to answer the questionnaire but did not complete).
- complete (prescribers that fully complete the questionnaire).

• Country of practice

8.3.2 Variables From Questions in the HCP Questionnaire

HCPs that fulfilled the eligibility criteria are henceforth referred to as prescribers. The following variables will be collected through the questions in the HCP questionnaire.

Variables related to prescriber's characteristics (Q1 to Q5):

• Practice information

- primary specialty (oncologist, haematologist, haematologist-oncologist, other)
- duration of practice in primary specialty

• Involvement as investigator in clinical trials regarding Glofitamab

• Past experience with Glofitamab

- number of patients treated (1 to 4, 5 to 10, >10 patients)
- time since last prescription (last 7 days, 8-30 days ago, 2-5 months ago, 6-12 months ago)

Variables related to the prescriber's awareness of the Glofitamab EMs (Primary objective 1, Questions 6 and 7):

• Receipt of Glofitamab EMs (yes, no, I do not remember)

• Access to Glofitamab EMs from other sources (hospital's website, Roche's website, National Regulatory Agency website, others, no)

• Reading Glofitamab HCP brochure (yes, no)

Prescribers who are not aware of the EMs, i.e., who answered "did not receive" the EMs and/ or "did not read" the HCP brochure, are allowed to continue answering the questionnaire.

Variables related to the prescriber's knowledge/comprehension of the risk of TF associated with the use of Glofitamab (Primary objective 2, Questions 8 to 10):

• Knowledge/comprehension of TF (true and false statements)

• Knowledge/comprehension of risk of TF associated with the use of Glofitamab (true and false statements)

• Knowledge/comprehension of the specific guidance and recommendations for minimising the risk of TF, as described in the HCP brochure (tick boxes)

Variables related to the prescriber's adherence to the safety messages in the HCP brochure (Primary objective 3- Questions 11 to 15):

• Distribution of the Patient Card to patients receiving Glofitamab (yes, no)

• Counselling of patients to carry the Patient Card (yes, no)

• Inform patients on the risk of CRS and ICANS associated with the use of Glofitamab (yes, no)

• Inform patients to seek medical attention immediately if they have any CRS and ICANS symptom (yes, no)

• Evaluate the lymphoma distribution to anticipate the potential spectrum of clinical manifestations of TF (yes, no)

Variables related to the usefulness of Glofitamab HCP brochure (Secondary Objective, Questions 16 and 17):

• Use of the HCP brochure as a source to gain awareness and knowledge of TF (yes, no)

• Use of other source to gain awareness and knowledge of TF (SmPC, Glofitamab website, guidelines, scientific literature, scientific conference materials, internet, others, no)

In order to evaluate the effectiveness of Glofitamab aRMMs, the proportion of correct and appropriate answers to selected questions in the survey will be evaluated. Outcomes for effectiveness will be defined *a priori* as target percentages of correct/ appropriate answers (see Section 8.7.4.2 and Appendix 2), considering a successful risk minimisation outcome when the proportion of prescribers with correct answers reaches or exceeds the predefined target.

Further details will be provided in the statistical analysis plan (SAP).

8.4 DATA SOURCES

8.4.1 Data Sources

The survey represents primary data collection from HCPs conducted through a web-based questionnaire. Answers will be submitted anonymously and collected using a secure electronic data capture (EDC) system that will be used to create the dataset for analysis.

OneKey™ database will be used to identify potential HCPs to participate in the survey in the selected countries (OneKey 2023). Data held on HCPs in the OneKey™ include personal/individual information, affiliation, specialties, contact information, and workplace. The OneKey™ mailing list covers over 26,000 oncologists and 11,000 oncologist-haematologists (OneKey 2023). The OneKey™ lists have been used in

aRMM effectiveness survey studies because of their large coverage of physicians' population in European countries. In the countries to be surveyed for this study, OneKey™ list covers 100% of physician's population targeted (oncologists/ haematologists) as assessed by comparison to publicly available statistics sources[1].

8.4.2 Collection of Data

Questionnaire development

The questionnaire will be initially developed in English. It will contain a set of standard questions in the form of single or multiple-choice and closed-ended questions. The options "unknown" or "don't know" will be allowed as answers, where applicable.

The questionnaire was pilot-tested among 4 Glofitamab prescribers' for its comprehensibility/understandability, consistency and the appropriateness of medical terms. Comments from these 4 HCPs were sought, and implemented, if necessary, in the questionnaire.

Questions are programmed to ensure that they are asked in the appropriate sequence. Skip patterns are clearly indicated. Respondents cannot go back to a question once the question has been answered and they cannot skip ahead. Response options presented in a list are randomised to minimise positional bias. All questions are mandatory, and the questionnaire can only be submitted when fully completed. Programming will be reviewed by Quality Control prior to implementation.

Participants will complete the questionnaire in their local language. The questionnaire will be translated into the relevant local languages for each of the selected countries. Translation will be done using the back-and-forth method (i.e., from English into the local language and then from local language into English) to ensure an accurate translation.

Completion of the questionnaire is estimated to take about 10 to 15 minutes.

Conduct of survey

Data collection is expected to be conducted between Q2 and Q4 2026. The fieldwork is anticipated to last about 6-month, consisting of 3 months of active data collection in each country with the possibility of extending for an additional 3 months if the target sample size is not achieved.

The distribution of the updated EMs in each country will be used as a proxy for starting the fieldwork within 12-18 months following the implementation of the local aRMMs. Table 1 provides the reimbursement dates by country and respective implementation of the updated EMs.

[1] Statistics source data on the Universe of HCPs by specialty: Bundesärztekammer (Germany), Österreichische Ärztekammer (Austria), Eurosta (Croatia and Greece), Statistisk Sentralbyrå (Norway), Socialstyrelsen (Sweden), ISTAT (Italy), RIZIV (Belgium), Annuaire Santé (France), Estatísticas da Ordem dos Médicos (Portugal), Bulgarian Medical Association (Bulgaria)

Table 1. Glofitamab reimbursement and implementation of the Educational Materials period in each country

Country	Reimbursement *	Implementation of the updated Educational Materials++
Germany	Q3 2023	Q1 2025
Austria	Q3 2023	Q1 2025
Italy	Q1 2024	Q2 2025
Belgium	Q2 2024	Q3 2025
Norway	Q1 2025	Q1 2025
Bulgaria	Q1 2025	Q2 2025
Sweden	Q2 2025	Q2 2025
Croatia	Q1 2025	Q1 2025
Portugal	Q2 2025	Q2 2025
Greece	Q1 2025	Q3 2025
France	Q1 2026	Q2 2025

* Reimbursement dates as shared by the MAH in September 2025. In France this is considered a planned reimbursement, meaning it refers to the expected timing of a reimbursement decision, which may not necessarily translate in reimbursement, in case of negative recommendation.
++ The Educational Materials have been updated in accordance with the Pharmacovigilance Risk Assessment Committee's (PRAC's) recommendation on 11 July 2024, to include the important identified risk of immune effector cell-associated neurotoxicity syndrome (ICANS).

The survey fieldwork will be conducted by IQVIA Primary Intelligence.

HCPs invitation

HCPs will be mainly contacted by email and followed up by phone call if applicable. Their recruitment will be done according to the following process:

- Potential respondents will be invited by email to participate in the survey. The survey background, objectives, the contact information for questions, and the proposed compensation will be explained to them at this step.
- If they agree to participate in the survey, they can click on a unique link to access the online survey.
- If no answer to the invitation or link not used or partial complete questionnaire, the HCPs will be sent a reminder by email, usually 3 weeks after the initial invitation.
- If the target sample is not achieved within each country, a reminder will be conducted about 2 weeks after the first reminder.
- If the target sample is still not achieved, a last reminder will be sent approximately 2 weeks after the previous reminder.

HCP enrolment will be voluntary. The recruitment will stop when the target number of complete surveys in each country is reached, or the list of targeted HCPs has been exhausted.

Approaches for increasing response rate

Although online surveys constitute the majority of survey modes implemented worldwide, its overall low response rate remains a major issue (Shiyab et al. 2023; Daikeler 2020). The strategies to maximise response rates in online surveys include: well-designed survey format, pilot test the survey before dissemination, provide financial incentives, personalised invitations to participate and regular reminders (Shiyab et al. 2023).

In attempt to increase the response rate among HCPs, several actions will be applied to the survey:

- A compensation fee will be proposed to HCPs for their participation in the survey. Compensation will be compliant with relevant guidelines of each country and will compensate the actual effort and time needed to fill up the questionnaire.
- The survey will be short with its completion estimated to take 10-15 minutes.
- All HCPs will be sent an email or contacted by experienced operators of IQVIA Primary Intelligence team with extensive experience in conducting health related surveys.
- Each HCP will be emailed or called 3 to 5 times, during the course of data collection (3 months), before being considered as “not reachable”, and reminders will be sent by email if IQVIA Primary Intelligence does not receive the web questionnaire.
- IQVIA will highlight in the HCP invitation letter the regulatory purpose of the study, which in the past has shown to increase the willingness of HCPs to participate.

8.5 STUDY SIZE

8.5.1 Sample Size Calculation

The sample size formula, based on the normal approximation to the binomial distribution, for calculating the number of subjects required for a proportion is the following:

$$N = z_{1-\frac{\alpha}{2}}{}^{2} * \frac{P\,(1-P)}{e^{2}}$$

Where P is the expected proportion, e is one half of the desired width of the confidence interval (CI), and $z_{1-\frac{\alpha}{2}}$ is the standard normal Z value corresponding to a cumulative probability of $1-\frac{\alpha}{2}$ (e.g., if α = 0.05 then Z = 1.96).

The proportions of interest of this study are the proportions of HCPs providing correct/appropriate answers to the different questionnaire items (see Section 8.7.4.2 and Appendix 2). Since the true proportion is not known in advance, we use 50% as a conservative estimate, which yields the largest sample size. Table 2 shows the sample size based on various margins of error for 95% CI and proportions of interest. For example, the minimum required sample size would be 196 participants with completed questionnaire per target population for a proportion of 50% and a margin of error of 7%.

Table 2. Sample size based on various margins of error for 95% CI and proportions of interest/precision of the proportion estimate for a range of sample sizes

Proportion of interest	Margin of error for 95% CI (absolute precision)				
	10%	8%	7%	6%	5%
10%	35	55	71	97	139
30%	81	127	165	225	323
50%	97	151	196	267	385
70%	81	127	165	225	323
80%	62	97	126	171	246
90%	35	55	71	97	139

CI=Confidence Interval

Given the small size of the anticipated target population, the sample size of this survey is defined based on its feasibility, rather than an *a priori* calculation of the sample size. Table 3 shows the margin of error (width of 95% CI around the estimate) for a range of sample sizes to detect a proportion of 50% (lowest precision) and 80% (target proportion), which provides the rationale on the feasibility and the assumptions used. For the target population of HCPs in this survey, we assume a sample size of 120 participants with completed questionnaire for inclusion in the analysis. Assuming a participation rate of 5% in this target based on IQVIA previous experience, at least 2400 HCPs will need to be invited to complete the questionnaire to achieve the sample. Therefore, the sample will be adjusted at the time of the survey if the total number of HCPs is below this number.

Table 3. Margin of error (width of 95% CI around the estimate) for a range of sample sizes to detect a proportion of 50%

Sample size	Margin of error (%) for a proportion of 50%	Margin of error (%) for a proportion of 80%
90	± 10.3	± 8.3
120	± 8.9	± 7.2
150	± 8.0	± 6.4
200	± 6.9	± 5.5
250	± 6.2	± 5.0
300	± 5.7	± 4.5
400	± 4.9	± 3.9

8.5.2 Sampling Plan

A target total sample size of 120 participants with completed questionnaire is based on above practical considerations and assumptions (see Section 8.5.1). Although the defined objective is to reach the targeted sample size of 120 completed questionnaires, participation is dependent on the country-level HCPs and their interest in participating in the survey.

Ideally, the sample of 120 participants should be proportionally split between the selected countries based on the number of HCPs in each country and their real proportion. However, due to the large-expected variance of the number of HCPs in the targeted countries, pragmatic splits will be implemented to ensure that a sufficient size of participants is allocated in the smaller countries, while larger countries are not overrepresenting the samples.

As per the suggested sample size defined in Section 8.5.1 and the number of selected countries, country coverage characteristics and HCPs specialties, participants could be stratified according to the distribution in Table 4. In particular, these numbers are calculated by considering different weights depending on the size of OneKey™ universe of HCPs in each country and assuming at least 24 respondents in the bigger countries and 5 in the smaller ones. However, as the universe of Glofitamab prescribers, in each country is unknown, at the time of the survey, the sample size may need to be adjusted. Table 4 shows illustrative numbers based on the country coverage proxy.

Table 4. Illustrative sample distribution of HCPs by country

Selected country	Universe of oncologists (OneKey™ specialities 1.2.3)	Universe of haematologists (OneKey™ specialities 1.2.3)	Pragmatic splits based on overall proportion	Weight of the target sample size (based on pragmatic splits)	Estimated number of respondents (based on pragmatic splits)
Croatia	305	162	Small	4%	5
Austria*	605		Small	4%	5
Bulgaria	429	225	Small	4%	5
Norway	588	141	Small	4%	5
Sweden	671	291	Medium	6%	7
Belgium	749	306	Medium	6%	7
Portugal	756	375	Medium	6%	7
Greece	524	655	Medium	6%	7
Germany*	3430		Large	20%	24
France	5984	2368	Large	20%	24
Italy	7953	5716	Large	20%	24

Sample sizes are an estimate based on country coverage and the universe of Glofitamab prescribers. The final feasibility will depend on Glofitamab uptake in each country.

*In Austria and Germany there is no distinction between specialty.

The recruitment will continue until the target number of participants will be included in each country for an anticipated period of 3 months,. Once a country is completed, the recruitment is stopped to avoid unbalanced sizes between countries. An additional 3-month extension may be considered if the target sample in a given country is not met during the first 3-month of data collection period.

8.6 DATA MANAGEMENT

IQVIA will be responsible for data management of this study, including quality checking of the data.

The MAH will perform oversight of the data management of this study, including approval of IQVIA data management plans and specifications.

For the online questionnaire, data will be collected using an EDC system developed following a full validation process. The internet-based repository will be used to store survey data and other relevant programme information.

8.6.1 Data Quality Assurance

Collected data will be stored in a central database specific to the survey. HCP identifying information will be stored separately from study data.

The survey will be conducted according to the Standard Operating Procedures (SOPs) of IQVIA.

Before analysis, data will be checked in terms of consistency:

- Removal of duplicates (if required)
- Data labelling and data formatting
- Range and consistency checks for each variable, to identify potential non-admissible values
- Cross-check of the consistency of data for related variables (if applicable)

The study database will be locked once validated.

In case of phone interviews, if applicable, IQVIA will not query the reasons/choices of the HCPs' answers to questions in the questionnaire.

Automatic checks for plausibility and consistency will be programmed into the questionnaire tool, which will prevent contradicting values from being entered.

Non-admissible values will be avoided by implementation of the appropriate controls in the questionnaire at the time of its completion by the HCPs. Any non-admissible values identified after database lock (if any) will be excluded from the analysis.

8.7 DATA ANALYSIS

The survey analysis and reporting will be conducted by IQVIA Real-World Solutions. The statistical analyses will be detailed in the SAP.

8.7.1 General Statistical Considerations

The statistical analysis will be conducted using either Statistical Analysis Software (SAS®) (Version V9.4 or above) on Windows™ (SAS Institute, North Carolina, USA) or R software (Version V4.0 or above).

All the analyses will be descriptive, and no comparative analysis will be reported. The statistical results will be presented by prescribers' specialty and per country (if possible, given the number of respondents), and overall.

Continuous variables will be described by their mean, standard deviation, and median, first quartile (Q1), third quartile (Q3), minimum and maximum. Categorical variables will be described as the total number and relative percentage per category. CI of 95% will be evaluated, when applicable.

8.7.2 Handling of Missing Data

The web questionnaire will be programmed in such a way that participants cannot skip questions and it can only be submitted when fully completed. Therefore, missing data are not expected to occur for the submitted questionnaire.

In case eligible HCPs respond to the survey during phone contact or non-submitted questionnaire (partially complete), missing values might exist. No imputation method is planned to replace these missing values. If any, the number of variables with missing values will be indicated and missing values will be excluded from the calculation of percentages.

Analysis of Participation Rate

The following different cases will be distinguished:

- HCPs who did not respond (neither refused nor accepted) the study invitation (R1).
- HCPs who refused to participate in the study (R2): HCPs who explicitly indicated their refusal to participate.

- HCPs who accepted to participate in the study:
  - who did not start completing the screener or did not answer all the screening questions (R3).
  - who did not meet the study inclusion criteria (non-eligible after screening questions) (R4).
  - who met the study inclusion criteria (eligibles after screening questions) and did not start completing the questionnaire (R5).
- HCPs who accepted to participate in the study and started the questionnaire:
  - partially answered questionnaires (P): HCPs who clicked on the link provided in the invitation email, and who passed the screening section (eligibles) and began answering the questionnaire but never submitted it.
  - completed questionnaire (C): HCPs who clicked on the link provided in the invitation email, who passed the screening section (eligibles) and who completed the entire questionnaire.
- HCPs willing to participate: HCPs who accepted to participate in the study besides of their eligibility and completion= C+P+ R3+R4+R5.
- Contacted HCPs: HCPs who were reached by phone or who received a web link to the online survey via email = C+P+R1+R2+R3+R4+R5.
- Eligible HCPs: HCPs who met the study inclusion criteria (eligibles after screening questions) = C+P+R5.

The participation in the survey will be examined as follows (adapted from: American Association for Public Opinion Research 2016):

- Complete response rate $= \frac{C}{C+P+R1+R2+R3+R4+R5}$
- Refusal rate $= \frac{R2}{C+P+R1+R2+R3+R4+R5}$
- Partial response rate $= \frac{P}{C+P+R1+R2+R3+R4+R5}$

Last, the number and percentage of HCPs by individual cases (C, P, R1, R2, R3, R4, R5) will be reported.

8.7.4 Questionnaire Analysis

The general statistical considerations described in Section 8.7.1 will be applied.

Analysable questionnaires will be those completed and submitted by the participants. The proportions of answers to selected questions (see Section 8.3.2) will be evaluated by reporting the frequency of each option provided by the participants in the statistical results, as depicted in Table 5. The results will be reported overall, both weighted and unweighted, as described in Section 8.7.4.1 and depicted in Table 5.

To assess the presence of selection bias, the distributions of available characteristics retrieved by the OneKey™ of respondents and non-respondents will be reported. Moreover, the profile of participants with incorrect answers will be identified and described with all available relevant covariates collected in the questionnaire (practice information, participation on clinical trials, and previous experience with Glofitamab) (see Section 8.3.2). A descriptive analysis of the knowledge/comprehension of the risk of TF stratified by the variable “EMs awareness” will be performed. Not aware is defined as answering "No" or “I do not remember” to receiving the EMs and “No” to reading the HCP brochure, and aware as answering "Yes" to reading the HCP brochure.

Table 5. Example of mock table for answers provided by participants

	Country 1	Country 2	Country 3	Overall (unweighted)	Overall (weighted)
Question 1	(N=xx)	(N=xx)	(N=xx)	(N=xxx)	(N=xxx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Question 2	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Question 3	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Question 4	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Question 5	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

8.7.4.1 Weighting

Since the relative proportion of each country of HCPs in the final sample may be different from their real proportion in the target population, the raw survey results will need to be adjusted to allow their extrapolation to the overall target population. Thus, the results will be weighted back according to the real proportion of each stratum to allow the representativeness of the overall sample. Both unweighted and weighted results will be reported.

Specifically, a weight variable will be applied to each statistical unit (i.e., the HCPs) during the results calculation to correct any over- or under-sampling that may have occurred for a country. This weight variable will indicate how many unit(s) of the population of interest an observation will count in a statistical procedure. Its value will change per country. The weights will be normalised to obtain their sum equal to the sample size.

8.7.4.2 Assessment of success

Success of the aRMMs for HCPs will be defined using set thresholds based on the percentage of prescribers classified as aware of, knowledgeable about and adherent to the aRMMs. Such prescribers can be identified using definitions of individual success on each domain based on percentage of domain statements (primary endpoint variables) with correct or appropriate answers (more information on Appendix 2).

- Awareness (Primary objective 1- Questions 6 and 7): Success $\geqslant$ 80%
  - $\geqslant$ 80% of prescribers acknowledge having received the EMs and read the HCP brochure.
- Knowledge (Primary objective 2 - Questions 8 to 10): Success $\geqslant$ 80%

- ⩾ 80% of prescribers with correct answers about the risk of TF that may occur with Glofitamab use and on the requirements for specific monitoring for TF.

• Adherence (Primary objective 3 - Questions 11 to 15): Success ⩾ 80%

- ⩾ 80% of prescribers acknowledge having provided the Patient Card or another HCP provided it, reminded patients to keep the Patient Card with them at all times, informed patients about CRS and ICANS symptoms associated with Glofitamab, informed patients the need to seek medical attention if they have CRS and ICANS symptoms, and evaluate the lymphoma distribution to anticipate the potential manifestation of TF.

Previous PASS surveys showed no consensus in the selection of thresholds for success (Vora et al. 2018), and there is no established scientific criteria in the education or risk communication for it. Therefore, the results will be contextualised considering other available information in the study (time since the original and updated EMs were distributed, time since last Glofitamab prescription, duration of prescriber practice, number of patients treated).

8.7.5 Sensitivity Analyses

A sensitivity analysis including partially completed questionnaires as well, if any, will be conducted as depicted in Table 5 in Section 8.7.4. No assessment of success will be performed.

8.7.6 Interim/Final Analysis and Timing of Analyses

The statistical analysis is planned to be conducted in Q2 2027. The final results will be discussed with and approved by the MAH.

The final study report will be based on the template included in the GVP module VIII (EMA 2017b) and following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations in MS Word format (von Elm et al. 2007). The final study report is planned for submission to EMA in Q4 2027.

8.8 QUALITY CONTROL

8.8.1 Study Documentation

Data will be collected using a questionnaire administered online and by phone call if applicable.

Testing of questionnaire

The programmed questionnaire will be tested and validated in accordance with IQVIA SOPs. Programming will be reviewed by Quality Control prior to implementation.

Approaches for language testing of the questionnaires

The HCP online questionnaire will be translated from English into the local language. The translated questionnaires will be checked by native speakers with medical expertise.

Approaches for validating the results

The Quality Control for validating the results will be conducted at 5 levels:

1. Every effort will be undertaken to collect complete and valid data.

2. At the study database level, final data quality checks will be applied to count the number of missing values (if any) and estimate the associated relative percentage.

3. At the statistical analysis level, all data management and statistical analysis programmes developed and used in the analysis will be documented. All versions generated will be dated, kept with accompanying documentation and archived. The original database will be stored. A derived database will be created for the new versions of the data in order to include recoding and computing of new variables, especially stratification of continuous variables, combination of modalities for categorical variables, calculation of composite indicators, etc.

4. At the results level, a data review will be done to ensure data integrity. A statistical analysis report including all the results will be provided for review and discussion. The final statistical report will take into account the reviewer's comments.

5. At the study level, all aspects of the study will be conducted according to the SOPs of IQVIA Real-World Evidence Solutions. The study documents have been approved by people competent in medical and safety areas of IQVIA. According to the SOPs, an independent review of the study results and report will be conducted by a person who is not in charge of their preparation.

8.8.2 Safeguards, Security and Traceability of Contacts

Operators of the call centres specialised in health surveys will be assigned to the project and trained on the survey methodology prior to fieldwork. The email contacts and phone calls will be traced using management software.

HCPs will access the questionnaire via a secure link that is unique to each participant. The answers provided will be collected in an anonymous way.

Data will be recorded in a central database and tracked using an audit trail. The system will enable retrieving all introduced data at any time and will include security elements to prevent anyone other than authorised staff from accessing data. Each user will have a specific profile which will limit his/her use of the database. A security copy of the database and the application files will be made in a separate location.
Description of all elements of security and traceability will be available upon request.

8.8.3 Retention of Records

The study documentation will be stored in the study master file and data on the study database. Data storage will be in line with national data protection requirements for each of the countries where the study will be conducted.

All documentation pertaining to the study will be retained for a minimum of 5 years after the end of the study, in accordance with IQVIA SOPs.

Archiving the study documentation has to be for at least 5 years after final study report or first publication of study results, whichever comes later; or according to local regulation.

All supporting functional parties will comply with the MAH procedures regarding archiving and record management.

8.9 LIMITATIONS OF THE RESEARCH METHOD

Selection bias

The potential for selection bias of participants in a survey is an inherent limitation to any study based on volunteer participation. For instance, it is possible that prescribers willing to participate in the study will have the highest awareness of risks associated with use of Glofitamab. In order to quantify any selection bias, the distribution of each stratification

criterion of HCPs (country, specialty, and any other available characteristics) will be compared between participants and non-participants, if possible.

The non-response sample can be large regardless of the sampling frame used, as it is common for physicians to lack interest in participating in surveys. The number of HCPs who did not respond to the study invitation and who refused to participate in the study will be monitored, as described in Section 8.7.3. Also, to increase the response rate among HCPs, the following measures will be used: compensation for participation in the survey, a short survey, emails and contact with reminders, and an invitation letter explaining the regulatory purpose of the study.

Non-response bias may also be introduced into the study if targeted participants have activated filters in their mailbox that block spam and unsolicited emails. Having multiple email addresses could also affect responsiveness, especially if the one used for sending the invitation is not the HCPs primary address. Targeted participants who do not check their email frequently might not receive the invitation during the recruitment period. These are among the reasons why HCPs could also be contacted by phone.

Information bias

All data supplied will be self-reported by the prescribers, and it will not be possible to objectively verify information. The quality of the data is dependent on the completeness and accuracy of the data entered. The questionnaire will contain validated questions with standardised response formats, and the EDC will contain automated quality checks to improve data quality for analysis. Additionally, to reduce information bias, questions will be closed-ended to avoid errors in interpreting free-text during analysis. However, prescribers will not have the possibility to come back and change their responses once submitted and will not be contacted to clarify or revise their survey responses.

Web surveys may promote information bias that may result from social desirability, which refers to the tendency of participants to give socially desirable/expected responses instead of choosing those reflecting their current knowledge or behaviour, e.g., prescribers can copy-paste or refer to information gathered online instead of giving their own opinions (Wyatt 2000).

Social desirability can affect the validity of survey research findings, but the use of pre-populated items in the questionnaire tends to reduce this bias (Nederhof 1985).

Recall bias may lead to an underestimation of the prescribers recalling having received the EMs. On the other hand, prescribers may have an acceptable understanding of the risks associated with Glofitamab obtained from other sources, despite not having received or recalled receipt the EMs. To interpret the accuracy of the recollections retrieved when answering the survey, if any, we will provide updated information about the period (month/year) of the distribution of EMs in each participating country.

Limitations inherent to surveys

Surveys collect and analyses self-reported data, thus introducing the Hawthorne effect, i.e., respondents may improve or modify an aspect of their behaviour in response to their awareness of being observed.

In web surveys, the generalisation and external validity of the results is restricted to HCPs who have an active email address and are willing (and able) to answer a questionnaire online. These participants may not be fully representative of the whole targeted population (Wyatt 2000).

The access to the web questionnaire interface will be strictly limited to the invited HCPs, with the possibility to participate only once via a traceability system. Thus, stakeholder bias (multiple answers of people who have a personal interest in survey results and/or who incite peers to fulfil the survey in order to influence the results) or unverified respondents (when it is not possible to verify who responds) are not applicable.

Generalizability of results

The raw survey results can only be generalised to the overall target population(s) provided a sample adjustment is applied. For more transparency and accuracy, both unweighted (i.e., raw survey results) and weighted results will be presented in the report.

8.10 OTHER ASPECTS

Strengths of the research methods

1. Use of OneKey™. The information contained in the OneKey™ file of each country is updated constantly with proactive updates. Quality controls are implemented on a regular basis. OneKey™ is the most comprehensive list of HCPs in the world with very high coverage in most countries.

2. Stratified random sampling. The sampling of potential participants will follow a stratified randomised method which guarantees the representativeness of the contacted population to limit selection bias due to voluntary participation.

3. Mitigation of information bias. The questionnaire will include general questions followed by specific ones to limit a learning process during the survey. As the participants may understand the right answer in subsequent questions, it will not be possible to go back in the questionnaire and edit answers in former questions.

4. Tested questionnaire. The questionnaire will be tested for its clarity before implementation. It will also be checked whether there are questions which would suggest a specific answer for any reason for example social desirability.

5. Participation level. Multiple reminders will be sent to potential participants and incentives will be proposed to maximise the response rate.

6. Team experience. The study will be conducted by an experienced team specialised in the design and conduct of such surveys in the area of safety. It will follow IQVIA SOPs as well as the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) methodological guidelines and EMA GVP.

9. PROTECTION OF HUMAN SUBJECTS

The survey is non-interventional and totally anonymous to the study sponsor. It will accumulate HCPs' opinions rather than healthcare data and will not involve any patient data collection. Data collected will remain confidential and only aggregated data will be analysed and communicated in a report. The study will be conducted in agreement with the regulation (EU) 2016/679 of the European Parliament on the protection of natural persons regarding process of personal data and on the free movement of such data (General Data Protection Regulation, GDPR).

9.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for Good Pharmacoepidemiological Practice published by the International Society of Pharmacoepidemiology and the laws and regulations of each country in which the research is conducted.

The study will comply with national and EU requirements for ensuring the well-being and rights of participants in non-interventional PASS.

As this survey is about collection of opinions rather than healthcare data, it is technically considered market research in most countries. IQVIA will follow the European Pharmaceutical Marketing Research Association (EphMRA) code of conduct guidelines (EphMRA 2022).

Although the EU Pharmacovigilance Directive (DIR 2010/84/EU) is a legal act, it does not carry the same binding force of regulation; each Member State can determine how best to transpose the Directive into local legislation. As a result, the submission requirements for PASS consisting in survey vary throughout the EU, with some countries being more onerous than others. IQVIA includes experts dedicated to the review and advice on the regulations and guidelines applicable to this study in the participating countries.

9.2 INFORMED CONSENT

The potential HCPs participating in the survey will be informed about the purposes of the investigation, the nature of the transmitted data, the intended use of data, recipients of these data, and their right of access and rectification to their personal data, as well as their right of objection to use their data or to IQVIA keeping their data. They must agree with the terms electronically via a checkbox in the questionnaire before any information is stored.

9.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

Submission for approval to Clinical Research Ethics Committee or Independent Review Board as per local applicable requirements is not required. A notification to the competent authorities before study initiation is anticipated to be needed in all the targeted countries.

9.4 CONFIDENTIALITY

HCPs will access the survey website (https: secured site) via a personal secure link. This link is unique to each participant.

Only aggregated data presented as a synthesis will be transmitted to the MAH in the form of the final study report.

9.5 FINANCIAL DISCLOSURE

HCPs will be offered a compensation for the time spent participating in this survey (that they may refuse). The time to complete the survey is estimated to be between 10 to 15 minutes.

The amount of this compensation will be in line with the Sunshine Act, and determined according to the EphMRA recommendations and the Association of Opinion and Behaviour in health field research companies charter, which states:

“When it is necessary to compensate an HCP in return to the time spent during an interview or a group meeting, the compensation must not exceed the fees commonly

taken by the HCP for his/her advice or consultation and must be proportional to the time provided. The compensations should be clearly stated prior to the HCPs participation in the survey. They must be declared to the tax authorities in accordance with applicable laws".

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

This study is a survey to evaluate the effectiveness of EMs implemented as aRMMs. This survey does not involve data collection on clinical endpoints for individual patients.

Although adverse effects are not being measured directly in this survey, any safety information for an individual patient provided by participating prescribers during the study must be reported as described below. In the event that a participating prescriber reports a safety event associated with a Roche product, IQVIA will forward any information on AE along with the prescriber's contact information (upon prior consent of the prescriber) to Roche Drug Safety and Pharmacovigilance department using Roche AE reporting form. This will be done within the timeline of 1 working day for serious AE or within 30 days for non-serious AE.

Any AE information received will be documented and reported following the EMA Guideline on GVP Module VI – Management and Reporting of Adverse Reactions to Medicinal Products (EMA 2017d) and in accordance with EMA regulations (Regulation 520/2012 on the performance of pharmacovigilance activities provided for in Regulation [EC] No 726/2004) (EU 2012).

11. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the MAH is dedicated to openly providing information on the study to HCPs and to the public. The MAH will comply with all requirements for publication of study results.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the MAH, except agreed otherwise.

The survey will be registered in the Heads of Medicine Agencies (HMA)-EMA Catalogue of real-world data sources and studies. The final study report will be communicated to the EMA after validation by the MAH. An abstract of the results will be uploaded to the HMA-EMA Catalogue of real-world data sources and studies.

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Appendix 1
ENCePP Checklist for Study Protocols

Study title: EVALUATION OF THE EFFECTIVENESS OF THE ADDITIONAL RISK MINIMISATION MEASURES FOR GLOFITAMAB: A PASS SURVEY AMONG HEALTHCARE PROFESSIONALS IN EUROPEAN COUNTRIES (BO44309)

HMA-EMA Catalogue of real-world studies number: to be registered
Study reference number (if applicable): not applicable

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	☒	☐	☐	5
1.1.2 End of data collection[3]	☒	☐	☐	5
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	5
1.1.6 Final report of study results.	☒	☐	☐	5

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6.2
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[2] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[3] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	8
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	8.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	8.1.1
4.2.2 Age and sex	☐	☐	☒	
4.2.3 Country of origin	☒	☐	☐	8.2.1
4.2.4 Disease/indication	☐	☐	☒	
4.2.5 Duration of follow-up	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2.3

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.7.4.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	8.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	8.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between-data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	8.5
10.3 Are descriptive analyses included?	☒	☐	☐	8.7
10.4 Are stratified analyses included?	☒	☐	☐	8.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	8.7.2
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	8.7.5

Comments:

Considered stratified analysis by specialty and by country.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.6
11.2 Are methods of quality assurance described?	☒	☐	☐	8.6.1/ 8.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	8.6.1

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	8.9
12.1.2 Information bias?	☒	☐	☐	8.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.9

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

Name of the main author of the protocol: [redacted]

Date:

Signature: _____

Appendix 2- Study Primary Endpoints

Study objective-domain	Question: Variable	Operational definition for correct answers	Success threshold
Primary objective 1- **Awareness** of Glofitamab EMs	**Question 6 (1 statement):** Receipt Glofitamab EMs (yes, no, I do not remember) **Question 7 (1 statement):** Reading Glofitamab HCP brochure (yes, no)	Statements will be evaluated individually. - [redacted]	≥ 80% prescribers with success (at least 2 out of 2 appropriate answers)
Primary objective 2- **Knowledge** of the risk of TF provided in the HCP brochure	**Question 8 (3 statements):** Knowledge/comprehension of TF (true and false statements) **Question 9 (4 statements):** Knowledge/comprehension of risk of TF associated with the use of Glofitamab (true and false statements) **Question 10 (3 statements):** Knowledge/comprehension of the specific guidance and recommendations for minimising the risks of TF, as described in the HCP brochure (tick boxes)	Statements will be evaluated individually. [redacted]	≥ 80% prescribers with success (at least 8 out of 10 correct answers)
Primary objective 3- **Adherence** to the safety messages in the HCP brochure	**Question 11, 12, 13, 14 and 15 (1 statement each)** (yes, no) **Q11-** Distribution of the Patient Card **Q12-** Remind to keep the Patient Card at all times **Q13-** Inform patients about the signs/ symptoms of CRS and ICANS **Q14-** Inform patients about the need to seek medical attention if they have CRS and ICANS symptoms **Q15-** Evaluate lymphoma distribution to anticipate the potential risk of TF	Statements will be evaluated individually. [redacted]	≥ 80% prescribers with success (at least 4 out of 5 appropriate answers)

CRS: Cytokine Release Syndrome; EMs: Educational Materials; HCP: Health Care Professional; ICANS: Immune Effector Cell-Associated Neurotoxicity Syndrome; TF: Tumour Flare

Appendix 3

Health Care Professional (HCP) questionnaire

Note:
Blue, is for data and will not appear in the questionnaire,
Green, and **Red** are for internal use and will not appear in the questionnaire to the respondents,
Black will be in the questionnaire.

Before starting the main questionnaire, we will first ask some screening questions to ensure you can participate in this survey.

S1. Are you currently employed by Roche, IQVIA, or contracted by regulatory bodies? (e.g., European Medicines Agency (EMA) or local regulatory agency)

( ) YES *Thank you for your interest in participating, but unfortunately you cannot proceed with the survey.* [redacted]

( ) NO [redacted]

Data: single punch

S2. Are you actively involved in treatment of patients with Diffuse Large B-cell Lymphoma (DLBCL)?

( ) YES [redacted]

( ) NO, I'm not involved (e.g., insurance prescribers, etc.) *Thank you for your interest in participating, but unfortunately you cannot proceed with the survey.* [redacted]

Data: single punch

S3. Have you prescribed Glofitamab to patients with relapsed/refractory Diffuse Large B-cell Lymphoma (DLBCL) outside of the context of clinical trials/ post-approval programmes/ compassionate use programmes <u>at least once during the last 12 months</u>?

( ) YES [redacted]

( ) NO *Thank you for your interest in participating, but unfortunately you cannot proceed with the survey.* [redacted]

Data: single punch

Practice Information

Q1. What is your main medical specialty? If you have more than one specialty, please select which you consider to be your main specialty.

1	Oncologist	( )
2	Haematologist-oncologist	( )
3	Haematologist	( )
4	If other, please specify (open text)	( )

Data: single punch

Q2. For how many years have you been practicing in this specialty?

1	< 1 year	( )
2	1 – 5 years	( )
3	6 – 10 years	( )
4	> 10 years	( )

Data: single punch

Q3. Were you actively involved as an investigator in a clinical trial regarding Glofitamab?

1	Yes	( )
2	No	( )

Data: single punch

Q4. In the past 12 months, how many patients have you prescribed Glofitamab? Please consider only patients outside of clinical trials/ post-approval programmes/ compassionate use programmes.

1	1 – 4 patients	( )
2	5 – 10 patients	( )
3	>10 patients	( )

Data: single punch

Q5. When did you last prescribe Glofitamab outside of clinical trials/ post-approval programmes/ compassionate use programmes?

1	within the last 7 days	( )
2	8 to 30 days ago	( )
3	2 to 5 months ago	( )
4	6 to 12 months ago	( )

Data: single punch

Awareness of Educational Materials for Glofitamab

Q6. Have you received (either from post, email, or from other channel) the Educational Materials (HCP brochure and Patient Card)* regarding the additional Risk Minimisation Measures (aRMMs) of Glofitamab?

1	Yes	( )
2	No	( )
3	I do not remember	( )

Hyperlink with Blurred image of the EMs

Data: single punch per row

If Q6= "Yes", go to Q7

If Q6= "No" or "I do not remember" go to Q6a

[redacted]

Q6a. Have you had access to the above-mentioned Educational Materials from other sources? *Please choose all that apply*.

1	Hospital's website	( )
2	Roche's website	( )
3	*National Regulatory Agency website	( )
4	If others, please specify (open text)	( )
5	No	( )

Data: multi-punch
option will be country specific

[redacted]

If Q6a= 1,2,3 or 4, go to Q7, If Q6a= "No" skip Q7 and record response as "No" and go to Q8

Q7. Have you read the HCP brochure regarding the additional risk minimisation measures (aRMMs) of Glofitamab?

1	Yes	( )
2	No	( )

Data: single punch

[redacted]

Knowledge/Comprehension of the Risk of Tumour Flare Associated with Glofitamab

Q8. According to your knowledge of the information in the HCP Brochure, which of the following statements about Tumour Flare are true?

		TRUE	FALSE	I do not know
1	Tumour Flare is typically characterised by localised responses, which can manifest as tumour pain, volumetric enlargement of tumour sites, swelling or inflammation and depending on tumour size and anatomic location may result in mass effects on surrounding structures that can compromise organ function	( )	( )	( )
2	Tumour pseudoprogression is primarily a radiological diagnosis, in contrast to the clinical manifestations that characterise Tumour Flare	( )	( )	( )
3	Tumour Flare is associated with some anti-cancer therapies where the mechanism of action that includes redirecting the immune response towards tumour killing results in the activation and trafficking of immune cells to tumour sites	( )	( )	( )

Data: single punch per row, random order

[redacted]

Q9. According to your knowledge of the information in the HCP Brochure, which of the following statements about Tumour Flare <u>with the use of Glofitamab</u> are true?

		TRUE	FALSE	I do not know
1	During Glofitamab treatment most cases of Tumour Flare events have been reported to occur during cycle 1 and no Tumour Flare events occurred beyond cycle 2	( )	( )	( )
2	Glofitamab treatment should be discontinued permanently in the occurrence of Tumour Flare	( )	( )	( )
3	Adverse events of Tumour Flare involving lymph nodes in the head and neck and involving lymph nodes in the thorax have been reported with Glofitamab	( )	( )	( )
4	The median duration of Tumour Flare event with Glofitamab is 3.5 days	( )	( )	( )

Data: single punch per row, random order

[redacted]

Q10. According to your knowledge of the information in the HCP Brochure, which of the following statements are specific guidance for minimising the risk of Tumour Flare? ***Please choose all that apply.***

1	Proactive monitoring of vital signs, physiological parameters, or implementing prophylactic procedures (e.g., tracheostomy) may be required	( )
2	Patients with tumours involving critical anatomic locations should be closely monitored for Tumour Flare, and prospective preventive or interventional measures may need to be considered or planned prior to dosing	( )
3	Tocilizumab should be considered to treat Tumour Flare	( )

Data: multi-punch, random order

[redacted]

Self-reported Adherence to the Safety Messages in the HCP Brochure

Q11. When a patient is receiving Glofitamab for the first time, do you (or other HCPs) usually distribute to the patient the Patient Card?

1	Yes	( )
2	No	( )

Data: single punch

[redacted]”

Q12. Do you (or other HCPs) usually inform patients to carry the Patient Card with them at all times?

1	Yes	( )
2	No	( )

Data: single punch

[redacted]

Q13. When starting treatment, do you (or other HCPs) usually inform the patients on the risk of Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) associated with Glofitamab?

1	Yes	( )
2	No	( )

Data: single punch

[redacted]

Q14. Do you (or other HCPs) usually inform patients to seek medical attention immediately if they have any Cytokine Release Syndrome (CRS) symptoms and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) symptoms associated with Glofitamab treatment?

1	Yes	( )
2	No	( )

Data: single punch

[redacted]

Q15. Prior to the initiation of Glofitamab treatment, do you evaluate the lymphoma distribution to anticipate the potential spectrum of clinical manifestations of Tumour Flare?

1	Yes	( )
2	No	( )

Data: single punch

[redacted]

Usefulness of Educational Materials for Glofitamab

Q16. Have you used the HCP brochure as a source to gain awareness and knowledge of Tumour Flare associated with Glofitamab?

Q16 To be asked only if question 7 is "YES"

1	Yes	( )
2	No	( )

Data: single punch

[redacted]"

Q17. Have you used other sources to gain awareness and knowledge of Tumour Flare associated with Glofitamab? *Please choose all that apply*.

1	Yes, I used Glofitamab Summary of Product Characteristics (SmPC)	( )
2	Yes, I used Columvi™/ Glofitamab website	( )
3	Yes, I used clinical guidelines	( )
4	Yes, I used scientific articles about Glofitamab (scientific articles published in peer review journals)	( )
5	Yes, I used scientific conference materials about Glofitamab (lectures, abstracts)	( )
6	Yes, I used other sources from internet	( )
7	If others, please specify (open text)	( )
8	No	( )

Data: multi-punch

[redacted]

Thank you for your participation in this study

Signature Page for Protocol - BO44309 - COLUMVI - v3 - Global/Core
System identifier: RIM-CLIN-1103758

Approval Task	[redacted] Company Signatory 07-Nov-2025 09:59:00 GMT+0000