VERTEX PHARMACEUTICALS INCORPORATED

PASS / Study 102 Information

Title	Healthcare Professional Survey (HCP) to Assess the Effectiveness of the Additional Risk Minimization Measures (aRMM) for Casgevy® (exagamglogene autotemcel)
Protocol version identifier	3.0
Date of last revision of protocol	Not applicable
HMA-EMA Catalogues of Real-World Data register number	Not yet registered
Active substance	B06AX05, exagamglogene autotemcel
Medicinal product	Casgevy
Product reference	EMEA/H/C/005763
Procedure number	Not applicable
Marketing authorisation holder(s)	Vertex Pharmaceuticals (Ireland) Limited
Joint PASS	No
Research question and objectives	The HCP Survey will assess the following: 1. The HCPs' understanding of the important safety information in the Guide for HCPs regarding the important identified risk of delayed platelet engraftment, the important potential risks of neutrophil engraftment failure and gene editing-related oncogenesis, and the missing information on long-term effects. 2. The HCPs' awareness of the aRMM tools. 3. The HCPs' utilization of the aRMM tools (behavior)
Country(-ies) of study	All EU countries where Casgevy has launched.
Author	Vertex Pharmaceuticals (Ireland) Limited

Marketing Authorisation Holder(s)

Marketing authorisation holder(s)	Vertex Pharmaceuticals (Ireland) Limited
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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
α	apparent distribution rate constant
aRMM	additional risk minimization measure
ATC	authorized treatment center
β	apparent elimination rate constant
Cas9	CRISPR-associated protein 9
CIOMS	Council for International Organizations of Medical Sciences
CRISPR	clustered regularly interspaced short palindromic repeats (occurring in the genome of certain bacteria)
CRO	contract research organization
DNA	deoxyribonucleic acid
EDC	electronic data capture
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
γ	sigmoidicity factor (Hill coefficient)
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HbA	adult hemoglobin
HbF	fetal hemoglobin
HbS	sickle hemoglobin
HCP	healthcare professional
HLA	human leukocyte antigen
HSC	hematopoietic stem cell
ICH	International Conference for Harmonisation
IEA	International Epidemiological Association
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KRM	Key Risk Message
MAH	Marketing Authorization Holder
MSL	Medical Scientific Liaison
NCA	National Competent Authority
PAS	Post-authorization Study
PASS	Post-authorization Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
RBC	red blood cell
RMP	risk management plan
RNA	ribonucleic acid
SCD	sickle cell disease
TDT	transfusion-dependent β-thalassemia
US	United States
USA	United States of America
VOC	vaso-occlusive crisis
WHO	World Health Organization

3 RESPONSIBLE PARTIES

Sponsor	Vertex Pharmaceuticals (Ireland) Limited
CRO	United BioSource, USA

4 ABSTRACT

Title	Healthcare Professional Survey (HCP) to Assess the Effectiveness of the Additional Risk Minimization Measures (aRMM) for Casgevy® (exagamglogene autotemcel)
Rationale and Background	Casgevy received Marketing Authorization from the European Commission on 09 February 2024 for the indications of: • The treatment of transfusion-dependent β-thalassemia (TDT) in patients 12 years of age and older for whom hematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available. • The treatment of severe sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso-occlusive crises (VOCs) for whom HSC transplantation is appropriate and an HLA-matched related HSC donor is not available. Delayed platelet engraftment is an important identified risk for Casgevy. Neutrophil engraftment failure and gene editing-related oncogenesis are important potential risks. As the long-term effects of Casgevy are not known, the long-term effect of Casgevy is considered to be missing information. aRMMs, consisting of a Guide for HCPs, a Guide for Patients/Carers and a Patient Card, have been developed to inform HCPs and patients of the important identified and important potential risks and the missing information. This survey will evaluate the effectiveness of these aRMMs.
Research Question and Objectives	This study aims to measure the effectiveness of the aRMM for Casgevy by assessing HCPs' knowledge and behaviour in relation to the educational materials. It will specifically assess: 1. The HCPs' understanding of the important safety information in the Guide for HCPs regarding the important identified risk of delayed platelet engraftment, the important potential risks of neutrophil engraftment failure and gene editing-related oncogenesis, and the missing information on long-term effects. 2. The HCPs' awareness of the aRMM tools. 3. The HCPs' utilization of the aRMM tools (behavior).
Study Design	This is a multi-national, observational cross-sectional design
Population	The target population will be HCPs at Authorized Treatment Centers (ATC) in EU countries who have counseled patients regarding Casgevy as a treatment option.

Variables

The following variables will be collected:

- Response to questions about important safety information detailed in the Guide for HCPs.
- HCPs' awareness of the Guide for HCPs, Guide for Patients/Carers and Patient Card.
- Whether or not the Guide for Patients/Carers and the Patient Card are being distributed to patients treated with Casgevy.
- Demographic information
- Source of safety information

Data Sources

The data source will be surveys completed by HCPs who have counseled patients regarding Casgevy as a treatment option at ATCs.

Study Size

The target sample size is approximately 30 completed surveys. Invitations will be sent to all potentially eligible HCPs at ATCs in EU countries where Casgevy has launched with the expectation to obtain approximately 30 completed surveys.

Data Analysis

Data collected from the survey will be reported as descriptive statistics. Categorical variables will be summarized using counts and percentages. The main analysis will be based upon completed surveys. Subgroup analyses may be performed depending upon counts.

Percentages of correct answers will be calculated for each of the 4 Key Risk Messages (KRMs). If at least 80% of HCPs understand a KRM, that message of the aRMM will be considered successful.

Milestones

Milestone	Planned Date[a]
Start of data collection	18 months after first drug availability has been achieved in any EU country. Estimated to be Q4 2026.
End of data collection	24 months after first drug availability has been achieved in any EU country. Estimated to be Q2 2027.
Registration in HMA-EMA Catalogue of RWD Studies	Upon approval of protocol by the PRAC and prior to start of data collection. Estimated Q3 2025.
Final report of study results	6 months after end of data collection. Estimated Q4 2027.

ATC: authorized treatment center; EU: European Union; PAS: post-authorization study; PRAC: Pharmacovigilance Risk Assessment Committee; Q: Quarter

[a] Planned dates are provisional and are dependent upon first drug availability in each country. Drug availability is defined as drug delivery to an ATC.

5 AMENDMENTS AND UPDATES

Number	Date	Section of Study Protocol	Amendments or Updates	Reason
None				

6 MILESTONES

Milestone	Planned Date[a]
Start of data collection	18 months after first drug availability in any EU country. Estimated to be Q4 2026.
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ATC: authorized treatment center; EU: European Union; PAS: post-authorization study; PRAC: Pharmacovigilance Risk Assessment Committee; Q: Quarter

[a] Planned dates are provisional and are dependent upon first drug availability in each country. Drug availability is defined as drug delivery to an ATC.

7 RATIONALE AND BACKGROUND

TDT is the most severe form of β-thalassemia and is characterized by very severe anemia requiring regular transfusions. Frequent transfusions can lead to iron overload with related complications that include diabetes and other endocrine diseases, cardiomyopathy, and liver fibrosis and cirrhosis, whereas insufficient transfusion therapy can be responsible for growth retardation, skeletal abnormalities, leg ulcers, and spleen and liver enlargement due to extra-medullary hematopoiesis.[1-7] Symptoms of TDT first become apparent as early as 6 months of age as fetal hemoglobin (HbF) decreases and can be fatal in early life if untreated.

In 2008, the World Health Organization (WHO) estimated about 25,511 patients with TDT are born globally each year. The exact global prevalence of TDT is unknown. According to 2008 WHO estimates, there were 97,630 known patients with β-thalassemia globally, including all disease phenotypes and not limited to TDT. Within Europe this included an estimated minimum of 1,019 annual births with β-thalassemia including 920 with TDT.[8]

SCD is an inherited group of hematological disorders characterized by the production of sickle hemoglobin (HbS), a structural variant of normal adult hemoglobin (HbA).[9] The sickle β-globin mutation can be heterozygous (e.g., HbAS) or homozygous (HbSS). HbSS individuals experience a severe shortage of healthy red blood cells (RBCs) leading to acute and chronic complications across the lifespan. The homozygous HbSS genotype, commonly referred to as sickle cell anemia, accounts for over 80% of cases of SCD.[10]

Globally, SCD incidence was estimated at approximately 112 per 100,000 live births, varying significantly by region.[11] Due to a lack of robust screening programs and national registries, data on the global SCD prevalence are of variable quality and availability. Overall, of the 20 to 25 million individuals with SCD worldwide, 12 to 15 million are estimated to be from sub-Saharan Africa, 5 to 10 million from India, and about 3 million distributed in different

parts of the world.[12] In the European Economic Area, it is estimated that there are approximately 52,000 patients with SCD.[13]

Casgevy is a cell-based gene therapy consisting of autologous $CD34^+$ human hematopoietic stem and progenitor cells edited ex vivo by clustered regularly interspaced short palindromic repeats-associated 9 nuclease (CRISPR/Cas9) technology. The highly specific guide RNA enables CRISPR/Cas9 to make a precise DNA double-strand break at the critical transcription factor binding site, GATA1, in the erythroid specific enhancer region of the *BCL11A* gene. As a result of the editing, GATA1 binding is irreversibly disrupted and *BCL11A* expression reduced. Reduced *BCL11A* expression results in an increase in γ-globin expression and HbF protein production in erythroid cells, addressing the absent globin in TDT and the aberrant globin in SCD, which are the underlying causes of disease. In patients with TDT, γ-globin production is expected to correct the α-globin to non-α-globin imbalance, thereby reducing ineffective erythropoiesis and hemolysis and increasing total hemoglobin levels. In patients with severe SCD, HbF expression is expected to reduce intracellular HbS concentration, preventing the RBCs from sickling.

Casgevy received Marketing Authorization from the European Commission on 09 February 2024 for the indications of:

- The treatment of TDT in patients 12 years of age and older for whom HSC transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available.
- The treatment of severe SCD in patients 12 years of age and older with recurrent VOCs for whom HSC transplantation is appropriate and an HLA-matched related HSC donor is not available.

Delayed platelet engraftment is an important identified risk for Casgevy. Neutrophil engraftment failure and gene editing-related oncogenesis are important potential risks. As the long-term effects of Casgevy are not known, the long-term effects of Casgevy is considered to be missing information.

The aRMMs, consisting of a Guide for Healthcare Professionals (HCPs), a Guide for Patients/Carers and a Patient Card, have been developed to inform HCPs and patients of the important identified and important potential risks and the missing information. These materials are distributed to HCPs at EU centers with experience in hematopoietic stem cell transplantation who are authorized to treat patients with Casgevy. HCPs are required to provide the Guide for Patients/Carers and the Patient Card to patients when presenting Casgevy as a treatment option and prior to the patient's decision for Casgevy treatment.

This survey will evaluate the HCPs' understanding of the Casgevy safety information detailed in the Guide for HCPs and evaluate the level of their awareness and utilization of the Guide for HCPs, Guide for Patients/Carers and Patient Card.

8 RESEARCH QUESTIONS AND OBJECTIVES

This study aims to measure the effectiveness of the aRMM for Casgevy by assessing HCPs' knowledge and behaviour in relation to the educational materials. It will specifically assess:

1. The HCPs' understanding of the important safety information in the Guide for HCPs regarding the important identified risk of delayed platelet engraftment, the important potential risks of neutrophil engraftment failure and gene editing-related oncogenesis, and the missing information on long-term effects.

2. The HCPs' awareness of the aRMM tools.
3. The HCPs' utilization of the aRMM tools (behavior).

9 RESEARCH METHODS

9.1 Study Design

This study uses a multi-national, observational cross-sectional design. It is a web-based survey using close-ended multiple-choice questions.

9.2 Setting

Data collection via a web-based survey will be initiated in all countries in the EU where Casgevy is launched approximately 18 months after first drug availability has been achieved in any EU country.

The Guide for HCPs, the Guide for Patients/Carers and the Patient Card are provided to HCPs who are trained on the use of Casgevy at authorized treatment centers (ATCs) in each country in accordance with local distribution/communication plans as agreed by National Competent Authorities (NCAs). As both TDT and SCD are rare diseases and Casgevy is a new novel therapy, there are a limited number of HCPs per country who counsel eligible patients.

The target population will be all HCPs who have counseled patients regarding Casgevy as a treatment option across all ATCs in all EU countries where Casgevy is launched. The same survey will be used for all participating countries to ensure consistency in testing the target population. As such, variability of survey results based on geography is not anticipated.

In the event that the target number of completed surveys is not obtained after the survey has been implemented and should additional ATCs be activated, the Marketing Authorization Holder (MAH) will extend the survey, in order to reach the target number of completed surveys.

The survey will be administered via the internet, which will allow respondents to participate at a time and location that is convenient for them.

Eligible HCPs who respond to the survey invitation will make up the study population. Survey invitations will be sent to all potentially eligible HCPs at all ATCs in the EU where Casgevy is launched, with the expectation to obtain approximately 30 completed responses (see Section 9.5 Study Size).

9.2.1 Inclusion Criteria

HCPs must meet the following criterion for inclusion in the survey:

- Have counseled at least 1 patient regarding Casgevy as a treatment option.

9.2.2 Exclusion Criteria

HCPs who meet the following criterion will not be permitted to take the survey:

- Individuals who currently work directly for, or whose immediate family members currently work directly for Vertex or any of its affiliates, the EMA or any NCA.

9.3 Variables

The survey will commence with screening questions and will collect responses to each question required to address the study objectives:

- Response to questions about important safety information detailed in the Guide for HCPs.
- HCPs' awareness of the Guide for HCPs, Guide for Patients/Carers and Patient Card.
- Whether or not the Guide for Patients/Carers and the Patient Card are being distributed to patients treated with Casgevy.

In addition, demographic information and information on where the HCP sourced the safety information will be collected.

9.4 Data Sources

The data source will be surveys completed by HCPs who have counseled patients regarding Casgevy as a treatment option at ATCs.

The HCPs will receive an invitation letter to participate in the survey. The invitation letter (APPENDIX 1.2) will include: an overview of the rationale for the survey, information on how to access the survey online and a unique invitation code to ensure that the invitation is used only once. Based on survey uptake, reminder notices will be sent to those who have been invited but have not yet participated. Participating HCPs' identifying information will be collected for the purposes of providing financial compensation based on Fair Market Value, as allowed by local laws and country regulations and to comply with laws and regulations regarding notification of payments made on behalf of a pharmaceutical company.

A structured, self-administered questionnaire will be used to collect survey data (APPENDIX 1.1). It is comprised of closed-ended questions and statements with multiple response choices.

User testing will be performed prior to finalization of the questionnaire. The user testing procedure is designed to assess comprehension among HCPs regarding the words and phrases used in survey questions and response options. User testing will also assess the clarity of the survey questions as presented to the HCPs and the flow and ease of completing the survey. Findings and recommendations from the user testing will be incorporated into the survey.

The survey will be voluntary. The collection of any personal, identifying information (e.g., first name, last name, address) from respondents will only be used for processing of HCPs' financial compensation, as stated above and will be stored in a separate database.

Each individual will be randomly assigned a unique code to access the survey. Each unique code will be deactivated upon use to prevent the code from being used to complete the survey multiple times. Individuals will not have to actively "decline to complete the survey." Participants who agree to respond to the survey will begin with a screening module with questions to confirm eligibility.

9.5 Study Size

The target sample size is approximately 30 completed surveys. Invitations will be sent to all potentially eligible HCPs at all ATCs in the EU where Casgevy is launched, with the expectation to obtain approximately 30 completed surveys. The study size is not based on statistical considerations but has been determined by considering the rarity of SCD and TDT and the small number of HCPs who will counsel patients regarding use of Casgevy as a treatment option. Depending upon the country population and healthcare organization, it is estimated that there will typically be fewer than 10 centers per country that will treat patients with Casgevy. Thus, the potential pool of HCPs eligible to participate in the survey is small.

While it is generally accepted that uptake to invitations for survey participation is generally low, it is anticipated that the response rate to the Casgevy survey will be higher for the following reasons: the MAH has well-established relationships with the potential participants and field medical liaisons are in regular face-to-face contact with potential participants and these contacts will be used to encourage participation. However, as stated in Section 9.2 above, survey invitations will be extended in time if the target of 30 completed surveys is not reached, should additional ATCs be activated. Estimated precision based upon a sample size of 30 is set out in Table 1 below.

Table 1 Estimated Precision, by Sample Size and Proportion

Sample Size	Proportion of Correct Responses Observed (%)	Precision[a] Low (%)	Precision[a] High (%)
30	20	7.7	38.6
	40	22.7	59.4
	60	40.6	77.3
	80	61.4	92.3
	90	73.5	97.9
	100	88.4	100.0

[a] 95% confidence interval, 2-sided (Clopper-Pearson 1934 method[14]).

9.6 Data Management

All data collected during the survey will be confidential. The electronic data capture (EDC) system used for data collection does not include any respondent-identifying information. Respondent identifiers are stored in a separate encrypted electronic database from the survey responses and are used solely for the purposes of payment to respondents where allowed by local regulations and to comply with laws and regulations regarding notification of payments made on behalf of a pharmaceutical company. No respondent contact information will be included in the tables or in the final report.

The survey is programmed to ensure that respondents cannot go back or skip ahead. Survey knowledge questions for the Key Risk Messages (KRM) which are described in Section 9.7.4 will not be categorized by subject, rather all questions will be presented individually in a random order to minimize positional bias. There will be no follow-up questions to respondents.

Throughout the course of the study, a full back-up of the data will be performed on a nightly basis and cumulative back-ups will also be performed on a weekly basis. Back-up files will be stored at a secure off-site location.

9.7 Data Analysis

Data collected from the survey will be reported as descriptive statistics. Categorical variables will be summarized using counts and percentages.

9.7.1 Analysis Sets

All Respondents – The All Respondents population consists of respondents that have accessed the survey using a unique code. These respondents will be used as the denominator for percentages in select HCP Participation analyses.

Completed Surveys (Primary Population) – The Primary population for all remaining analyses includes only those with completed surveys. "Completed" is defined as an eligible respondent who has no missing data with the exception of data from programmed skip patterns. An eligible respondent is defined as one who completed all eligibility questions and has met all inclusion criteria and none of the exclusion criteria.

If a sufficient number of HCPs log in but do not complete the survey, additional analyses may be conducted on these partial completers.

Subgroup analyses may be performed depending upon counts. Additional analyses may be conducted as requested by regulators.

9.7.2 Summary of HCPs' Participation

The following will be summarized:

- The number of survey invitations.
- The number and percent of survey invitations/reminders returned due to incorrect mailing/emailing address of HCPs invited to participate in the survey.
- The number and percent of HCPs who responded to the invitation to participate in the survey.
- The number and percent of HCPs who meet the inclusion criteria for participation in the survey.
- The number and percent of HCPs who do not meet the inclusion criteria along with the reasons for ineligibility.
- The number and percent of HCPs who meet the inclusion criteria who completed the survey.
- The number and percent of HCPs who meet the inclusion criteria who partially completed the survey.

9.7.3 Summary of HCP Characteristics

The following demographic information of participants will be summarized using the Completed Surveys analysis set:

- Number and percent of HCPs by age groups.
- Number and percent of HCPs by number of patients counseled regarding Casgevy as a treatment option.
- Number and percent of HCPs by profession.

9.7.4 Analysis for Objective of HCPs' Understanding of the Important Safety Information in the Guide for HCPs

Eighteen knowledge questions will test the HCPs understanding of 4 KRMs. The response to each of the 18 questions will be categorized as correct or incorrect. The table below outlines the 4 KRMs and the individual questions evaluating each message.

Using the Completed Surveys analysis set, the rate of correctness (percentage of correct answers) will be summarized for each of the 4 KRMs. The aRMM pertaining to each KRM will be considered successful if the correct rate for the specific KRM is at least 80%.

In addition, the source of knowledge of the safety information will also be summarized.**KRM**	**Desired Response**
Please indicate if each provided statement is correct or incorrect.	
KRM 1 Delayed Platelet Engraftment	
8. Casgevy has not been associated with delayed platelet engraftment. 9. Patients receiving Casgevy should be counseled on signs and symptoms of bleeding. 10. If a patient experiences petechiae prior to achieving platelet engraftment, there is no need to perform a platelet count. 11. After achieving platelet engraftment, a patient does not require management in case of severe thrombocytopenia. 12. Patients receiving Casgevy should be monitored and managed for platelet counts according to standard guidelines and medical judgement.	9 and 12 marked as correct.
KRM 2 Neutrophil Engraftment Failure	
13. For patients who have neutrophil engraftment failure a second dose of Casgevy should be considered. 14. Patients who receive CD34+ backup cells will still obtain the benefits of Casgevy. 15. Patients who have neutrophil engraftment failure should receive CD34+ backup cells. 16. Patients should be advised to seek medical assistance if they experience fever, chills or infections because they could be symptoms of low white blood cells. 17. On top of monitoring and managing absolute neutrophil counts and infections according to standard guidelines and medical judgement, a regular biopsy should be performed.	15 and 16 marked as correct
KRM 3 Gene Editing-related Oncogenesis	
18. Patients should be advised to seek medical assistance if they experience any signs or symptoms of a hematologic malignancy. 19. Patients should be monitored annually, including complete blood counts, and managed according to standard guidelines and medical judgement. 20. Patients should get a bone marrow biopsy 2 years after Casgevy treatment. 21. If blood and/or bone marrow are collected for confirmation of a hematologic malignancy, additional samples should be taken for analysis by the marketing authorization holder to evaluate the association of malignancy with Casgevy treatment.	18, 19, and 21 are marked as correct
KRM 4 Long-term Effect	

22. Long-term effects of Casgevy are not yet known and therefore a registry-based study to follow patients who have received Casgevy is undertaken. 23. A registry-based study will be set up in which patients are followed up and treated according to standard clinical practice. 24. Patients should be informed about the importance of enrolling in a registry-based study with 15-year follow-up. 25. Only patients enrolled in the registry-based study for Casgevy can receive treatment with Casgevy.	22, 23, and 24 are marked as correct

9.7.5 Analysis for Objectives of HCPs' Awareness of the aRMM Tools

The following will be summarized using the Completed Surveys analysis set:

- The proportion who report being aware of the Guide for HCPs.
- The proportion who report having received the Guide for HCPs.
- The proportion who report having read the Guide for HCPs.
- The proportion who report being aware of the Guide for Patients/Carers.
- The proportion who have received copies of the Guide for Patients/Carers.
- The proportion who report being aware of the Patient Card.
- The proportion who have received copies of the Patient Card.

9.7.6 Analysis for Objectives of HCPs' Utilization of the aRMM Tools

The following will be summarized using the Completed Surveys analysis set:

- The proportion distributing the Guide to Patients/Carers prior to treatment decision.
- The proportion distributing the Patient Card prior to treatment decision.

9.8 Quality Control

Data will be collected using a secure and validated online EDC system. The Information Technology applications are governed by a development approach to ensure compliance to international regulations and guidance: US FDA (Guidance for Industry: Computerized Systems Used in Clinical Trials[15] and Code of Federal Regulations Title 21 Part 11[16]), European Commission (EudraLex Annex 11: Computerised Systems[17]), EMA (e.g., EU Good Pharmacovigilance Practices [GVP][18]) and International Council for Harmonisation (ICH).[19] The system is compliant for the entry, storage, handling, analysis, and transmission of electronic information.

Respondent-identifying information will be stored separately from the survey responses.

The EDC system will be set up such that HCPs who do not answer screening questions or who provide responses indicating ineligibility will be automatically unable to complete the survey. These ineligible HCPs will be provided with a message thanking them for their time and explaining their ineligibility to participate.

9.9 Limitations of the Research Methods

Participants will be self-selected since they will voluntarily respond to the invitation to participate, so those who choose to respond to the survey may differ in their understanding of

the important safety information from those who elect not to participate. This is a common limitation of all studies that rely on voluntary participation.

It is also possible that the respondents have an acceptable understanding of the important safety information despite not using the Guide for HCPs. The survey can assess the HCPs' understanding of the important safety information but cannot clearly determine if their knowledge is a result of reading the Guide for HCPs.

All data from the survey are self-reported and therefore susceptible to possible reporting bias. An HCP may know and report the desired behavior even if they do not undertake such behavior to provide a socially desirable response.

There is also the possibility that the email invitation may be blocked or marked as spam in the HCPs' email. This can be mitigated by field staff (Medical Scientific Liaisons [MSLs]) personally discussing this study with relevant HCPs during encounters.

As TDT and SCD are rare diseases and Casgevy is a novel therapy, the number of centers treating patients with Casgevy, the number of patients eligible for Casgevy treatment, and the number of HCPs counseling eligible patients is likely to be small. To increase response rates to the survey invitation, the MSLs will emphasize the importance of the survey as part of a regulatory commitment during encounters with relevant HCPs.

9.9.1 Controls to Minimize Bias

A number of controls will be in place to ensure that the survey is conducted to minimize bias, including the following:

- Knowledge questions will be randomized and presented individually to minimize the potential for positional bias.
- HCPs cannot skip ahead or go back to a question once the question has been answered. All questions presented must be answered in order to complete the survey.
- HCPs will be provided with a unique code during the recruitment process in order to gain access to the internet-based systems. The code will be inactivated after use to minimize exposure bias and fraud.
- Respondent identifiers will be stored separately from survey responses thus limiting HCP concerned that their answers will be identified. This is likely to minimize the social desirability bias and improve response rates.

9.10 Other Aspects

Not Applicable

10 PROTECTION OF HUMAN SUBJECTS

10.1 Personal Information and Consent

All data collected during the survey will be kept confidential and used only for the purposes stated in the survey instructions. The collection of any personal, identifying information (first name, last name, address) from respondents will only be used for the processing of the HCPs' financial compensation and to comply with laws and regulations regarding notification of payments made on behalf of a pharmaceutical company. Respondent identifiers will be stored in a separate encrypted electronic database from the survey responses. The EDC system used for data collection of the survey responses does include any identifiable information.

By answering the first question of the survey ("*Do you agree to participate in this survey?*"), respondents are providing informed consent for participation in the research study.

10.2 Respondent Withdrawal

Respondents can decline to participate or stop taking the survey at any time.

10.3 Ethics Committee

Approval of this protocol by the respective local Ethics Committee will be obtained prior to initiating the survey in each country, where applicable.

10.4 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor, and follow generally accepted research practices described in:

- *Guideline on Good Pharmacovigilance Practices (GVP) Module XVI - Risk Minimisation Measures: Selection of Tools and Effectiveness Indicators*[20],
- *Guidance for Good Pharmacoepidemiological Practice* issued by the International Society of Pharmacoepidemiology (ISPE)[21],
- *International Ethical Guidelines for Epidemiological Research* issued by the Council for International Organizations of Medical Sciences (CIOMS)[22], and
- *Guide on Methodological Standards in Pharmacoepidemiology* issued by the EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).[23]

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS / ADVERSE REACTIONS

Adverse events will not be actively collected as this study is assessing HCPs' understanding of the important safety information detailed in the Guide for HCPs and the distribution of the Patient/Carer Guide and Patient Card to patients being treated with Casgevy.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The final report will be submitted to the EMA and other regulatory agencies as applicable. The study, including the final report, will also be registered in the Heads of Medicines Agencies - EMA Catalogues of real-world data sources and studies. The study findings may be submitted to a scientific congress and/or to a peer-reviewed journal.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Title
1	Appendix 1.1	Healthcare Professional Survey
2	Appendix 1.2	Sample Draft Survey Invitation Letter for Healthcare Professional
3	Appendix 1.3	Guide for HCPs, Guide for Patients/Carers and Patient Card