Post-Authorisation Safety Study Protocol

Non-Interventional Post-Authorisation Safety Study (PASS) survey to evaluate the effectiveness of the Isatuximab Educational Materials, to minimise the Risk of Interference for blood typing (minor antigen) (positive indirect Coombs' test).

SARCLISA (Isatuximab)

Study No.:	SARSAC09715
EU PAS Register No.:	EUPAS46988
Sponsor (MAH):	Sanofi-Aventis Groupe
Protocol edition No.:	1.4
Date of protocol edition:	21 October 2021

PASS Information – Study SARSAC09715 – Non-Interventional PASS survey to evaluate the effectiveness of the Isatuximab Educational Materials

Study title:	Non-Interventional Post-Authorisation Safety Study (PASS) survey to evaluate the effectiveness of the Isatuximab Educational Materials, to minimise the Risk of Interference for blood typing (minor antigen) (positive indirect Coombs' test)
Protocol edition No.:	1.4
Date of protocol edition:	21 October 2021
EU PAS register No.:	EUPAS46988
Active substance:	Isatuximab (ATC code: L01XC38)
Medicinal product:	SARCLISA
Product reference:	EMEA/H/C/004977/XXXX
Procedure No.:	EMEA/H/C/004977/XXXX
Marketing Authorisation Holder:	Sanofi-Aventis Groupe
Joint PASS:	No
Research question and objectives:	The study aims to assess the effectiveness of the isatuximab Educational Materials in terms of process indicator, meaning implementation, knowledge ar behaviour with respect to the safety messages conveyed in these materials. Objectives: 1) Describe the implementation of the additional Risk Minimisation Measures (aRMMs) to the target population, the time period(s) of implementation in each participating country (starting from local regulatory approval) and materials used, 2) Assess the knowledge of the target audience about the risk and its management 3) Assess the behaviour of HCPs with respect to the safety messages
Countries of study:	5 countries confirmed for participation: France, Switzerland, Austria, Sweden, and the Netherlands. 9 countries will be included, and the other potential countries include (but are not restricted to): Germany, Finland, United Kingdon (UK), Italy, Poland and Hungary
Author:	Epidemiology and Benefit-Risk, Global Pharmacovigilance

Marketing Authorisation Holder

Marketing Authorisation Holder (MAH):	Sanofi-Aventis Groupe 54 rue La Boétie, 75008 Paris France
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2 List of Abbreviations

AE	Adverse event
aRMM	Additional risk minimisation measures
ASCT	Autologous stem cell transplant
ATC	Anatomical therapeutic chemical
CD	Cluster differentiation
DTT	Dithiothreitol
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GVP	Good pharmacovigilance practices
HCP	Healthcare professional
IAT	Indirect Antiglobulin test
MAH	Marketing Authorisation Holder
MM	Multiple myeloma
PASS	Post-authorisation safety study
PL	Package leaflet
PSUR	Periodic Safety Update Report
Q1	First quantile
Q3	Third quantile
RBC	Red blood cell
SAP	Statistical analysis plan
SmPC	Summary of Product Characteristics
WHO	World Health Organization
UK	United Kingdom

3 Responsible Parties

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4 Abstract

Title
Non-Interventional PASS survey to evaluate the effectiveness of the isatuximab Educational Materials, to minimise the Risk of Interference for blood typing (minor antigen) (positive indirect Coombs' test.

Study No.
SARSAC09715

Protocol Edition No. and Date
1.4, 21 October 2021

Author
Epidemiology and Benefit-Risk, Global Pharmacovigilance

Rationale and Background

Multiple myeloma (MM) is a malignant plasma cell disease that is characterised by clonal proliferation of plasma cells in the bone marrow and the production of excessive amounts of a monoclonal immunoglobulin. The estimated 5-year prevalence of multiple myeloma reported by the International Association for Research on Cancer (in 2018) is 120 391 (16.2 per 100,000).(1) MM is a disease predominantly associated with advanced age with more than 80% of patients aged 60 years or older. Patients with MM are likely to develop bone pain, bone fractures, fatigue, anaemia, infections, hypercalcemia, and renal function impairment, because of their disease.(2)

The disease course for MM varies with the aggressiveness of the disease and related prognostic factors. Treatment options and survival are based on the patient's age, fitness, and disease status. Patients under the age of 65, and presenting with symptomatic active disease in good physical health, will generally receive initial therapy with autologous stem cell transplantation (ASCT).(3) To achieve cytoreduction of the disease before collecting stem cells, induction chemotherapy is administered. In the long term, however, there is currently no cure for multiple myeloma, which is characterised with frequent relapses.

Isatuximab is a naked monoclonal antibody targeting a cluster of differentiation (CD) 38, a cell surface antigen expressed in haematological malignancies from B-lymphocyte, T-lymphocyte and myeloid origin. Isatuximab has been investigated with various regimens, including in combination with pomalidomide and dexamethasone for the treatment of multiple myeloma in a Phase 3 randomised, open-label, multicentre study in patients with refractory or relapsed and refractory multiple myeloma (ICARIA-MM).(4)

The approved therapeutic indication for SARCLISA (isatuximab) is in combination with pomalidomide and dexamethasone, for the treatment of adults patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy. On 25 February 2021, the CHMP Positive Opinion was received and on 15 April 2021, the European Commission decision was issued for the extension of indication for SARCLISA (isatuximab) in combination with carfilzomib and dexamethasone (kd) for the treatment of adult patients with relapsed multiple myeloma who have received at least one prior therapy.

The European Commission decision for marketing authorisation approval was obtained on 30 May 2020. Routine pharmacovigilance will be carried out to monitor the safety of SARCLISA. Additional risk minimisation activities are proposed to minimise the following important identified risk: interference for blood typing (minor antigen) (positive indirect Coombs' test). The rationale for these additional risk minimisation activities is that isatuximab binds to endogenous CD38 found at low levels on red blood cells (RBC) and may interfere with blood bank compatibility testing, including antibody screening and cross-matching. Lack of RBC phenotyping prior to starting the isatuximab treatment, could therefore result in adverse clinical outcomes for the patient due to delaying a transfusion or, in the case of urgent transfusion, there is a small risk of transfusion related haemolysis. In clinical trials, specific instructions are provided to investigational sites to have blood typed and screened performed prior to the initiation of therapy; in the pivotal clinical trial (Study EFC14335),

the proportion of patients who needed red blood cells transfusion was 30% and no RBC transfusion-related complications associated with interference for blood typing were reported.

Some countries (Australia) have established a policy for phenotype screening prior to the initiation of therapy with CD38 class agents, following the marketing approval of the first in class anti-CD38 (daratumumab) and/or methods to mitigate the risks of interference,(5) and such methods will be included in the educational materials developed for isatuximab. The extent of the compliance to this risk mitigation in clinical practice, however, is not known.

It is critical to ensure that key safety precautions conveyed in the educational materials are well understood and adhered to by prescribing healthcare professionals (HCPs) and blood banks in the real-world setting. Additional risk minimisation measures (aRMM) in the form of Educational materials will be distributed to relevant HCPs such as clinicians and blood banks professionals, as well as Patient Cards will be provided to patients via their HCPs. According to the GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2) dated 28 March 2017,(6) evaluating the effectiveness of aRMM is necessary to establish whether an intervention has been effective, and, if not, why and which corrective actions are necessary.

This study is therefore designed to evaluate the following aspects of the aRMM: the process itself (i.e. to which extent the materials have been implemented as planned) and its impact on knowledge and behavioural changes in the target audience.

Research Questions, Objectives and Hypotheses

The study aims to assess the effectiveness of the isatuximab Educational Materials in terms of process indicator, meaning implementation, knowledge and behaviour with respect to the safety messages conveyed in these materials.

Objectives:

1) Describe the implementation of the aRMMs to the target population, the time period(s) of implementation in each participating country (starting from local regulatory approval) and materials used
2) Assess the knowledge of the target audience about the risk and its management
3) Assess the behaviour of HCPs with respect to the safety messages

Hypothesis:

We hypothesize that:

- At least 80% of the HCPs (both prescribers and non-prescribers) will provide correct responses to the first knowledge question, which is identified as the key question.

AND

- 80% of the prescribers will provide correct responses to at least five out of seven behaviour questions.

AND

- 80% of the non-prescribers will provide correct responses to at least two out of three behaviour questions.

Study Design

This is a non-interventional cross-sectional study among HCPs involved in the treatment of MM with SARCLISA (isatuximab) in selected European countries.

The study is a cross-sectional survey planned to be conducted within 12 to 18 months after implementation of educational materials in each country. The surveys will be conducted online, using structured questionnaires, comprising close-ended questions where the response format is either the selection of a single response or selection of a number of responses as appropriate. Information will be collected from HCPs using the online LiveTracker™ platform. LiveTracker™ is a cloud-based, real-time, continuous electronic data collection platform tracker that delivers real-world evidence data.

This PASS will be conducted according to the Guideline on good pharmacovigilance practices (GVP) – Module VIII (Rev 3) dated 9 October 2017 2017 (7) and according to scientific standards defined in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) guide on methodological standards(8)

Population

The survey will be self-administered through electronic communication in countries selected considering the following criteria:

- Target population size (haematology/oncology centres and blood banks/transfusion centres)
- Representativeness in terms of European region
- Feasibility in terms of regulatory implementation at national level

The GVP Module XVI guidelines recommend that effectiveness of aRMMs is measured within 12 to 18 months after implementation of the material(s). As a result, data collection would start within 3 months of protocol approval (between Q3 2021 and Q2 2022). The number of countries will be defined in order to reach the overall target sample size in representative areas of Europe. Based on the estimated launch sequence that will be progressive throughout 2021 and the due date for the final report in Q3 2023, the data collection will most likely take place until at least the end of 2022 and potentially up to Q1 2023.

Countries confirmed for participation: France, Switzerland, Austria, Sweden, and the Netherlands. There will be a maximum of nine countries included in this study and the other potential countries include (but are not restricted to): Germany, Finland, United Kingdom (UK), Italy, Poland and Hungary.

HCPs who meet each of the inclusion criteria and none of the exclusion criteria are eligible to participate in this study.

Inclusion Criteria

- The HCP is involved in the management and follow-up of multiple myeloma, such as oncology/haematology specialists and HCPs associated with blood banks/transfusion centres who have not necessarily prescribed isatuximab.
    - Prescribers (Oncologists/Haematologists): The HCP has prescribed isatuximab at least once.
    - Non-prescribers (Blood banks/transfusion centres): The HCP has provided blood products at least once for a patient treated with isatuximab.
- The HCP provides consent to participate.

Exclusion Criteria

- The HCP has previously been enrolled in this study.

Variables

Variables related to the following HCPs' characteristics will be collected:

- Participation (e.g. response rate)
- Practice setting
- Implementation:
    - Receipt of the educational materials
- **Knowledge** of each safety messages

Prescribers	Non-prescribers
1. **Key safety message:** Isatuximab is associated with risk of interference with blood compatibility tests. 2. There is currently no available information on how long the interference may persist after the last infusion of isatuximab. Based on the half-life of isatuximab, the interference with indirect antiglobulin tests may persist for approximately six months after the last infusion.	1. **Key safety message:** Isatuximab is associated with risk of interference with blood compatibility tests. 2. Isatuximab bound to CD38 on RBCs and may mask the detection of antibodies to minor antigens in the patient's serum. Isatuximab may interfere with routine blood compatibility tests with potential false positive reactions in Indirect Antiglobulin test (IAT).

	3. The determination of a patient's ABO and Rh blood type are not impacted.

- **Behaviour** with respect to the actions listed in the educational materials:

Prescribers	Non-prescribers
1. All patients should be blood typed and screened prior to start treatment with isatuximab. 2. Consider phenotyping prior to starting isatuximab treatment as per local practice. 3. If treatment with isatuximab has already started, inform the blood bank that the patient is receiving isatuximab. 4. In the event of a planned transfusion, notify blood transfusion centres about the risk of interference with indirect antiglobulin tests. 5. Verify standing orders for transfusions to determine if your patient received isatuximab within the last year. 6. Give the Patient Card to the patients and advise them to carry it at all time and until months after the last dose of isatuximab. Provide patient's pre-isatuximab compatibility profile, if available, to the blood bank. 7. Ask your patient to tell their other healthcare professionals that they have received isatuximab, particularly before a transfusion, and to show them their Patient Card.	1. In case of urgent need for transfusion, non-cross matched ABO/RhD compatible RBC units can be administered as per local bank practices. 2. The interference mitigation methods include treating reagent RBCs with DTT to disrupt isatuximab binding or other locally validated methods. 3. Since the Kell Blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.

Data Sources

This study will require primary data collection, as the most appropriate method of data collection for the study objectives is through questionnaires. A set of standard questions will be developed for each target group and validated after a testing phase. The target populations will include HCPs involved in the management and follow-up of multiple myeloma, such as oncology specialists and physicians associated with transfusion centres.

Multiple reminders will have to be sent in order to maximise the response rate. A small amount of incentive payment will be made to HCPs as a compensation for the time spent to complete the questionnaire (about 15 minutes).

Study Size

The proportions of interest (p) here are the proportions of HCPs knowledgeable and adherent to the aRMMs.

As the proportion of interest (p) is not known at the time of this document, we may consider it to be 50% (maximum uncertainty). Such a hypothesis yields the most conservative (largest) sample size. Based on a minimum level of precision of 5%, the minimum required sample size would be 384 for precision levels of 5% within each sub-population of interest. In order to obtain this number of completed questionnaires in our study, it is estimated that approximately 6,000 to 9,000 HCPs will be approached.

Feasibility will be evaluated to estimate the number of HCPs to invite in order to obtain the target number of questionnaires correctly answered.

Data Analysis

All the analyses will be descriptive. Continuous variables will be described by their mean, standard deviation, and median, first quantile (Q1), third quantile (Q3), minimum and maximum. Categorical variables will be described as total number and relative percentage per category.

Main analysis

A description of the following outcomes of interest related to process indicators will be performed:

- Measures of the extent of implementation of the original plan, and/or variations in its delivery, at each participating country level.
- Knowledge and Behaviour

The primary analysis population will include the total number of HCPs who returned a valid questionnaire. The proportions of correct and appropriate answers to selected questions will be expressed among HCPs who provided answers to those questions (the missing data will not be counted as a denominator in proportions). Also, the proportion of HCPs who provided correct answers to 70%, 80%, 90% and 100% of the questions will be derived. Last, the proportion of HCPs who have provided correct answers to each of the questions will also be generated.

The threshold of the satisfactory rate is defined as 80% of the HCPs providing correct responses for the following questions:

1 The first knowledge question (key question) for both prescribers and non-prescribers.
AND
2 At least five out of seven behaviour questions for prescribers.
AND
3 At least two out of three behaviour questions for non-prescribers.

The statistical results for knowledge and behaviour will be presented overall and then at country level broken down by subpopulation of interest, i.e. type of HCP.

Exploratory analysis

Of note, similar aRMMs were distributed to HCPs in Europe after the market authorisation was granted to the first-in-class compound (daratumumab). A research article published in February 2021 reported that a total of 408 participants completed the questionnaires. The risk and content of educational materials developed for daratumumab are similar and one can assume that the target population of HCPs is also similar to that of isatuximab. Therefore, a discussion about the proportions observed after the implementation of the risk minimisation measures could be considered against those reported from the daratumumab survey (i.e. pre-post designs), provided that they are available (i.e. publicly disclosed) at the time of this study report preparation/submission. However, due to the lack of access to patient-level data, no statistical comparison will be performed.

Milestones

Milestone	Planned date
Protocol submitted to PRAC	**December 2020** (based on EC decision in June 2020)
Protocol approval by PRAC	**Estimated Q1 2022**
Start of data collection	within 3 months after PRAC approval of protocol **(estimated Q1-Q2 2022)**
End of data collection	**Estimated Q1 2023**
Registration in the EU PAS register	Before data collection starts
Final report of study results	Within 6 months after end of data collection **(estimated Q3 2023)**

5 Amendments and Updates

Amendment or Update No.	Date	Section of Protocol	Amendment or Update	Reason
None	Not applicable	Not applicable	Not applicable	Not applicable

6 Milestones

Milestone	Planned date
Protocol submitted to PRAC	**December 2020** (based on EC decision in June 2020)
Protocol approval by PRAC	**Estimated Q1 2022**
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End of data collection	**Estimated Q1 2023**
Registration in the EU PAS register	Before data collection starts
Final report of study results	Within 6 months after end of data collection **(estimated Q3 2023)**

7 Rationale and Background

Multiple myeloma (MM) is a malignant plasma cell disease that is characterised by clonal proliferation of plasma cells in the bone marrow and the production of excessive amounts of a monoclonal immunoglobulin. The estimated 5-year prevalence of multiple myeloma in Europe reported by the International Association for Research on Cancer (in 2018) is 120 391 (16.2 per 100,000).(1) MM is a disease predominantly associated with advanced age with more than 80% of patients aged 60 years or older. Patients with MM are likely to develop bone pain, bone fractures, fatigue, anaemia, infections, hypercalcemia, and renal function impairment, because of their disease.(2)

The disease course for MM varies with the aggressiveness of the disease and related prognostic factors. Treatment options and survival are based on the patient's age, fitness, and disease status. Patients under the age of 65, and presenting with symptomatic active disease in good physical health, will generally receive initial therapy with autologous stem cell transplantation (ASCT).(3) To achieve cytoreduction of the disease before collecting stem cells, induction chemotherapy is administered. In the long term, however, there is currently no cure for multiple myeloma, which is characterised with frequent relapses.

Isatuximab is a naked monoclonal antibody targeting a cluster of differentiation (CD) 38, a cell surface antigen expressed in haematological malignancies from B-lymphocyte, T-lymphocyte and myeloid origin. Isatuximab has been investigated with various regimens, including in combination with pomalidomide and dexamethasone for the treatment of multiple myeloma in a Phase 3 randomised, open-label, multicentre study in patients with refractory or relapsed and refractory multiple myeloma (ICARIA-MM).(4)

The approved therapeutic indication for SARCLISA (isatuximab) is in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy. On 25 February 2021, the CHMP Positive Opinion was received, and on 15 April 2021, the European Commission decision was issued for the extension of indication for SARCLISA (isatuximab) in combination with carfilzomib and dexamethasone (kd) for the treatment of adult patients with relapsed multiple myeloma who have received at least one prior therapy.(9)

The European Commission decision for marketing authorisation approval was obtained on 30 May 2020.

Routine pharmacovigilance will be carried out to monitor the safety of SARCLISA. Additional risk minimisation activities are proposed to minimise the following important identified risk: interference for blood typing (minor antigen) (positive indirect Coombs' test. The rationale for these additional risk minimisation activities is that isatuximab binds to endogenous CD38 found at low levels on red blood cells (RBC) and may interfere with blood bank compatibility testing, including antibody screening and cross-matching. Lack of RBC phenotyping prior to starting the isatuximab treatment, could therefore result in adverse clinical outcomes for the patient due to delaying a transfusion or, in the case of urgent transfusion, there is a small risk of transfusion related haemolysis. In clinical trials, specific instructions are provided to investigational sites to have blood typed and screened performed prior to the initiation of therapy; in the pivotal clinical trial (Study EFC14335), the proportion of patients who needed red blood cells transfusion was 30% and no RBC transfusion-related complications associated with interference for blood typing were reported.

The goal of the educational materials developed as additional risk minimisation measures (aRMMs) is to:

1. Inform healthcare professionals (HCPs) that isatuximab is associated with risk of interference with blood typing
2. Guide HCPs on the specific actions to manage the interference and avoid possible resulting adverse clinical consequences.

Safety messages listed in the educational materials target two types of HCPs:

1 Medical specialists, such as haematologists and oncologists who prescribe isatuximab to patients (prescribers)
2 HCPs who work in the blood banks and transfusion centres and provide blood product to patients treated with isatuximab (non-prescribers).

More specifically, messages that are targeting prescribers include the length of interference and the actions to take before, during and after isatuximab treatment (e.g., blood typing, blood compatibility profile in the Patient Card, manage blood transfusions); messages targeting non-prescribers include the mechanism of interference, specific types of blood compatibility test affected, and interference mitigation methods for blood transfusion.

Some countries (Australia) have established a policy for phenotype screening prior to the initiation of therapy with CD38 class agents, following the marketing approval of the first in class anti-CD38 (daratumumab) and/or methods to mitigate the risks of interference,(5) and such methods are included in the educational materials developed for isatuximab. The extent of the compliance to this risk mitigation in clinical practice, however, is not known.

It is critical to ensure that key safety precautions conveyed in the educational materials are well understood and adhered to by the HCPs (both prescribers and non-prescribers) in the real-world setting. Educational materials include a brochure (Appendix A) that will be distributed to both types of HCPs, as well as a Patient card (Appendix B) that will be provided to patients via their HCPs.

According to the GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2) dated 28 March 2017,(7) evaluating the effectiveness of aRMMs is necessary to establish whether an intervention has been effective, and, if not, why and which corrective actions are necessary.

This study is therefore designed to evaluate the following aspects of the aRMM: the process itself (i.e. to which extent the materials have been implemented as planned) and its impact on knowledge and behavioural changes in the target audience.

8 Research Questions and Objectives

The study aims to assess the effectiveness of the isatuximab Educational Materials in terms of process indicator, meaning implementation, knowledge and behaviour with respect to the safety messages conveyed in these materials.

Objective

1) Describe the implementation of the aRMMs to the target population, the time period(s) of implementation in each participating country (starting from local regulatory approval) and materials used.

2) Assess the knowledge of the target audience about the risk and its management
    - Messages specific to the prescribers (HCPs in oncology/haematology)
    - Messages specific to the non-prescribers (HCPs in blood banks/transfusion centres)

3) Assess the behaviour of HCPs with respect to the safety messages

- Messages specific to the prescribers (HCPs in oncology/haematology)
- Messages specific to the non-prescribers (HCPs in blood banks/transfusion centres)

Hypothesis

We hypothesize that:

- At least 80% of the HCPs (both prescribers and non-prescribers) will provide correct responses to the first knowledge question, which is identified as the key question.

AND

- 80% of the prescribers will provide correct responses to at least five out of seven behaviour questions.

AND

- 80% of the non-prescribers will provide correct responses to at least two out of three behaviour questions.

9 Research Methods

9.1 Study Design

This is a non-interventional cross-sectional study among HCPs involved in the treatment of MM with SARCLISA (isatuximab) in selected European countries.

The study is a cross-sectional survey planned to be conducted within 12-18 months after implementation of educational materials in each country. The surveys will be conducted online, using structured questionnaires, comprising close-ended questions where the response format is either the selection of a single response or selection of a number of responses as appropriate. Information will be collected from HCPs using the online LiveTracker™ platform. LiveTracker™ is a cloud-based, real-time, continuous electronic data collection platform tracker that delivers real-world evidence data.

This PASS will be conducted according to the Guideline on good pharmacovigilance practices (GVP) – Module VIII (Rev 3) dated 9 October 2017 (7) and according to the GVP Module XVI (Rev 2) dated 28 March 2017 (EMA/204715/2012 Rev 2).

9.2 Setting

The study will be conducted in selected European countries after the launch of isatuximab (SARCLISA) and the distribution of the educational materials to the HCPs (see Table 1). Up to 9 countries may be included in this study, where country inclusion will be based on:

- Isatuximab launch dates
- Date of distribution of the educational materials
- Target population size (oncology centres and blood banks)
- Feasibility in terms of regulatory implementation at national level
- Representativeness of Europe
    - Country population size
    - Country geographic location

Table 1 - List of launch date and distribution status of educational materials in each country

Country	Actual/Estimated Launch Date	Implementation of EMs	Recipients	Comments
Switzerland	**30 APR 2020**	JUN 2020 (digital) AUG 2020 (hardcopies) JUN 2021 (website)	About 50 maximum physicians in Onco/Haematology, blood banks (BB) and blood donation centres	Hospitals have either their own BB or work with a centralized one. In some cases, there is no BB and this is covered by the Blood donation center
Austria	**JUL 2020**	JUN- 2020 (hardcopies) Distribution of the revised version completed in July 2021	29 Internal Medicine, 16 Oncology, 9 Haemato-Oncology, 1 Haematology, 2 immunology serology transfusion medicine, 9 Blood bank transfusion medicine, regional blood donation centre, and 58 hospital pharmacies (for information)	Oncologists and Haematologists are specialised sub-units of Internal Medicine

Country	Actual/Estimated Launch Date	Implementation of EMs	Recipients	Comments
France	**SEP 2020** (post ATU*)	AUG 2020 Distribution of the revised version planned to be completed by 31Dec2021	778 Oncologists + 2,002 Haematologists + national centre of BB from where EMs will be forwarded to the 13 regional centres.	Based on ATU* experience (Aug 2019, 399 patients), Haematologists made most of prescriptions.
Sweden	**01-JUL- 2020** (not reimbursed)	JUN 2020 (mail+ website) Distribution of the revised version completed in June 2021	Haematologists (293) Head of Haematologist Department, BB and transfusion centres (104)	All prescriptions by Haematologists
Finland	**15 SEP 2020** (not reimbursed)	SEP / OCT and NOV 2020 + ad hoc distribution in Q1/Q2 2021 (email and mail) Distribution of the revised version completed in Sep 2021	Haematologist (76), BB (10)	All prescriptions by Haematologists
The Netherlands	**OCT 2020** (reimbursed)	SEP 2020 (mail + website)	1,335 Oncologists / Haematologists + 631 hospital pharmacists + 350 clinical chemists (all HCPs in-training included) and 21 blood banks relevant societies for professionals	
UK	01 JUN 2020	APR-AUG 2020 (mail)	N=5061	
Poland		AUG-SEP 2020 (email, mail and website) Distribution of the revised version completed in Sep 2021	Physicians: haematologists (326), oncologists (705), specialists in transfusiology (97). National and regional consultants in haematology, oncology and transfusiology (48).	

Country	Actual/Estimated Launch Date	Implementation of EMs	Recipients	Comments
			Multiple myeloma treatment centres (53). Regional and field blood-donation centres (163).	
Germany	01 MAR 2021	JAN -MAR 2021 (mail and website) Distribution of the revised version completed in June 2021	Oncologists and haematologists: 3655 Blood banks: 170	
Italy	29 MAR 2021	APR 2021 (email)	Haematologist, oncologists and scientific societies: 10 107	
Hungary	Planned NOV 2021	No distribution (product not yet launched)	**To be provided later**	

* ATU: temporary authorisation for use 'autorisation temporaire d'utilisation"
Abbreviations: BB = Blood Banks; EM = Educational Materials; HCP = healthcare professional; UK = United Kingdom

Since country inclusion is based on the date of launch and distribution of the educational materials, target population size, and representativeness of Europe, we will include, at minimum, the following five countries: France, Switzerland, Austria, Sweden, and the Netherlands. There will be a maximum of nine countries included in this study and the other potential countries include (but are not restricted to): Germany, Finland, United Kingdom (UK), Italy, Poland and Hungary. Also, the necessary Ethics/Regulatory requirements to conduct this study may generate some changes in this list.

Current countries listed are the ones with educational materials expected to be implemented by the end of 2021 (Table 1) as data collection will occur in each country 12-18 months post-implementation. The following EU countries cannot participate because SARCLISA (isatuximab) will not be marketed or educational materials will not be implemented by the end of 2021 in order to complete data collection by Q1 2023: Bulgaria, Cyprus, Estonia, Greece, Ireland, Latvia, Lithuania, Spain and Romania.

9.2.1 Study Sites

Not applicable

9.2.2 Study Population Selection Criteria

HCP selection is based on the inclusion and exclusion criteria listed below.

HCPs who meet each of the inclusion criteria and none of the exclusion criteria are eligible to participate in this study.

Inclusion Criteria

- The HCP is involved in the management and follow-up of multiple myeloma, such as oncology/haematology specialists and HCPs associated with blood banks/transfusion centres who have not necessarily prescribed isatuximab.
    - Prescribers (Oncologists/Haematologists): The HCP has prescribed isatuximab at least once.
    - Non-prescribers (Blood banks/transfusion centres): The HCP has provided blood products at least once for a patient treated with isatuximab.
- The HCP provides consent to participate.

Exclusion Criteria

- The HCP has previously been enrolled in this study.

9.2.3 HCP Recruitment

Recruitment of HCPs will occur mainly from a multi-national panel (the LiveTracker™ panel). LiveTracker™ is a cloud-based, real-time, continuous electronic data collection platform that allows collection of real-world evidence data from HCPs across multiple continents. Multi-national panels of physicians in LiveTracker™ exist across haematology-oncology therapeutic areas, including a panel for MM. In order to optimise recruitment, educational material distribution lists will be used when possible as a complement.

To be part of the LiveTracker™ physician panel, physicians are screened, including a credentials check, and fill out an initial profiling survey that includes answering questions about practice setting, caseload, specialities, etc. For participation in this study, HCPs will be screened based on the following criteria to identify qualified participants:

1) Prescribers: haematologist/onco-haematologist who prescribed isatuximab at least once.

   The prescribers are medical specialists who are responsible for initiating the treatment, communicate with the patient and make the appropriate decision(s) if a transfusion is needed. Depending on the country, they initiate the blood compatibility profile,

manage the transfusion, including the order of blood products or refer the patient to a transfusion department / blood bank.

2) Non-prescribers: HCPs work in the blood banks/transfusion centres who have provided blood products at least once for a patient treated with isatuximab.

   Depending on the country, HCPs affiliated with transfusion departments or blood bank may oversee the blood compatibility profile, identify and deliver the blood products. However, in most countries, they do not communicate with the patient.

The potential pool of HCP participants is shown in Table 2, which is mainly based on the current number of HCPs in the haematologist and haemato-oncologist panels in LiverTracker™. LiveTracker™ is actively building up a panel of HCPs working in the blood banks/transfusion centres to have sufficient number of HCPs to send invitation emails to, as presented in Table 3 Column C.

Table 2. LiveTracker™ haematologist and haemato-oncologist panels in each country.

	Total Number of HCPs
Austria	538
Switzerland	1,135
Germany	4,696
Finland	156
France	3,549
UK	4,061
Hungary	120
Italy	3,298
Netherlands	647
Sweden	594
Poland	288
Total	**19,082**

Abbreviations: HCP = healthcare professional; UK = United Kingdom

HCP prescribers (haematologist/onco-haematologist) and non-prescribers (HCPs working in the blood banks/transfusion centres) will be recruited the same way through the LiveTracker™ panel. From the overall country-specific list of HCPs, invitation e-mails will be sent to HCPs to explain the objective of the study and their expected involvement, as well as provide a link to the electronic survey.

To maximise the response rate if the objective of 400 HCPs is not reached, multiple reminders will be sent. If recruitment rate is low after three reminders, we may consider different strategies including broadening the inclusion criteria to also include any HCPs who have prescribed other anti-CD38 therapy (prescribers) or who have provided blood products for a

patient treated with other anti-CD-38 therapy (non-prescribers). This change would be implemented after a protocol amendment is approved.

To minimise selection bias, the number of HCPs is targeted based on the combination of the country population, target population (haematology and haemato-oncology centres and blood banks), and date of distribution of educational materials. Since this survey is targeting HCPs instead of patients, this recruitment approach will reflect the proportion of HCP prescribers/non-prescribers within these countries. Approximately 400 HCPs will be included in this study. It is expected that the European Union countries with a large population will have a greater number of HCPs included in the study compared to countries with a smaller population. In addition, the number of HCPs included per country will vary based on the volume of distribution of educational materials for each country. Recruitment strategy for HCPs will vary among countries as the aim will be to recruit HCPs who properly represent the HCP specialities and practice settings where educational materials are distributed in each country. Additional factors that will be considered during recruitment, in efforts for representativeness, include recruiting HCPs from different regions in each country, and recruiting HCPs with varying numbers of patients treated with isatuximab.

The final response rate is estimated to be 4.4%-6.8% based on historical LiveTracker™ data (17% of HCPs will respond to communication emails, and of those who respond, approximately 26% to 40% will be eligible and will complete the survey). In order to obtain close to 400 completed questionnaires, a total of approximately 6,000 to 9,000 invitation emails will be sent (it varies among country and will be adjusted based on the response rates of each country and each types of HCPs).

These invitation emails are planned to be sent using a stratified random sampling method, however, further random sampling steps after the initial email is likely not feasible since the goal is to maximize responses. A few reasons it is not feasible include 1) the low numbers of HCPs in some countries; 2) the low expected response rate (4.4%-6.8%).

HCP non-prescribers are targeted to be, at minimum, 10% to 25% of the total HCPs, meaning that the prescribers are targeted to be, at maximum, 75% to 90% of the total HCPs. Considering that the proportion of each types of HCPs may vary among countries based on the country-specific distribution of educational materials, it is acceptable that, in certain countries, the final proportion of non-prescribers may exceed 25%.

Table 3 presents the number of invitation emails to be sent and the estimated target numbers of prescribers and non-prescribers in each potential study country.

Table 3. Estimated target number of HCPs per country

Country	**A Estimated Total Number of Invitation Emails***	B Estimated Number of Invitation Emails to HCP Prescribers	C Estimated Number of Invitation Emails to HCP Non-prescribers (10-	**D Target Total Number of HCPs (4.4-6.8% of column A)**	E Target Number of HCP Prescribers (75-90% of column D)	F Target number of HCP Non-prescribers (10-25% of column D)

		(75-90% of column A)	25% of column A)			
Austria	250-400	190-360	25-100	10–15	8-14	1-4
Switzerland	250-400	190-360	25-100	10–15	8-14	1-4
Germany	1250-1750	940-1580	125-440	50–70	38-63	5-18
Finland	100-150	75-135	10-40	5–10	4-9	1-3
France	1250-1750	940-1580	125-440	50–70	38-63	5-18
UK	1250-1750	940-1580	125-440	50–70	38-63	5-18
Hungary	250-400	190-360	25-100	10–15	8-14	1-4
Italy	1250-1750	940-1580	125-440	50–70	38-63	5-18
Netherlands	250-400	190-360	25-100	10–15	8-14	1-4
Sweden	100-150	75-135	10-40	5–10	4-9	1-3
Poland	100-150	75-135	10-40	5–10	4-9	1-3
Total	**6000 - 9000**	**4500-8100**	**600-2250**	**up to 400**	**300–360**	**40–100**

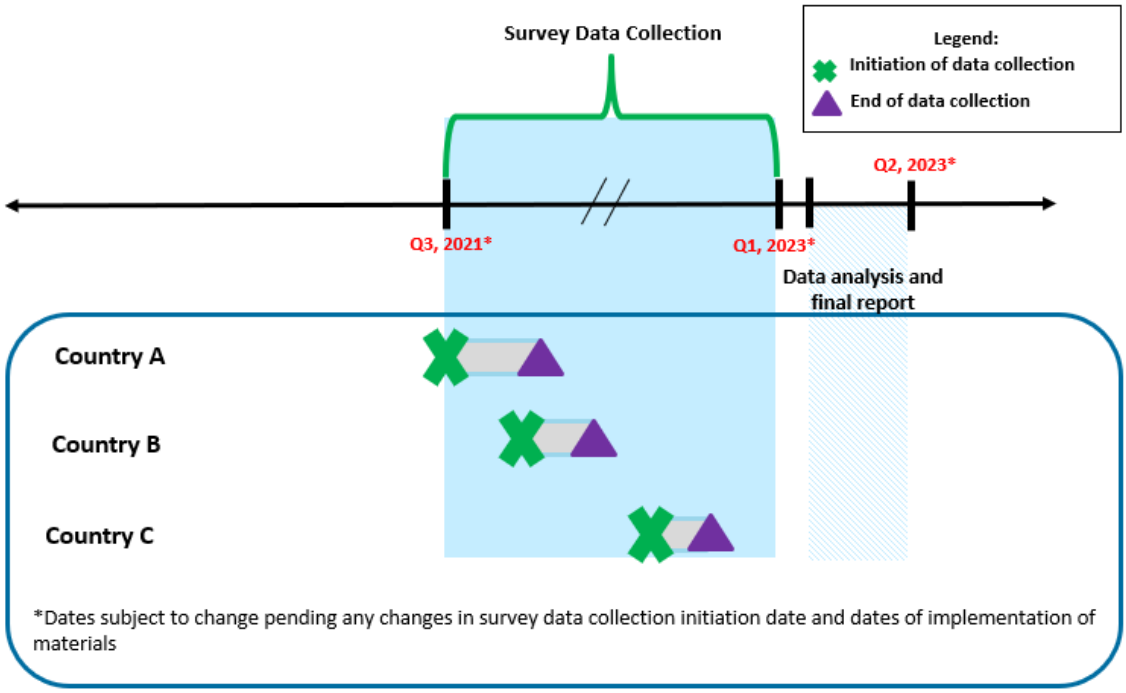
* Estimated based on historical LiveTracker™ data.
Abbreviations: HCP = healthcare professionals; UK = United Kingdom

HCPs will provide consent and data will be anonymous for the Market Authorisation Holder (MAH).

9.2.4 Study Period

The GVP Module XVI guidelines(7) recommend that effectiveness of aRMMs is measured within 12 to 18 months after implementation of the educational material(s). As a result, data collection would start no earlier than Q3 2021 and no later than Q2 2022. Based on the estimated launch sequence that will be progressive throughout 2021, data collection will most likely take place until at least the end of 2022 and potentially up to Q1 2023.
Figure 1 presents the study design schematic, including periods of survey data collection.

Figure 1. Study Design Schematic



9.3 Variables

Variables related to the following HCPs' characteristics will be collected:

- Participation (e.g. response rate)
- Practice setting
- Receipt of the educational materials
- Knowledge of each safety messages
- Behaviour with respect to the actions listed in the educational materials

Please refer to Appendix C for detailed survey questionnaire.

9.3.1 Practice setting and selection criteria

The following will be collected from the LiveTracker™ database:

- Country and region of practice
- Primary specialty

- Primary setting of practice (e.g. blood bank, transfusion centre, private practice, local hospital, regional hospital, university hospital, private hospital)

The following will be used to assess the selection criteria and will collected via the survey questionnaire:

- Number of patients to whom the physician has prescribed isatuximab in the past year
- Length of time since last prescription of isatuximab

9.3.2 Implementation

All HCPs:

- Reception of the education materials (brochure and maybe Patient Card depending on the type of HCPs).

9.3.3 Knowledge of each safety messages

Key safety message for All HCPs:

- Isatuximab is associated with risk of interference with blood compatibility tests

Prescribers:

- There is currently no available information on how long the interference may persist after the last infusion of isatuximab. Based on the half-life of isatuximab, the interference with indirect antiglobulin tests may persist for approximately six months after the last infusion.

Non-prescribers:

- Isatuximab bound to CD38 on RBCs and may mask the detection of antibodies to minor antigens in the patient's serum. Isatuximab may interfere with routine blood compatibility tests with potential false positive reactions in IAT.
- The determination of a patient's ABO and Rh blood type are not impacted

9.3.4 Behaviour with respect to the safety messages

Prescribers:

- All patients should be blood typed and screened prior to start treatment with isatuximab.

- Consider phenotyping prior to starting isatuximab treatment as per local practice.
- If treatment with isatuximab has already started, inform the blood bank that the patient is receiving isatuximab.
- In the event of a planned transfusion, notify blood transfusion centres about the risk of interference with indirect antiglobulin tests.
- Verify standing orders for transfusions to determine if your patient received isatuximab within the last year.
- Give the Patient Card to the patients and advise them to carry it at all time and until six months after the last dose of isatuximab. Provide patient's pre-isatuximab compatibility profile, if available, to the blood bank.
- Ask your patient to tell their other healthcare professionals that they have received isatuximab, particularly before a transfusion, and to show them their Patient Card.

Non-prescribers:

- In case of urgent need for transfusion, non-cross matched ABO/RhD compatible RBC units can be administered as per local bank practices.
- The interference mitigation methods include treating reagent RBCs with DTT to disrupt isatuximab binding or other locally validated methods.
- Since the Kell Blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.

9.3.5 Exposure

Not Applicable

9.4 Data Sources

This study will require primary data collection, as the most appropriate method of data collection for the study objectives is through questionnaires. The questionnaire will be short (approximately 15 minutes). A set of standard questions will be developed for each target group. Questions will be 1) concise and understandable; 2) close-ended (e.g. yes/no/I don't know/Not-Applicable to my setting answers or true/false/I don't know answers; 3) including some traps (e.g. some questions will present false statements). The HCPs will have the possibility to fill in the questionnaire either in English or in their native language. The questionnaire in English and its translations will be validated via pilot interviews with two HCPs in each country after a user acceptance testing phase.

Questions in questionnaire will not be revealed before the HCP opens it. Once the HCP has saved their answers, they will not be allowed to go back and change the answers. Both of these strategies are in an effort to reduce the possible Hawthorne effect.

The target populations will include HCPs involved in the management and follow-up of multiple myeloma, such as haematology/oncology specialists and HCPs associated with transfusion centres.

9.5 Study Size

The proportions of interest (p) here are the proportions of HCPs knowledgeable and adherent to the aRMMs. As the proportion of interest (p) is not known at the time of this document, we may consider it to be 50% (maximum uncertainty). Such a hypothesis yields the most conservative (largest) sample size. Based on a minimum level of precision of 5%, the minimum required sample size would be 384 for precision levels of 5% for the overall population. The sub-populations of interest will include prescribers (75% to 90%) and non-prescribers (10% to 25%) but the study is not powered for the analysis by sub-population.

Of note, similar aRMMs were distributed to HCPs in Europe after the market authorisation was granted to the first-in-class compound (daratumumab). Based on the information published in February 2021, a total of 408 participants completed the questionnaires.

In order to obtain 400 completed questionnaires in our study, it is estimated that approximately 6,000 to 9,000 HCPs will be approached. This is based on the details provided in section 9.2.3.

9.6 Data Management

A data management plan will be prepared and will detail the data management and data handling procedures.

Data for this study will be collected electronically by Evidera, the owner of LiveTracker™ platform. LiveTracker™ is a cloud-based, real-time, continuous electronic data collection platform that delivers real-world evidence data. LiveTracker™ has the capability to perform automatic checks of data quality and missing-ness. The administration of measures will be conducted according to the protocol.

9.6.1 Data Collection

Data for this study will be collected electronically by Evidera, the owner of LiveTracker™ platform. LiveTracker™ is a cloud-based, real-time, continuous electronic data collection platform that delivers real-world evidence data. LiveTracker™ has the capability to perform automatic checks of data quality and missing-ness. The administration of measures will be conducted according to the protocol.

Once HCPs click on their unique online data collection form link, they will be tracked through a unique identifier within the LiveTracker™ platform. The HCP will be asked to complete the self-reported items. The questionnaire is assumed to take approximately 15 minutes to complete. Each HCP has ultimate responsibility for the self-reporting of all data entered in the LiveTracker™, and ensuring that they are accurate, complete, consistent, legible and timely (contemporaneous).

HCPs who delay in completing the survey or who do not complete all contents of the survey in a session will be encouraged to complete their forms through e-mail and/or phone reminders. Any queries to the HCPs will be monitored until resolution within the LiveTracker™ platform through the electronic query report. The survey is considered valid if all questions are completed.

A small amount of incentive payment (country-specific fair market value payments based on physician contracts through the LiveTracker™ Panel, as allowed per the local law and regulations) will be made to HCPs as a compensation for the time spent to complete the questionnaire (about 15 minutes).

9.6.2 Data Monitoring

The de-identified data entered by physicians into LiveTracker™ will be remotely supervised and the following metrics will be collected:

- Percentage of participation and completion
- Physician location, type of practice setting

There will be automated quality control mechanisms built into LiveTracker™ at the time of data entry (e.g., verification of data completeness, standardised response formats, validations and edit checks) in accordance with the data monitoring plan.

9.6.3 Record Keeping

The MAH must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the MAH, whichever is longer.

9.7 Data Analysis

9.7.1 Statistical Analysis Plan

The planned statistical analyses are summarised in sections 9.7.2 to 9.7.6. The statistical analyses will be described in detail in a stand-alone *Statistical Analysis Plan* (SAP) (**Error! Reference source not found.**).

9.7.2 Analysis Populations

- Primary analyses: The primary analysis population will include the total number of HCPs who returned a valid questionnaire.

- Additional analyses: In order to identify any selection bias, basic variables recorded in the LiveTrackerTM database will be compared between the responders and the population of non-responder HCPs from the LiveTrackerTM panel.

9.7.3 Descriptive Statistics

All assessment data will be summarised using descriptive techniques. Unless otherwise specified, continuous variables will be described by their mean, standard deviation, and median, first quantile (Q1), third quantile (Q3), minimum and maximum. Categorical variables will be described as total number and relative percentage per category.

As a first step, the participant characteristics (practice settings and inclusion criteria) will be described.

9.7.4 Primary Analyses

A description of the following outcomes of interest related to process indicators will be performed:

- Measures of the extent of implementation of the original plan, and/or variations in its delivery, at each participating country level.

- Knowledge and Behaviour

For each question, the proportion of HCPs who have provided correct and appropriate answers will be calculated.

Questions common to all HCP types will be analysed for all HCP and by type of HCP (prescribers vs. non-prescribers). Questions specific to prescribers or non-prescribers will be analysed for each type of HCPs.

In addition, the number of correct answers by HCP will be calculated, from which the average number and percentage of correct answers will be computed. The proportion of HCPs who provided correct answers to 70%, 80%, 90% and 100% of the questions will be derived, for all questions, knowledge questions, and behaviour questions.

The threshold of the satisfactory rate is defined as 80% of the HCPs providing correct responses for the following questions:

1 The first knowledge question (key question) for both prescribers and non-prescribers;

AND

2 At least five out of seven behaviour questions for prescribers;

AND

3 At least two out of three behaviour questions for non-prescribers.

The first knowledge question regarding the safety message "*isatuximab is associated with risk of interference with blood compatibility tests*" is defined as the key question. This knowledge question has more weight than all the other questions to assess the effectiveness of aRMM, because it provides an overarching safety message to inform both prescribing and non-prescribing HCPs about the major risk. Thus, at least 80% of the HCPs are expected to provide correct responses to this key question.

In addition, this threshold of 80% also applies to the behaviour questions—without identification of specific key questions —as part of the satisfactory criteria to assess the effectiveness of aRMM. The rationale for not identifying key questions from these behaviour questions is that prescribers and non-prescribers have different risk mitigation approaches to manage the interference and to avoid possible resulting adverse clinical consequences. Also, prioritization of questions could not be done within the behaviour questions. The pre-defined threshold for correct responses on a proportion of behaviour questions (i.e., 5/7 or 2/3) has been set to be similar between prescribers and non-prescribers.

The satisfactory threshold has been set at 80% to be in line with similar previous research.(10)

This combined approach of a satisfactory threshold of 80% on the key knowledge question and a certain proportion of behaviour questions intends to systematically assess the overall effectiveness of aRMM.

9.7.5 Exploratory Analyses

Of note, similar aRMMs were distributed to HCPs in Europe after the market authorisation was granted to the first-in-class compound (daratumumab). A research article published in February 2021 reported that a total of 408 participants completed the questionnaires. The risk and content of educational materials developed for daratumumab are similar and one can assume that the target population of HCPs is also similar to that of isatuximab. Therefore, a discussion about the proportions observed after the implementation of the risk minimisation measures could be considered against those reported from the daratumumab survey (i.e. pre-post designs), provided that they are available (i.e. publicly disclosed) at the time of this study report preparation/submission.

However, due to the lack of access to patient-level data, no statistical comparison will be performed.

9.7.6 Subgroup Analyses

In addition to the analyses by HCP type (prescribers and non-prescribers) as described above, analyses will also be performed at country level.

Other sub-groups analysis will include (if sample size allows):

- Characteristics of responders who provided correct answers to 70%, 80%, 90% and 100% of the questions vs responders who did not reach the threshold
- Comparison of responders and non-responder's characteristics[1]
- Comparison of responders and overall target population characteristics[2]
- Analyses among HCPs who actually received the EMs vs. those who did not.

9.7.7 Handling of Missing Data

No imputation method will be used to replace missing data.

9.7.8 Statistical Software

The analyses will be performed using the statistical software SAS®, Version 9.4 (SAS Institute Inc. Cary, NC).

9.8 Quality Control

The procedures to ensure data quality and integrity, including the accuracy and legibility of the data collected storage of records, and archiving of the statistical programming performed to generate the results will be extensively described in the *Data Management Plan* and the SAP. Both documents will be stand-alone documents (**Error! Reference source not found.**).

9.9 Limitations of the Research Methods

All data supplied will be self-reported by the HCP, and it will not be possible to objectively verify information. The number of HCPs included will vary among countries, so the precision of country-level subgroup analyses will vary. The study uses descriptive statistics only. Therefore, it is not possible to determine whether findings are statistically significant or could be due to chance. However, given that the main objectives are to describe implementation of the aRMMs and to assess knowledge and behaviours, descriptive statistics are sufficient.

The survey will be completed by HCP on a voluntary basis. Thus, there is always the possibility that HCP accepting to participate will have different characteristics and different behaviours than non-responders. In order to identify any such selection bias, the characteristics of responders and non-responders will be described. Detailed description on minimizing selection bias during recruitment can be found in Section 9.2.

In addition, in order to reduce information bias and the possible Hawthorne effect, questions will be close-ended to avoid errors in interpreting free-texts during assessment; questions in questionnaire will not be revealed before the HCP opens it; HCPs will not have the possibility to come back and change their answers once submitted and will not be contacted to clarify or revise their survey responses. The results will reflect the knowledge, understanding and

[1] Non-responder's characteristics available in the LiveTracker™ panel profile.

[2] Overall target population characteristics available in the LiveTracker™ panel profile.

behaviour in countries where isatuximab was launched in 2020 or planned to be launched by early 2021, therefore not fully representative of all European countries where isatuximab will eventually be used. In addition, the volume of isatuximab use in the selected countries could also vary and may fluctuate, therefore, the proportion of HCPs in selected countries is based on the potential pool of HCPs rather than the volume of isatuximab use in each country. The educational material distribution strategy the definition and size of the target audience is expected to vary across countries. Consequently, the proportion of HCPs having received the educational material among the invited and participating HCPs might also vary across countries. The implementation results will need to be interpreted in the light of each country-specific distribution strategy.

10 Protection of Human Subjects

10.1 Subject Information and Consent

HCPs will be informed of the modalities and procedures of the survey and will be asked to provide their consent to participate in the survey.

10.2 Data Protection

The data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. No subject-identifying information will be collected. The data collected will be pseudonymised (anonymous to study staff and MAH).

10.3 Ethics Committees

The MAH will ensure that any required approvals from Ethics Committees, Independent Review Committees, Regulatory Authorities, and/or other local governance bodies are obtained before study initiation in each participating country.

10.4 Competent Authorities

Notification to local authorities are needed for this PASS survey.

11 Management and Reporting of Adverse Events/Adverse Drug Reactions

This study is not designed to capture safety events associated with the use of isatuximab

12 Plans for Disseminating and Communicating Study Results

12.1 Overview

Sanofi will monitor the data collected while the study is being conducted and consider their implications for the effectiveness of the isatuximab educational materials.

Any new information about the minimisation of the risk of interference for blood typing (minor antigen) (positive indirect Coombs' test) will be evaluated for a potential study protocol amendment.

12.2 Study Report

Upon completion of the study, a study report will be prepared by Sanofi and Evidera.

The study report will be sent to the EMA in accordance with the guidelines and the study results will also be presented in the *Periodic Safety Update Report* (PSUR) and in the *Risk Management Plan*, as applicable.

12.3 Data Ownership

The data collected in this study are the property of Sanofi.

Copying or spreading information related to this study without Sanofi's agreement is prohibited.

12.4 Publications

Study findings will be published in a peer reviewed journal.

Any publication will be guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE), updated April 2010.

All reporting will be consistent with the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) Initiative checklist for cohort studies (STROBE 2008).

Still in line with the EMA guideline, and in order to allow competent authorities to review in advance the results and interpretations to be published, the MAHs should communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within two weeks after first acceptance for publication.

13 References

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Appendix A. Isatuximab Brochure

SARCLISA®
(isatuximab)

IMPORTANT INFORMATION

SARCLISA (ISATUXIMAB) IS ASSOCIATED WITH RISK OF INTERFERENCE FOR BLOOD TYPING

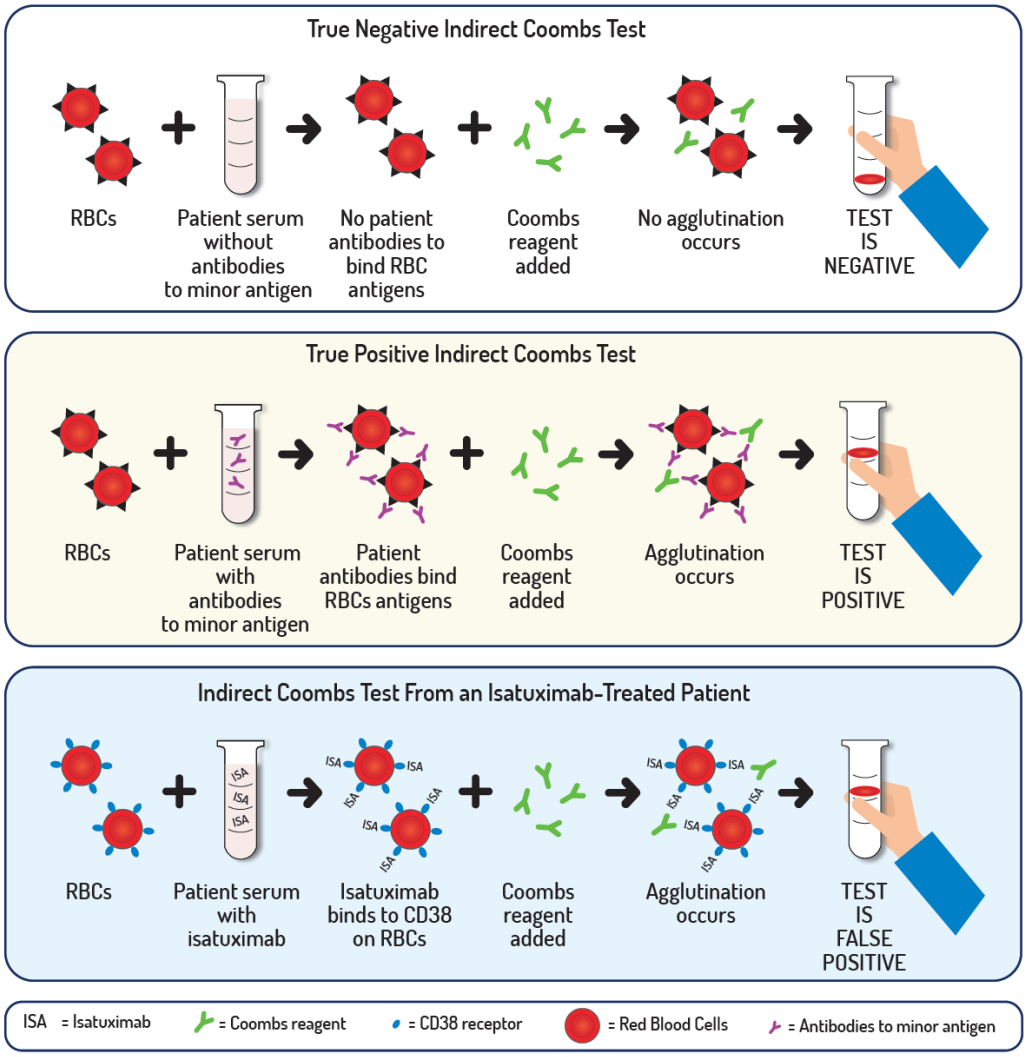
HEALTHCARE PROFESSIONALS AND BLOOD BANKS BROCHURE

HCPs Leaflet: version 12 MAR 2021

SANOFI

WARNING FOR BLOOD BANKS

- Isatuximab is bound to CD38 on red blood cells (RBCs) and may mask the detection of antibodies to minor antigens in the patient's serum. Thus, isatuximab may interfere with routine blood compatibility tests with **potential false positive reactions in indirect antiglobulin tests (indirect Coombs tests)**.
- This interference is limited to the minor blood groups and does not affect the determination of a patient's ABO and Rh blood type.
- Isatuximab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt isatuximab binding or other locally validated methods. Since the Kell Blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.
- If an emergency transfusion is required, you can give non-cross-matched ABO/Rh-compatible RBCs as per local blood bank practices.



WARNING FOR HEALTHCARE PROFESSIONALS

APPROPRIATE MEASURES TO MANAGE ISATUXIMAB INTERFERENCE AND AVOID POSSIBLE RESULTING ADVERSE CLINICAL CONSEQUENCES

- Conduct blood type and screen tests on your patient prior to the first infusion of isatuximab.
- Consider phenotyping prior to starting isatuximab treatment as per local practice.
- Give your patient the latest version of the **Patient Card**.
- If treatment with isatuximab has already started, inform the blood bank that the patient is receiving isatuximab.
- In the event of a planned transfusion, please notify blood transfusion centers about the risk of interference with indirect antiglobulin tests.
- There is currently no available information with regards to how long the interference with the indirect Coombs test may persist after the last infusion of isatuximab. Based on the half-life of isatuximab, it is anticipated that isatuximab mediated positive indirect Coombs test may persist for approximately **6 months** after the last infusion. Therefore, please advise your patient to carry the Patient Card at all times and until 6 months after the last dose of isatuximab.
- It is important you always advise your patient to consult the Package Leaflet (PL) for further information on isatuximab.

REPORTING OF SUSPECTED ADVERSE REACTIONS

Isatuximab is subject to additional monitoring of its benefit/risk balance. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system at the following:

- **[TELEPHONE NUMBER OF LOCAL MEMBER STATE NATIONAL COMPETENT AUTHORITY]**
- Or **[ADDRESS OF LOCAL MEMBER STATE NATIONAL COMPETENT AUTHORITY]**

ADDITIONAL RESOURCES

For additional information on isatuximab, **please refer to the Summary of Product Characteristics (SmPC)** or contact SANOFI by using one of the following methods:

- **Phone: [TO BE COMPLETED DURING LOCAL ADAPTATION]**
- **Email: [TO BE COMPLETED DURING LOCAL ADAPTATION]**
- **Website: [TO BE COMPLETED DURING LOCAL ADAPTATION]**

FOR TIMELY TRANSFUSIONS

REMINDER FOR HEALTHCARE PROFESSIONALS

- Conduct blood type and screen tests on your patient prior to the first infusion of isatuximab. Inform the blood bank that your patient has been treated with isatuximab which may interfere with indirect antiglobulin tests (indirect coombs tests).

- Verify standing orders for transfusions to determine if your patient received isatuximab within the last year.

- In the event of a planned transfusion, notify blood transfusion centers about the risk of interference with indirect antiglobulin tests.

- Give your patient a Patient Card to be carried at all times and until **6 months** after the last dose of isatuximab. Provide your patient's pre-isatuximab compatibility profile, if available, to the blood bank.

- Ask your patient to tell their other healthcare professionals that they have received isatuximab, particularly before a transfusion, and to show them their Patient Card.

REMINDER FOR BLOOD BLANKS

- Identify the blood sample of your patient as containing isatuximab.

Appendix B. Patient Card

MY INFORMATION

Patient's name:	
Patient's date of birth (DD / MMM / YYYY):	_____/_____/_____
Patient's phone:	
Emergency contact (name):	
Emergency contact (phone):	

MY TREATMENT DETAILS

Please complete this section or ask your doctor to do it.

Isatuximab recommended dose of 10 mg/kg and dosing schedule:

	Start date (DD / MMM / YYYY):		End date (DD / MMM / YYYY):
Cycle 1: Days 1, 8, 15 & 22 (weekly)	NA		
Cycle 2 and beyond: Days 1 & 15 (every 2 weeks)	_____/_____/_____		_____/_____/_____

MY BLOOD RESULTS

Before starting isatuximab, the results of my blood test collected on: _____/_____/_____ (DD / MMM / YYYY)

were:

Blood type: ☐ A ☐ B ☐ AB ☐ O ☐ Rh+ ☐ Rh-

The result of my indirect antiglobulin test (indirect Coombs test) was:

☐ Negative ☐ Positive for the following antibodies:

MY DOCTOR'S INFORMATION

In case of emergency, or if you find this card, please contact my doctor using the details below.

Doctor's name:	
Doctor's phone:	

Patiend Card: Version 21 MAR 2021

SANOFI

PATIENT CARD

— DEAR PATIENT RECEIVING SARCLISA (ISATUXIMAB) —

- Provide this card to healthcare providers **before** blood transfusion.
- Keep this card with you at all times and until **6 months** after the last dose of isatuximab.
- This medicine is subject to additional monitoring. This will allow for the identification of new safety information. You can help by reporting any side effects you may get. If you notice any side effects, talk to your doctor or pharmacist. You can also report side effects directly at **www.xxx.xxx**. Side effects should also be reported to SANOFI on **Tel: xxxxxxxxxx**. By reporting side effects, you can help provide more information on the safety of this medicine.
- For further information on isatuximab, you can consult the **Package Leaflet (PL)**.

— WARNING FOR HEALTHCARE PROVIDERS —

- Please note this patient is receiving treatment with **SARCLISA (isatuximab)**.
- This patient card contains important safety information that you need to be aware of before, during, and after treatment with isatuximab.
- Treatment with isatuximab binds to CD38 on red blood cells (RBCs) and is associated with a **Risk of Interference with blood typing (positive indirect Coombs Test)**, which may persist for approximately 6 months after the last isatuximab infusion.
- To avoid potential problems with RBC transfusion, you should perform blood type and screen tests prior to the first infusion of isatuximab. **Phenotyping may be considered as per local practice.**
- If treatment with isatuximab has already started and in the **event of a planned transfusion, you should notify** the blood bank that the patient is receiving isatuximab and its **risk of Interference with Indirect Antiglobulin Tests**.
- For additional information on isatuximab, please refer to the **Summary of Product Characteristics (SmPC)**.

Appendix C. Survey Questionnaire

HCP Characteristics and Screening Questions

P0. Our records show that your practice is in [insert country from contact information]. Is this correct?

1. Yes
2. No

PI – List Drop Down.
[DP:1]

P0a. Please select the country where you practice.
PI- show if P0=2
PI – List Drop Down.
[DP:1]

P1. Our records show that your primary specialty is [insert specialty]. Is this correct?

1. Yes
2. No

PI – List Drop Down.
[DP:1]

P1a What is your primary medical specialty?

- Medical oncology
- Haemato-oncology/onco-haematology
- Internal medicine
- Blood banking transfusion medicine
- Other, specify _____

PI- show if P1=2
PI – List Drop Down.
[DP:1]

P1b. Please select your sub-specialty from the following list
Medical Oncology subspecialities:

- Hematology Oncology
- Surgical Oncology
- Pediatric Hematology Oncology
- Blood bank transfusion medicine?
- Other specify_____

Hematology subspecialities:

- Bone marrow stem cell transplantation
- Blood bank transfusion medicine?
- Other specify_____

Internal medicine subspecialities:

- Vascular Medicine
- Medical Oncology
- Intensive Care
- Other specify_____

PI – List Drop Down.

PI- Drop down with list of subspecialties; show Medical Oncology subspecialities if P1a= Medical Oncology; show Hematology subspecialities if P1a= Haemato-oncology/onco-haematology; show Internal medicine subspecialities if P1a= Internal medicine

[DP:1]

----------Page Break----------

Px. For the treatment of Multiple Myeloma, please indicate your level of adoption of **isatuximab**.

- Prescribe on a regular basis
- Have prescribed at least once
- Are aware but have never prescribed
- Are not aware

PI- List drop down

[DP:1]

Px0. Please select your primary setting of practice

- Blood bank
- Transfusion centre
- Blood donation centre
- Private office/ Clinic
- Academic/ University hospital
- District General/ Community / Non-Teaching Public Hospital
- Private hospital
- Other, specify _____

PI – List Drop Down

[DP:1]

Px1. Please select if your primary setting at the office, clinic or hospital is one of the below

- Blood bank
- Transfusion centre
- Blood donation centre
- None of the above

PI- show if Px0= Private office/ Clinic, Academic/ University hospital, District General/ Community / Non-Teaching Public Hospital, Private hospital

Px2. Have you provided blood products to a Multiple Myeloma patient treated with **isatuximab**?

- Provided blood products on a regular basis
- Provided blood products at least once

- Have never provided blood products

PI- List drop down

[DP:1]

Screening criteria: Screen-in if

- **"Prescribe on a regular basis" or "at least once" on question Px**
  OR
- **"Provided blood products on a regular basis" or "at least once" on question Px2.**

----------Page Break----------

Questions for Prescribers

PI- Show if Px= "Prescribe on a regular basis" or "at least once"

1 **Have you received the educational material from Sanofi regarding the minimization of risk associated with isatuximab?**

- Yes
- No

PI- List drop down

[DP:1]

Knowledge questions: Q2-Q3

2 **Select true or false for the following statement on isatuximab:**
"Isatuximab is associated with risk of interference with blood compatibility tests"*

- True
- False

[Correct answer: True]

PI- List drop down

*Key safety question

[DP:1]

3 **Approximately how long may the isatuximab interference with indirect antiglobulin tests persist after the last infusion of isatuximab?**

A. One month

B. Three months

C. Six months

D. One year

[Correct answer: C]

PI- List drop down

[DP:1]

Behavior questions: Q4-Q10

4 Which of the following is correct regarding blood typing and screening?

A. Patients should not be blood typed and screened prior to start treatment with isatuximab

B. Only select patients should be blood typed and screened prior to start treatment with isatuximab

C. All patients should be blood typed and screened prior to start treatment with isatuximab

[Correct answer: C]
PI- List drop down

[DP:1]

----------Page Break----------

5 Select true or false for the following statement: *" You should consider phenotyping prior to starting isatuximab treatment, as per local practice"*

- True
- False

[Correct answer: True]
PI- List drop down

[DP:1]

6 Select true or false for the following statement: "*If treatment with isatuximab has already started, there is no need to inform the blood bank that the patient is receiving isatuximab*"

- True
- False

[Correct answer: False]
PI- List drop down

[DP:1]

7 Select true or false for the following statement regarding the recommended measures of isatuximab treatment: *"In the event of a planned transfusion, notify blood transfusion centre about the risk of interference with indirect antiglobulin tests."*

- True
- False

[Correct answer: True]
PI- List drop down

[DP:1]

----------Page Break----------

8 Select true or false for the following statement regarding the recommended measures of isatuximab treatment: *"For timely transfusions, verify standing orders for transfusions to determine if your patient received isatuximab within the last year"*

- True
- False

[Correct answer: True]

PI- List drop down

[DP:1]

9 Which of the following is correct regarding the Patient Card:

A. Give the Patient Card to the patients and advise them to carry it until the last dose of isatuximab.

B. Give the Patient Card to the patients and advise them to carry it at all time and until six months after the last dose of isatuximab.

C. Blood test results on the Patient Card are only from after starting isatuximab treatment.

[Correct answer: B]
PI- List drop down

[DP:1]

10 You should advise your patients:

A. To not tell their other healthcare professionals they have received isatuximab after a transfusion

B. That they do not need to show other healthcare professionals their Patient Card during a transfusion

C. To tell their other healthcare professionals they have received isatuximab, particularly before a transfusion and to show them their Patient Card

D. None of the above

[Correct answer: C]

PI- List drop down

[DP:1]

----------Page Break----------

Questions for Non-prescribers

"Provided blood products on a regular basis" or "at least once" on question Px2.

1 **Have you received the educational material from Sanofi regarding the minimization of a risk associated with isatuximab?**

- Yes
- No

PI- List drop down

[DP:1]

Knowledge questions: Q2-Q4

2 **Select true or false for the following statement on isatuximab:**
"Isatuximab is associated with risk of interference with blood compatibility tests"*

- True
- False

[Correct answer: True]

PI- List drop down

*Key safety question

[DP:1]

3 **Which of the following is correct regarding isatuximab interference?**

A. Isatuximab binds to CD20 on RBCs

B. Isatuximab binds to CD38 and may interfere with routine blood compatibility tests with potential false positive reactions in Indirect Antiglobulin Test (Indirect Coombs Test)

C. Isatuximab does not mask the detection of antibodies to minor antigens in the patient's serum

[Correct answer: B]

PI- List drop down

[DP:1]

----------Page Break----------

4 **Isatuximab interferes with:**

A. ABO typing
B. Rh typing
C. Indirect Antiglobulin Test (Indirect Coombs Test)
D. None of the above

[Correct answer: C]

PI- List drop down

[DP:1]

Behavior questions: Q5-Q7

5 Select true or false for the following statement: *"In case the patient has urgent need for transfusion, Non-cross matched ABO/RhD compatible RBC units cannot be administered."*

- True
- False

[Correct answer: False]

PI- List drop down

[DP:1]

6 The interference mitigation methods such as treating reagent RBCs with dithiothreitol (DTT) is mainly to:

A. Disrupt isatuximab binding to CD38
B. Destroy isatuximab so that it does not bind to CD38
C. Oxidize CD38 receptor bonds to prevent antibody from binding
D. None of the above

[Correct answer: A]

PI- List drop down

[DP:1]

7 Select true or false for the following statement: *"Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs, this is because Kell Blood group system is also sensitive to DTT treatment."*

- True

- False

[Correct answer: True]

PI- List drop down

[DP:1]

----------Page Break----------

Annex I

List of Stand-alone Documents

1. Data Management Plan
2. Statistical Analysis Plan

Annex II

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[3]	✓			6
1.1.2 End of data collection[4]	✓			6
1.1.3 Progress report(s)			✓	
1.1.4 Interim report(s)			✓	
1.1.5 Registration in the EU PAS Register®	✓			6
1.1.6 Final report of study results.	✓			6

Comments:

This is a cross-sectional HCP survey and no progress reports or interim reports are planned.

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)	✓			7 8
2.1.2 The objective(s) of the study?	✓			8
2.1.3 The target population? (i.e. population or sub-group to whom the study results are intended to be generalised)	✓			8 9.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	✓			7
2.1.5 If applicable, that there is no *a priori* hypothesis?	✓			9.9

Comments:

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)	✓			9.1

[3] 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.

[4] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	✓			9.4
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:

Since this is a cross-sectional survey assessing the effectiveness of Educational Materials in HCPs, descriptive statistics are sufficient. This study is not designed to assess occurrence, association, or to capture safety events.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	✓			9.2.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	✓			6 9.1
4.2.2 Age and sex			✓	
4.2.3 Country of origin	✓			9.2
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)	✓			9.2.3

Comments:

Since the study population is HCPs and the aim is to assess the implementation, knowledge and behaviour related to educational material, the age, sex, disease and indication as inclusion criteria do not apply to this study. Moreover, it is a cross-sectional survey, so there's no follow-up.

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:

Not applicable.

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?	✓			9.3 9.7.4
6.2 Does the protocol describe how the outcomes are defined and measured?	✓			9.7.4
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)	✓			9.5 9.7
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)	✓			9.7.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	✓			9.4 9.9

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)	✓			9.7.6

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)	✓			9.3 9.7
9.1.3 Covariates and other characteristics?			✓	
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)	✓			9.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)			✓	
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)	✓			9.6.1

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	✓			9.7.3 9.9
10.2 Is study size and/or statistical precision estimated?	✓			9.5
10.3 Are descriptive analyses included?	✓			9.7.3
10.4 Are stratified analyses included?	✓			9.7.6
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?	✓			9.7.7
10.8 Are relevant sensitivity analyses described?			✓	

Comments:

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)	✓			9.8
11.2 Are methods of quality assurance described?	✓			9.8
11.3 Is there a system in place for independent review of study results?		✓		

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?	✓			9.2.3 9.9
12.1.2 Information bias?	✓			9.9
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)	✓			9.2

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?	✓			10
13.2 Has any outcome of an ethical review procedure been addressed?			✓	
13.3 Have data protection requirements been described?	✓			10.2

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?	✓			5

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)?	✓			12.2
15.2 Are plans described for disseminating study results externally, including publication?	✓			12.4

Comments:

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

Date: 20/May/2021

Signature: _____