Title	A Survey of Healthcare Professionals in Europe to Evaluate the Effectiveness of the ENJAYMO™ Physician's Guide
Protocol version identifier	Version: 2.0
Date of last version of protocol	Date: 05 June 2024
EU PAS register number	Not yet registered
Active substance	sutimlimab (L04AA55)
Medicinal product	ENJAYMO™
Procedure number	EMEA/H/C/005776
Marketing authorisation holder(s)	Genzyme Europe BV
Joint PASS	(Select one below) ☐ Yes ☒ No
Research question and objectives	The overall goal of this study is to perform an effectiveness evaluation of the ENJAYMO™ Physician's Guide among healthcare professionals (HCPs) who treat patients with cold agglutinin disease (CAD).
Country(-ies) of study	Countries in the European Economic Area (EEA) where the product is expected to be commercially available for at least 6 months. Countries may include Austria, Germany, Italy, and the Netherlands.
Number of Sites or Data Sources	A convenience sample of approximately 50 HCPs will be recruited from the target population of HCPs who treat patients with CAD and may intend to prescribe ENJAYMO™ in the European countries included in this survey. The sample will be drawn from lists of European-based HCPs who were sent the ENJAYMO™ Physician's Guide in these countries, including but not limited to HCPs participating in the CAD Real-World Evidence (CADENCE) patient registry, and this list of HCPs may be supplemented through additional outreach based on internet research or outreach through applicable professional societies.
Authors	[redacted]

Marketing Authorisation Holder(s)

Marketing authorisation holder(s)	Genzyme Europe BV

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of main abbreviations should be those used specifically in the study protocol

Abbreviations	Description of abbreviations
AE	Adverse Event
aRMM	Additional Risk Minimisation Measure(s)
CADENCE	CAD Real-World Evidence
CAD	Cold Agglutinin Sisease
CA	Competent Authorities
CP	Complement Pathway
CI	Confidence Interval
ESCMID	European Society for Clinical Microbiology and Infectious Disease
EEA	European Economic Area
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FMV	Fair Market Value
GVP	Good Pharmacovigilance Practice
HCP	Healthcare Professional
IEC	Independent Ethics Committees
MAH	Marketing Authorisation Holder
PASS	Post-authorisation Safety Study
RBC	Red Blood Cell
RMM	Risk Minimisation Measure(s)
RMP	Risk Minimisation Plan
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SOP	Standard Operating Procedure(s)
SCOPE	Strengthening Collaborations for Operating Pharmacovigilance in Europe
UK	United Kingdom

List of main key terms unique in the study protocol.

Terms	Definition of terms
Adverse Event (AE)	An adverse event is any untoward medical occurrence in a subject administered a study drug and which does not necessarily have a causal relationship with this treatment.
Adverse Drug Reaction (ADR)	Any noxious and unintended response associated with the use of a drug in humans, at any dose, where a causal relationship (drug-event) is at least a reasonable possibility. See also suspected unexpected serious adverse reaction (SUSAR).
Convenience Sample	A convenience sample is one of the main types of non-probability sampling methods. A convenience sample is made up of people who are easy to reach.
Serious Adverse Event (SAE)	An adverse event is considered "serious" if, in the view of either the investigator or sponsor, it: results in death, is life threatening, results in persistent or significant disability/ incapacity or substantial disruption of the ability to conduct normal life functions, results in congenital anomaly, or birth defect, requires inpatient hospitalization or leads to prolongation of hospitalization, or is a medically important event.

3 RESPONSIBLE PARTIES

Qualified Person for Pharmacovigilance (QPPV) Sponsor Contact Details	[redacted]
Study Sponsor Contact:	[redacted]
Contract Research Organisation Contact:	[redacted]

4 SYNOPSIS

Date and Version # of Protocol Synopsis: 07 June 2021, V 0.2
Sponsor: Sanofi
Protocol Number ISN: CEF-0205
EU PAS #: Not yet registered
Name and Affiliation of Main Author:

[redacted]

Check one below:

☐ Mandated Study – European Medicines Agency

☒ Non-mandated Study

Check one below:

☒ Primary data collection

☐ Secondary data collection

☐ Mix of primary and secondary data collection

Check one below: f*or categorization, see STL-2544, Algorithm Categorization PAS*

☒ Post-authorization safety study (PASS)

For PASS studies only, select the appropriate reason to perform the study:

☐ *Category 1 – Imposed as a condition of the marketing authorization*

☐ *Category 2 – Imposed as a specific obligation in the context of a marketing authorization under exceptional circumstances*

☒ *Category 3 – Required in the risk management plan to investigate a safety concern or to evaluate the effectiveness of risk minimization activities*

☐ *Category 4 – Study conducted voluntarily*

☐ Post-authorization efficacy study (PAES)

☐ Post-authorization study (PAS, non-PASS and non-PAES)

☐ *Other

**Note: "Other" category refers to non-interventional studies that do not explicitly mention any Sanofi product in the title, objectives or inclusion criteria (e.g. a pre-approval study to investigate natural course of a disease history or treatment pathways might fit in this category). Provide rationale for when "Other" is selected.*

Title of Study:

A Survey of Healthcare Professionals in Europe to Evaluate the Effectiveness of the ENJAYMO™ Physician's Guide

Rationale and Background:

Cold agglutinin disease (CAD) is a chronic hemolytic anaemia in which activated C1 continually triggers the classical complement pathway (CP), resulting in hemolysis of red blood cells (RBCs). Individuals with CAD are at increased risk of thromboembolism (1). CAD is a rare condition; for instance, in 2020, a published study reported a CAD prevalence estimate of 20 per million in cold European climates versus a rate of 5 per million in warmer European regions.

ENJAYMO™ (sutimlimab, formerly BIVV009) is a first-in-class, humanized monoclonal antibody designed to target C1s, which is responsible for activating the classic complement pathway(1). Although ENJAYMO™ does not affect the lectin and alternative pathways, patients may still be at increased risk of serious infections, especially infections caused by encapsulated bacteria and meningococcal infections(2). To mitigate this risk, Sanofi anticipates non-routine risk minimization measures (RMM) may be required by the European Medicines Agency (EMA), and has developed the ENJYAMO™ Physician's Guide as an additional RMM (aRMM) to inform healthcare professionals (HCPs) of the indication for CAD patients and not those with cold agglutinin syndrome, important potential risks of serious infections and meningococcal infections, and recommendations for patient vaccination, monitoring, and counselling(3). The ENJYAMO™ Physician's Guide is also intended to increase implementation of vaccinations and patient counselling.

In accordance with Good Pharmacovigilance Practices (GVP) Module XVI requirements, Sanofi plans to conduct a study to evaluate the effectiveness of the ENJAYMO™ aRMM, with a specific aim to assess the effectiveness of the ENJAYMO™ Physician's Guide(3). This study will be included in the ENJAYMO™ Risk Management Plan (RMP) submission to EMA.

The proposed study utilizes a cross-sectional survey study design. Surveys are an accepted methodology to evaluate knowledge and are referenced as an appropriate tool in GVP Module XVI.

Research Question and Study Objective(s):

The overall goal of this study is to perform an effectiveness evaluation of the ENJAYMO™ Physician's Guide among HCPs who treat patients with CAD. Specific objectives are:

- Primary objective: Assess HCPs' knowledge levels of key information included in the ENJAYMO™ Physician's Guide across these 4 domains:
    - Indication for CAD patients only

- Important potential risks of serious infections including meningococcal infections
- Recommendations for vaccination of patients as per local regulations
- Recommendations for monitoring and counselling patients to promote real-world safe-use conditions

The primary endpoint is a composite endpoint comprised of a core question set (6 questions) regarding the above domains.

- Secondary objectives:
  - Describe HCPs' reported levels of receipt and reading of the ENJAYMO™ Physician's Guide,
  - Describe HCPs' knowledge levels for each question regarding the information included in the ENJAYMO™ Physician's Guide (i.e., all questions relating to all domains),
  - Describe HCP's reported levels of dissemination of the ENJAYMO™ Patient Guide to patients treated with ENJAYMO™ (questions asked to ENJAYMO™ prescribers only),
  - Describe HCPs' experience with patients' receptivity to vaccination (question asked to ENJAYMO™ prescribers only),
  - Assess implementation of vaccinations and patient counselling (questions asked to ENJAYMO™ prescribers only), and
  - Describe the primary source(s) from which HCPs learned about the information included in the ENJAYMO™ Physician's Guide.

Study Design:

This is a multinational, non-interventional, cross sectional survey study to evaluate the effectiveness of the ENJAYMO™ Physician's Guide among EEA-based HCPs.

The current study is planned to be conducted among HCPs in countries in the EEA where the product is expected to be commercially available for at least 6 months. The survey will be launched no sooner than 6 months, and no longer than 18 months, after the ENJAYMO™ Physician's Guide has been disseminated in each participating country. The survey may be conducted in up to 2 waves with the second wave of the same survey opening 6 to 12 months after the first wave is closed. Countries may include Austria, Germany, Italy, and the Netherlands. A convenience sample of HCPs will be recruited from the target population of HCPs who treat patients with CAD and may prescribe ENJAYMO™ in these countries.

The survey is anticipated to be open between 3 to 6 months per country per wave. Depending on response rates, follow-up reminders will be sent to non-respondents to endeavor to achieve the target sample size, and the medical scientific liaison team of Sanofi could also be involved in some countries to advocate via their personal contacts the participation to the

survey for HCPs already contacted via e-mail. In the event that less than 30 completed surveys are achieved in the first wave of the study, a second wave of the same survey will be triggered.

Data will be collected by web-based electronic data capture. Information collected will include the receipt and reading of the ENJAYMO™ Physician's Guide, knowledge of the key information included in the ENJAYMO™ Physician's Guide, the impact of the ENJAYMO™ Physician's Guide on clinical action, and HCP characteristics.

All data will be maintained in compliance with local regulations. Results will be analyzed using SAS. Results will be summarized in tables and figures (as applicable). A statistical analysis plan will be developed to describe the planned statistical analyses in detail and finalized prior to the end of data collection. A final study report will be prepared.

Population:

Inclusion criteria:

1. Prescribers, and potential prescribers, of ENJAYMO™.
2. Provides permission to share their responses in aggregate with EMA or national competent authorities, if requested

Exclusion criteria:

1. Is or has been a direct employee of Sanofi, the EMA, or ICON plc within the last five years.

Variables:

Primary endpoint

The primary endpoint is knowledge levels of key information included in the ENJAYMO™ Physician's Guide across these 4 domains:

- Indication for CAD patients only
- Important potential risks of serious infections and meningococcal infections
- Recommendations for vaccination of patients as per local regulations
- Recommendations for monitoring and counseling patients to promote real-world safe-use conditions.

The primary endpoint is a composite endpoint based on the percentages of HCPs with correct responses to questions included in the composite. The composite is the weighted average knowledge level across the core question set (6 questions) from the above domains. Success criteria for the primary endpoint percentage is at least 80% of HCPs have answered the item correctly (if the number of HCPs who answered is at least 30).

Secondary endpoints

- The distribution of HCPs' reported levels of receipt and reading of the ENJAYMO™ Physician's Guide,

- HCPs' knowledge levels for each question regarding the information included in the ENJAYMO™ Physician's Guide (i.e., all questions relating to all domains), assessed as the percentages of HCPs with correct responses to each question,
- The distribution of HCP's reported levels of dissemination of the ENJAYMO™ Patient Guide to patients treated with ENJAYMO™ (questions asked to ENJAYMO™ prescribers only),
- The distribution of HCPs' responses regarding their experience with patients' receptivity to vaccination (questions asked to ENJAYMO™ prescribers only),
- Implementation of vaccination (questions asked to ENJAYMO prescribers only), and
- The distribution of responses regarding the primary source(s) from which HCPs learned about the information included in the ENJAYMO™ Physician's Guide.

Other endpoints

- HCP characteristics (including whether or not the HCP has participated in a sutimlimab clinical trial or in the CADENCE registry observational study).

Data Sources:

A convenience sample of approximately 50 HCPs from the included countries will be recruited from the target population of HCPs who may treat patients with CAD in participating countries, with possibly 10 of these HCPs having actually prescribed ENJAYMO™ (this number depends on uptake of ENJAYMO™ and is difficult to predict). The sample will be drawn from lists of European-based HCPs who were sent the ENJAYMO™ Physician's Guide in included countries (where sharing HCP contact information is allowed). Recruitment lists will include but not be limited to HCPs participating in the CAD Real-World Evidence (CADENCE) patient registry and those who were initially contacted for CADENCE and declined participation. Lists may also be supplemented through additional outreach based on internet research or outreach through applicable professional societies.

The survey may be conducted in up to 2 waves. In the event that the survey has been open for 6 months in all countries and 30 completed surveys have not been achieved, with a minimum of 10 of those having been completed by ENJAYMO™ prescribers, a second wave of the same survey will be conducted 6 to 12 months later.

Invitations to participate in the survey may be sent to up to 1,000 HCPs by either email (preferred) or by post mail (if email is not available) using the available contact information.

All data for the actual survey will be collected by on-line data capture.

Sample Size:

The primary evaluation criteria are HCPs' knowledge of the ENJAYMO™ Physicians's Guide recommendations to minimise risk, expressed as the weighted composite percentage of HCPs with correct responses to the key question set. The sample size is based on the primary

endpoint, a sample size of 50 HCPs allows estimation of a minimum HCP knowledge level with a precision of 11.1% or better.

Table 1: Precision and 95% Confidence Intervals (CI) for Various Combinations of Sample Size and Knowledge Levels

Sample Size	Probable Respondent Knowledge Levels							
	60%		70%		80%		90%	
	Precision (%)	95% CI	Precision (%)	95% CI	Precision (%)	95% CI	Precision (%)	95% CI
25	19.2	40.8, 79.2	18.0	52.0, 88.0	15.7	64.3, 95.7	10.9	78.2, 100.0
50	13.6	46.4, 73.6	12.7	57.3, 82.7	11.1	68.9, 91.1	8.3	81.7, 98.3
75	11.1	48.9, 71.1	10.4	59.6, 80.4	9.1	70.9, 89.1	6.8	83.2, 96.8
100	9.6	50.4, 69.6	9.0	61.0, 79.0	7.8	72.2, 87.8	5.9	84.1, 95.9

Note: Calculated using PASS 12 software,* confidence intervals for 1 proportion, simple asymptotic formula.
* Hintze, J. (2014). PASS 12. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.

Data Analysis:

The primary analysis population will include all HCPs who have completed at least 1 of the primary effectiveness endpoint questions on the survey. The primary criteria is the weighted percentage of HCPs with correct responses to the key question set.

In the event that the study is conducted in 2 waves, HCP responses from both waves will be combined to comprise the primary analysis population.

Other criteria include measures of receipt and reading of the ENJAYMO™ Physician's Guide, knowledge levels for each question regarding the information included in the ENJAYMO™ Physician's Guide (i.e., all questions relating to all domains), assessed as the percentages of HCPs with correct responses to each question, the distribution of HCPs' responses regarding their experience with patients' receptivity to vaccination, and the distribution of responses regarding the primary source(s) from which HCPs learned about the information included in the ENJAYMO™ Physician's Guide.

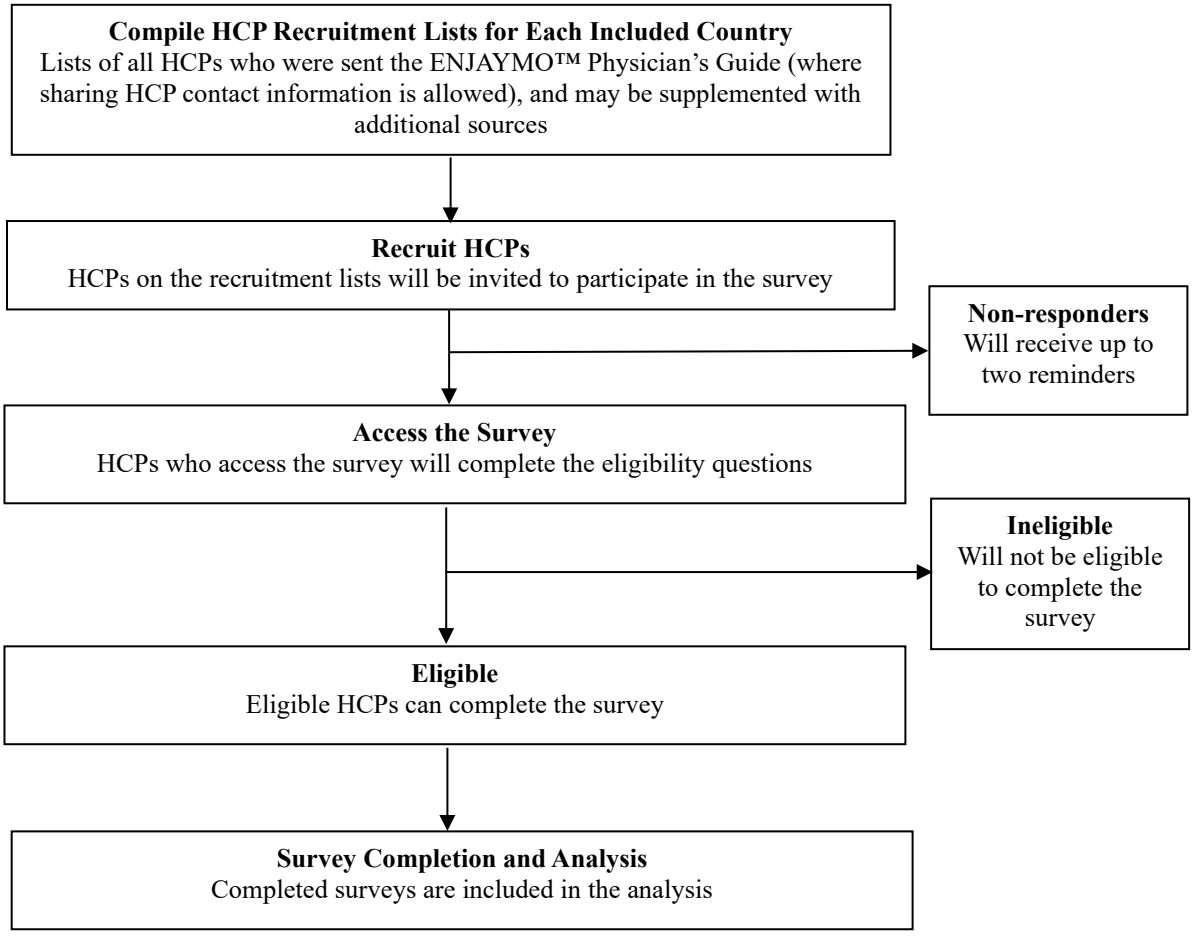
All analyses will be performed using appropriate statistical software (e.g., SAS® Version 9 or later). Data analyses will be descriptive. For continuous variables, counts, means (with standard deviations), medians (with interquartile ranges, minimum, and maximum) will be provided. For categorical variables, frequencies and percentages (with 95% CI) will be provided. Missing data will be reported, but no replacement or imputation will be performed.

Knowledge levels will be calculated with 95% 2-sided CI. Knowledge levels will also be reported by relevant subgroups (e.g., country, prescribers vs. potential, reads/uses vs. did not read/does not use the ENJAYMO™ Physician's Guide).

For each primary endpoint, the weighted average percentage of HCPs who answered all the questions in the core question set correctly will be estimated and assessed against the 80% (± 95% CI) target (if the number of HCPs who answered all questions is at least 30).

4.1 Flow Chart

Figure 4-1 provides a study flow chart.



5 AMENDMENTS AND UPDATES

None.

6 MILESTONES

The survey is planned to launch no sooner than 6 months, and no later than 18 months after the ENJAYMO™ Physician's Guide has been disseminated in each participating country. The study milestones below are as follows:

Milestone		**Planned periods**
EMA protocol submission		Q2 2022
Registration in the EU PAS register		Prior to start of data collection
Start of data collection		Q2 2024*
End of data collection		Q4 2025*
Final report of study results		Q1 2026*

*Dependant on launch dates

7 RATIONALE AND BACKGROUND

Cold agglutinin disease (CAD) is a chronic hemolytic anaemia in which activated C1 continually triggers the classical complement pathway (CP), resulting in hemolysis of red blood cells (RBCs). Individuals with CAD are at increased risk for thromboembolism. CAD is a rare condition; for instance, in 2020, a published study reported a CAD prevalence estimate of 20 per million in cold European climates versus a rate of 5 per million in warmer European regions.

ENJAYMO™ (sutimlimab, formerly BIVV009) is a first-in-class, humanized monoclonal antibody designed to target C1s, which is responsible for activating the classic complement pathway(1). Although ENJAYMO™ does not affect the lectin and alternative pathways, patients may still be at increased risk of serious infections, especially infections caused by encapsulated bacteria and meningococcal infections(2). To mitigate this risk, Sanofi anticipated that non-routine risk minimization measures (RMM) may be required by the European Medicines Agency (EMA), and has developed the ENJYAMO™ Physician's Guide as an additional RMM to inform HCPs of the indication for CAD patients and not those with cold agglutinin syndrome, important potential risks of serious infections and meningococcal infections, and recommendations for patient vaccination, monitoring, and counselling(3). The ENJYAMO™ Physician's Guide is also intended to increase implementation of vaccinations and patient counselling.

In accordance with Good Pharmacovigilance Practices (GVP) Module XVI requirements(3), Sanofi plans to conduct a study to evaluate the effectiveness of the ENJAYMO™ RMM, with a specific aim to assess the effectiveness of the ENJAYMO™ Physician's Guide. This

study will be included in the ENJAYMO™ Risk Management Plan (RMP) submission to EMA.

The proposed study utilizes a multi-country, cross-sectional survey study design. Surveys are an accepted methodology to evaluate knowledge and are referenced as an appropriate tool in GVP Module XVI.

8 RESEARCH QUESTION AND OBJECTIVES

The overall goal of this study is to perform an effectiveness evaluation of the ENJAYMO™ Physician's Guide among HCPs who treat patients with CAD. Specific objectives are described in Sections 8.1 and 8.2.

8.1 Primary Objective

Assess HCPs' knowledge levels of key information included in the ENJAYMO™ Physician's Guide across these 4 domains:

- Indication for CAD patients only
- Important potential risks of serious infections including meningococcal infections
- Recommendations for vaccination of patients as per local regulations
- Recommendations for monitoring and counseling patients to promote real-world safe-use conditions

The primary endpoint is a weighted composite endpoint comprised of a core question set (6 questions) regarding the above domains.

8.2 Secondary Objectives

- Describe HCPs' reported levels of receipt and reading of the ENJAYMO™ Physician's Guide,
- Describe HCPs' knowledge levels for each question regarding the information included in the ENJAYMO™ Physician's Guide (i.e., all questions relating to all domains),
- Describe HCP's reported levels of dissemination of the ENJAYMO™ Patient Guide to patients treated with ENJAYMO™ (questions asked to ENJAYMO™ prescribers only),
- Describe HCPs' experience with patients' receptivity to vaccination (questions asked to ENJAYMO™ prescribers only),
- Assess implementation of vaccinations and patient counselling (questions asked to ENJAYMO™ prescribers only), and
- Describe the primary source(s) from which HCPs learned about the information included in the ENJAYMO™ Physician's Guide.

No *a priori* hypothesis is defined for this study.

9 RESEARCH METHODS

9.1 Data Sources

9.1.1 Main Survey

All data for the actual survey will be collected by on-line data capture. The survey will be available for in the native language spoken in participating countries.

Sanofi launched the CADENCE Registry in late 2019 to help improve patient care through advanced CAD knowledge. CADENCE is an on-going observational, non-interventional registry that aims to enroll about 400 CAD patients in the US, Austria, Denmark, Germany, Italy, Japan, the Netherlands, and Norway.

For the current study, a convenience sample of approximately 50 HCPs from the included countries will be recruited from the target population of HCPs who may treat patients with CAD, with an estimated 10 of these HCPs having actually prescribed ENJAYMO™ (this number depends on uptake of ENJAYMO™ and is difficult to predict). Countries may include Austria, Germany, Italy, and the Netherlands. The sample will be drawn from lists of European-based HCPs who were sent the ENJAYMO™ Physician's Guide in these countries (where sharing HCP contact information is allowed). Recruitment lists will include but not be limited to HCPs participating in the CAD Real-World Evidence (CADENCE) patient registry and those who were initially contacted for CADENCE and have declined participation. Lists may also be supplemented through additional outreach based on internet research or outreach through applicable professional societies.

To endeavor to achieve a sample of at least 50 completed surveys, recruitment will remain open for a minimum of 3 months and up to 6 months in each country, and will not be closed early even if 50 completed surveys have been reached sooner. Metrics will be tracked to monitor survey progress (e.g., number of eligible/ineligible HCPs, number of completed surveys). Depending on response rates, follow-up reminders will be sent to non-respondents to achieve the target sample size. If after two reminders the target sample size has not been reached, the pool of potential HCP prescribers will be supplemented through additional outreach based on internet research or outreach through applicable professional societies, inclusion of additional countries within the European Union (EU)/European Economic Area (EEA), or extension of the survey period. The local teams of medical scientific liaison from Sanofi may also support the survey by reaching out to some of the HCPs contacted and whom they may already know or visit, so to encourage their participation.

The survey may be conducted in up to 2 waves. In the event that the survey has been open for 6 months in all countries and 30 completed surveys have not been achieved, with a minimum

of 10 of those having been completed by ENJAYMO™ prescribers, a second wave of the same survey will be conducted 6 to 12 months later.

Invitations to participate in the survey may be sent to up to 1,000 HCPs by either email (preferred) or by post mail (if email is not available) using the available contact information The invitation letter will include information about the survey, a unique code, and instructions for accessing the survey. The unique code will be used to track who has already completed a survey so that reminders are only sent to HCPs who have not yet completed the survey.

As an acknowledgement of their time and valuable input, HCPs who complete the survey will receive fair market value (FMV) compensation if allowed, feasible, and in accordance with local regulations.

9.1.2 Language Considerations

The survey questionnaire, HCP agreement and invitation letter will be translated to the local language for each country. To ensure that the questionnaire is easily understandable and conceptually equivalent in the local language, the linguists will align specific phrases with those used in the ENJAYMO™ Physicians Guide from each country. Translations will be independently proof-read by linguists and then reviewed and approved by a local Sanofi affiliate in each of the participating countries. These local Sanofi affiliate team members will be required to sign a validation of review that will be kept in the trial master file.

9.2 Endpoints

The survey includes a survey introduction and screening questions to ensure the HCP is eligible to participate in the survey. The main survey questions are described in Sections 9.2.1 and 9.2.2, and in Table 9-1 and 9-2.

9.2.1 Primary

The primary endpoint is knowledge levels of key information included in the ENJAYMO™ Physician's Guide across these 4 domains (assessed by 6 questions):

- Indication for CAD patients only (question 3)
- Important potential risks of serious infections including meningococcal infections (questions 4 and 6)
- Recommendations for vaccination of patients as per local regulations (question 5)
- Recommendations for monitoring and counseling patients to promote real-world safe-use conditions (questions 7 and 8).

The primary endpoint is a composite endpoint based on the percentages of HCPs with correct responses to questions included in the composite. The composite is the weighted average knowledge level across the core question set (6 questions) from the above domains. Success

criteria for the primary endpoint percentage is at least 80% of HCPs have answered the item correctly (if the number of HCPs who answered is at least 30).

9.2.2 Secondary

Secondary endpoint questions include:

- The distribution of HCPs' reported levels of receipt and reading of the ENJAYMO™ Physician's Guide,
- HCPs' knowledge levels for each question regarding the information included in the ENJAYMO™ Physician's Guide (i.e., all questions relating to all domains), assessed as the percentages of HCPs with correct responses to each question,
- The distribution of HCP's reported levels of dissemination of the ENJAYMO™ Patient Guide to patients treated with ENJAYMO™ (questions asked to ENJAYMO™ prescribers only),
- The distribution of HCPs' responses regarding their experience with patients' receptivity to vaccination (questions asked to ENJAYMO™ prescribers only),
- Implementation of vaccination (questions asked to ENJAYMO prescribers only), and
- The distribution of responses regarding the primary source(s) from which HCPs learned about the information included in the ENJAYMO™ Physician's Guide.

Table 9-1 Outcomes/endpoints collected in the survey

Study Objective Domains Assessed	Corresponding variable	Operational definition/derivation "Calculated as the percentage of HCPs who"*
HCPs' knowledge of the indication for ENJAYMO™ treatment in adult patients with CAD (not patients with cold agglutinin syndrome)	Knowledge that ENJAYMO™ is indicated for the treatment of hemolytic anemia in CAD patients	For question 3: "Checked" hemolytic anemia
	Knowledge that ENJAYMO™ is not indicated for the treatment of jaundice	For question 3: "Not checked" jaundice
	Knowledge that ENJAYMO™ is not indicated for the treatment of cardiac arrhythmia	For question 3: "Not checked" cardiac arrhythmia
	Knowledge that ENJAYMO™ is not indicated for the treatment of nausea and vomiting	For question 3: "Not checked" nausea and vomiting
	Knowledge that ENJAYMO™ is not indicated for the treatment of patients with cold agglutinin syndrome	For question 3: "Not checked" indicated for patients with cold agglutinin syndrome

Study Objective Domains Assessed	Corresponding variable	Operational definition/derivation "Calculated as the percentage of HCPs who"*
HCPs' knowledge of important potential risks of serious infections from encapsulated bacteria	Knowledge that ENJAYMO™ should only be prescribed to patients who have received appropriate vaccinations, especially against encapsulated bacteria	Checked "true" to question 4
	Knowledge of current local vaccine guidelines or recommendations in patients with persistent complement deficiencies	Checked "true" to question 5
Knowledge of important potential risks of serious infections from encapsulated bacteria	Knowledge that *Neisseria meningitides* infection warrants caution	For question 6: "Checked" *Neisseria meningitides* infection warrants caution
	Knowledge that *Hemophilus influenza* infection warrants caution	For question 6: "Checked" *Hemophilus influenza* infection warrants caution
	Knowledge that *Streptococcus pneumoniae* infection warrants caution	For question 6: "Checked" *Streptococcus pneumoniae* infection warrants caution
	Knowledge that urinary tract infection warrants caution	For question 6: "Checked" urinary tract infection warrants caution
HCPs' knowledge of the need to monitor and counsel patients	Knowledge to monitor for signs and symptoms of serious infections	Checked "yes" to question 7b
	Knowledge of caution in patients with chronic infections (Hep B, C or HIV)	Checked "yes" to question 7c
	Knowledge to counsel patients about the risks including meningitis	Checked "yes" to question 7d
	Knowledge that monitoring for kidney damage is not indicated	Checked "no" to question 7a
	Knowledge that thyroid function does not need to be assessed	Checked "no" to question 7e
	Knowledge that patients do not need to be counselled to monitor heart function	Checked "no" to question 7f
HCPs' knowledge to counsel patients to monitor for symptoms of relevant serious infections	Knowledge to counsel patients to seek	Checked "false" to question 8c
	Knowledge that swelling in legs, ankles and feet is not a symptom of interest	Checked "false" to question 8e
	Knowledge that polyuria, dry mouth and blurred vision is not a symptom of interest	Checked "false" to question 8f
Assess whether HCPs received and read the ENJAYMO™ Physicians' Guide	Received ENJAYMO™ Physician's Guide	Checked "yes" to question 1
	Read ENJAYMO™ Physician's Guide	Checked "yes" to question 2
Primary source of the indication, risk and	Response choices: SmPC, ENJAYMO™ Physician's Guide, Professional society or	Checked each of the response choices to question 9

Study Objective Domains Assessed	Corresponding variable	Operational definition/derivation "Calculated as the percentage of HCPs who"*
recommendations for ENJAYMO™	congress, EMA website, Clinical practice guidelines, Other	

*Denominator to include "I don't know/am not sure"

9.2.3 Other Endpoints

The survey includes HCP characteristics and other outcomes that may be treated as covariates for data analysis. These questions are described in Table 9-2.

Table 9-2 Other outcomes collected in the survey

Data collected	Variable type	Operation definition/derivation
Years practicing as a physician	Categorical	< 5 years, 5 to <10 years, 10 to <15 years, ≥15 years, prefer not to answer
Number of patients for which the HCP has prescribed ENJAYMO™	Categorical	None, <5 patients, 5-10 patients, >10 patients, prefer not to answer
HCP confirmed distribution of the ENJAYMO™ Patient Guide	Categorical	Yes, no, I don't know/am not sure
HCP confirmed vaccination status in the patient most recently prescribed ENJAYMO™	Categorical	Yes, no, I don't know/am not sure
Vaccines HCP checked in the patient most recently prescribed ENJAYMO™	Categorical	Meningococcal conjugate vaccine(s), meningococcal serogroup B vaccine(s), pneumococcal vaccine(s), Other (please specify), I don't know/am not sure
Vaccines up-to-date in the patient most recently prescribed ENJAYMO™	Categorical	Yes, no, I don't know/am not sure
HCP administered or prescribed vaccines to the patient most recently prescribed ENJAYMO™	Categorical	Yes, no, I don't know/am not sure
Reason HCP did not provide vaccines to the patient most recently prescribed ENJAYMO™	Categorical	The patient refused vaccination, the patient received vaccination elsewhere, I don't know/am not sure
Timing of vaccination relative to starting ENJAYMO™ in the patient most recently prescribed ENJAYMO™	Categorical	At the same time ENJAYMO™ treatment was started, less than two weeks before ENJAYMO™ treatment was started, two weeks before ENJAYMO™ treatment was started, I don't know/am not sure

HCP counselled the patient most recently prescribed ENJAYMO™ to seek immediate medical attention if they experience symptoms of serious infection	Categorical	Yes, no, I don't know/am not sure
Investigator in ENJAYMO™ clinical trial	Categorical	Yes, no, prefer not to answer
Involvement with CADENCE patient registry	Categorical	Yes, no, prefer not to answer

9.3 Study Design

This is a multinational, non-interventional, cross-sectional survey study to evaluate the effectiveness of the ENJAYMO™ Physician's Guide among EEA-based HCPs.

The current study is planned to be conducted among HCPs in countries in the EEA where the product is expected to be commercially available for at least 6 months. The survey will be launched no sooner than 6 months, and no longer than 18 months, after the ENJAYMO™ Physician's Guide has been disseminated in each participating country. Countries may include Austria, Germany, Italy, and the Netherlands. A convenience sample of HCPs will be recruited from the target population of HCPs who treat patients with CAD and may prescribe ENJAYMO™ in these countries.

The survey is anticipated to be open between 3 to 6 months per country per wave. Depending on response rates, follow-up reminders will be sent to non-respondents to endeavor to achieve the target sample size, and the medical scientific liaison team of Sanofi may also be involved in some countries to advocate for the participation in the survey through their personal contacts with HCPs already contacted via e-mail. In the event that less than 30 completed surveys are achieved in the first wave of the study, a second wave of the same survey will be triggered.

Data will be collected by web-based electronic data capture. Information collected will include the receipt and reading of the ENJAYMO™ Physician's Guide, knowledge of the key information included in the ENJAYMO™ Physician's Guide, the impact of the ENJAYMO™ Physician's Guide on clinical action, and HCP characteristics.

All data will be maintained in compliance with local regulations. Results will be analyzed using SAS. Results will be summarized in tables and figures (as applicable). A statistical analysis plan will be developed to describe the planned statistical analyses in detail and finalized prior to the end of data collection. A final study report will be prepared.

9.4 Study Population

Generally, it is preferable to conduct surveys to assess HCPs' knowledge and awareness of product-specific aRMM amongst HCPs actually engaging with the product (e.g., prescribers or HCPs managing care for patients receiving the product). However, since ENJAYMO™ is used to treat CAD, a rare disease, and will also be a newly authorised product where reimbursement applications and decisions will be ongoing, the number of prescribers may be low and therefore it may be challenging to identify a sufficient number of HCP prescribers to obtain robust and precise estimates of knowledge level. This survey will therefore be open to any HCP who was targeted to receive the aRMM for the product and is likely to prescribe (even though may not have yet prescribed) ENJAYMO™.

9.4.1 Selection of Study Population

To determine HCPs' eligibility, screening questions will be presented in the on-line survey in the order presented in Sections 9.4.2 followed by 9.4.3.

9.4.2 Inclusion Criteria

HCPs will be eligible for this survey if they meet the following criteria:

1. Prescribers, and potential prescribers, of ENJAYMO™.
2. Provides permission to share their responses in aggregate with EMA or national competent authorities, if requested.

9.4.3 Exclusion Criteria

HCPs will not be eligible for this survey if they meet the following criteria:

1. Is or has been a direct employee of Sanofi, the EMA, or the study vendor (ICON plc) within the last five years.

9.5 Treatments and Evaluation

No tests or reference treatments are evaluated in this cross-sectional survey study.

9.5.1 Discontinuation Criteria

Participation in this survey is voluntary and will not affect HCPs' ability to prescribe ENJAYMO™. HCPs may withdraw from the study for any reason, at any time, without penalty or prejudice. If requested by an HCP, their survey responses will be removed from the analysis database and not used in the final study report.

9.6 Variables

The survey questionnaire includes the following:

- Screening questions to determine eligibility for survey participation,

- Questions regarding the receipt, reading, and use of the ENJAYMO™ Physician's Guide,
- Questions regarding the dissemination of the ENJAYMO™ Patient Guide,
- Questions to assess knowledge of the core messages included in ENJAYMO™ Physician's Guide,
- Questions to assess HCPs' experience with patients' receptivity to vaccination (asked of HCPs who have prescribed ENJAYMO™ only), and
- Brief questions on HCP characteristics.

The main survey questions are described in Sections 9.2.1 and 9.2.2 and Table 9-1 and 9-2.

9.7 Study Size

A sample of 50 completed surveys is targeted for this study, with possibly 10 of the HCPs having actually prescribed ENJAYMO™ (this number depends on uptake of ENJAYMO™ and is very difficult to predict). Although reasonable efforts will be made to reach the target, the actual sample size will depend on actual prescribing of ENJAYMO™ as well as HCPs' willingness to participate. The sample size was determined based on both feasibility and statistical considerations, giving the rarity of CAD and therefore anticipated low number of actual ENJAYMO™ prescribers.

A recent meta-analysis of data from 23 HCP surveys found the proportions of HCPs who completed a survey among those invited ranged from 0.5% to 26.0%, with a pooled estimated proportion of 2.1% (95% confidence interval [CI]: 2.1-2.2) based on a fixed effects model, or 4.7% (95% CI: 3.0-6.6) based on a random effects model(4). Based on this plus the ICON's anecdotal experience with similar surveys, this survey estimates that a response rate of 5% is achievable. Based on this estimated response rate, at least 1,000 HCPs may need to be contacted to obtain 50 completed surveys.

Error! Reference source not found. below provides the precision and 2-sided 95% CI for different assumptions regarding levels of knowledge and number of completed surveys for this study. The primary evaluation criteria is the composite weighted average knowledge levels for the core question set. With a response from 50 HCPs and an observed knowledge level of 80%, the true value would be estimated to lie within the margin of 68.9-91.1% (i.e. with a precision of 11.1%).

Table 9-3: Precision and 95% Confidence Intervals for Various Combinations of Sample Size and Knowledge Levels

Sample Size	Probable Respondent Knowledge Levels							
	60%		70%		80%		90%	
	Precision (%)	95% CI	Precision (%)	95% CI	Precision (%)	95% CI	Precision (%)	95% CI
25	19.2	40.8, 79.2	18.0	52.0, 88.0	15.7	64.3, 95.7	10.9	78.2, 100.0
50	13.6	46.4, 73.6	12.7	57.3, 82.7	11.1	68.9, 91.1	8.3	81.7, 98.3
75	11.1	48.9, 71.1	10.4	59.6, 80.4	9.1	70.9, 89.1	6.8	83.2, 96.8
100	9.6	50.4, 69.6	9.0	61.0, 79.0	7.8	72.2, 87.8	5.9	84.1, 95.9

Note: Calculated using PASS 12 software,* confidence intervals for 1 proportion, simple asymptotic formula.
* Hintze, J. (2014). PASS 12. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.

9.8 Data Management

Survey data collection will be completed on-line in Confirmit, a software platform specifically designed for the creation and delivery of multi-lingual surveys. Data collected will be stored at secure servers and will be maintained to ensure compliance with applicable local and national regulations.

Response sets for multiple-choice questions will be randomised to minimise bias. To minimise likelihood that respondents would look up answers and/or discuss the survey while taking it, respondents will be asked to complete survey in 1 sitting and will not be allowed to revise their answers after they advance to the next question.

Survey database lock is anticipated to occur shortly after the survey is closed in all countries. To reduce opportunity for bias, survey respondents will not be contacted to clarify or revise their responses to knowledge assessment-related questions.

Data management will be in accordance with the ICON's standard operating procedures (SOPs). Additional details regarding data collection, management of missing data, data storage, and validation procedures will be detailed in the survey manual and statistical analysis plan (SAP).

9.9 Data Analysis

9.9.1 Statistical Analysis

All analyses will be performed by ICON Plc.

A SAP will be developed and will describe all planned analyses in detail, along with any specifications for tables, listings, and figures to be produced. The SAP will be finalized prior to database close. Any changes to analyses outlined in the SAP will be captured in the final study report as changes to the SAP.

9.9.1.1 Analysis Populations

The primary analysis population will include all HCPs who have completed at least 1 of the primary effectiveness endpoint questions in the survey. Denominators used to calculate knowledge levels for individual survey questions will reflect the number of respondents who completed the particular survey question including responses of 'I don't know/not sure'.

In the event that the study is conducted in 2 waves, HCP responses from both waves will be combined to comprise the primary analysis population.

9.9.1.2 Statistical Methods

Data analysis will be performed by ICON qualified personnel in accordance with ICON's SOPs for statistical analysis and programming. All analyses will be performed using appropriate statistical software (e.g., SAS® Version 9.0 or later). A report summarising the results of the survey will be developed.

The primary criteria is the composite knowledge level for the core question set. The composite will be an opportunity/denominator based weighted percentage of HCPs who have answered each item correctly (if at least 30 HCPs have completed the item).

Other criteria include measures of receipt and reading of the ENJAYMO™ Physician's Guide, knowledge levels for each question regarding the information included in the ENJAYMO™ Physician's Guide (i.e., all questions relating to all domains), assessed as the percentages of HCPs with correct responses to each question, the distribution of HCPs' responses regarding their experience with patients' receptivity to vaccination and the implementation of vaccination (date of vaccination versus treatment start, if the prescriber administered the vaccinations), and the distribution of responses regarding the primary source(s) from which HCPs learned about the information included in the ENJAYMO™ Physician's Guide.

Descriptive data analyses will be conducted for all primary and secondary objectives. Descriptive statistics for continuous data will include N, means, and standard deviations. Results for some continuous variables may include ranges (minimums and maximums) and medians as well. Categorical data will be summarised using frequency counts and percentages. Knowledge levels will be calculated with 95% 2-sided CI. Knowledge levels will also be stratified by items with potential to confound the knowledge level (e.g., country, specialty, reads/uses vs. did not read/does not use the ENJAYMO™ Physician's Guide,

prescribing status). Missing data will be reported, but no replacement or imputation will be performed.

For each primary endpoint, the weighted average percentage of HCPs who answered the core question set correctly will be estimated and assessed against the 80% (± 95% CI) target (if the number of HCPs who answered the item is at least 30).

9.10 Quality Control

ICON is responsible for following their SOPs as well as Sanofi' SOPs whenever appropriate to ensure data quality and integrity, including archiving of statistical programmes, appropriate documentation of data cleaning and validation of derived variables, and description of available data.

9.11 Limitations of the Research Methods

A primary limitation of this cross-sectional survey is potential selection bias due to use of a convenience sample and/or low response rates. Moreover, the rarity of CAD and the relatively recent approval (meaning reimbursement in many EU countries may not yet or may only recently be available) may compromise the ability to identify a sufficiently large number of ENJAYMO™ prescribers to complete the survey. Therefore, the survey will be conducted amongst HCPs who treat CAD and were sent the ENJAYMO™ Physician's Guide, rather than limiting the survey to only ENJAYMO™ prescribers. Analyses will be performed stratified by ENJAYMO™ prescribing status.

The impact of selection bias can be minimized through robust outreach to recruit a representative sample of HCPs who have received the ENJAYMO™ Physician's Guide. For this survey, to minimize selection bias, HCPs from a broadly representative sample of European countries, geographically and via market-share, will be invited to participate. Countries in the EEA where the product is expected to be commercially available for at least 6 months may be included.

Generalizability of the study results may be limited in that the study population is based on a convenience sample. To improve generalizability, all HCP potential prescribers from included countries who were sent the ENJAYMO™ Physician's Guide, will be invited to participate in the survey (where sharing HCP contact information is allowed/available). To further endeavor to minimize selection bias:

- HCPs who have not responded will receive up to two reminders to encourage their participation.
- The HCP eligibility criteria are limited to target a broad population of HCPs available to prescribe ENJAYMO™.
- Where appropriate, HCPs will be offered a small reimbursement, based on FMV, for their time to complete the survey.

- Where HCPs are not able to commit to completing the survey, they will be provided the option to respond to one question indicating their reason for not participating in the survey.

Another limitation is reliance on self-reporting which can result in social desirability reporting bias(5). In a web-based survey of 3625 HCPs across 9 EU countries conducted under the Strengthening Collaborations for Operating Pharmacovigilance in Europe (SCOPE) joint action initiative, a range from 28% to 97% of HCPs reported receiving and sometimes reading risk communication materials. Given the results were not uniformly high, this survey suggested that HCPs may be comfortable providing truthful responses to this type of question (even if possibly "socially undesirable")(6, 7). Recall bias can also impact study results, e.g. if there is a long lag time between the distribution of the ENJAYMO™ Physician's Guide and completing this survey. This will be assessed by stratifying the primary endpoint analyses by duration between distribution of the Physcian's Guide and completion of the survey.

Some survey items, such as those assessing HCPs' experience with patients' receptivity to vaccination and implementation of vaccination (date of vaccinations versus treatment start, if the prescriber administered the vaccinations), are only answerable by HCPs who have prescribed ENJAYMO™. Depending on the distribution of prescribers vs. non-prescribers in the survey, the number of responses may be low for these items, decreasing the precision of this secondary endpoint.

10 PROTECTION OF HUMAN PATIENTS

Although there are no patients in this study, the HCPs are research subjects. As such, this study will be conducted in compliance with national and EU requirements for ensuring the rights of participants in non-interventional studies.

10.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) / Competent Authorities (CA)

It is the responsibility of ICON to have prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., recruitment advertisements), if applicable, from the independent ethics committees (IEC). Where applicable, all correspondence with the IEC will be retained in ICON's study-specific file.

10.2 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 rigour and follow generally accepted research practices described in Good Pharmacoepidemiology Practice issued by the International Society for Pharmacoepidemiology (ISPE), the EMA European Network of Centres for

Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and GVP Module VIII – post-authorisation safety studies.

10.3 Patient Information and Consent

Although there are no patients in this study, the HCPs are considered study subjects. Survey participants will be asked to provide acknowledgement of consent to participate in the survey as part of the on-line consulting agreement completed by HCPs prior to accessing the survey.

10.4 Patient Confidentiality

Although there are no patients in this study, the HCPs are considered study subjects. HCPs' survey responses will be reported in aggregate and de-identified. Data will be stored in a secure validated database and shall be treated in compliance with all local applicable laws and regulations.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 Primary Data Collection

This direct-to-HCP survey does not involve patient-specific data collection and does not involve exposure to a study drug. In this survey, HCPs are the research subjects and will complete an online survey to assess knowledge via a secure website. The online survey does not include questions that could potentially identify an adverse event (AE).

However, during survey conduct, an HCP may provide unsolicited information to study personnel that could constitute an AE (e.g., while seeking information about the purpose of the survey). Since this would occur under a study, it would be considered as a solicited report.

In the event that an HCP survey participant reports an AE associated with the use of ENJAYMO™, ICON will complete an AE report form and submit it to Sanofi immediately (within 24 hours of awareness) for serious adverse events (SAEs), while non-serious AEs will be reported within 30 days of awareness. Included in the completion of the AE report form is the HCP's contact information as the reporter. Complete contact information should be obtained so that, once the AE report form is transferred to Sanofi, it can be assessed and processed according to Sanofi SOPs, including requests for follow-up regarding the AE to the HCP survey participant. As this study is not designed to collect AEs reports, additional details regarding procedures to follow in case an unanticipated AEs report is received will be included in the study-specific survey manual.

11.2 Definitions

11.2.1 Definitions of Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered a study drug, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product whether or not considered related to the medicinal (investigational) product.

An abnormality identified during a medical test is defined as an AE per the following criteria:

- Any abnormal laboratory test result (e.g., haematology, clinical chemistry, or urinalysis) or other safety assessment (e.g., electrocardiograms, radiolographic scans, vital signs measurements, physical examination), including those that worsen from baseline, that is considered to be clinically significant in the medical and scientific judgment of the investigator and not related to underlying disease, is to be reported as an (S)AE.
- Any clinically significant abnormal laboratory finding or other abnormal safety assessment which is associated with the underlying disease does not require reporting as an (S)AE, unless judged by the investigator to be more severe than expected for the subject's condition.
- Repeating an abnormal laboratory test or other safety assessment, in the absence of any of the above criteria, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

11.2.2 Definitions of Adverse Drug Reaction

An Adverse Drug Reaction is defined as 'Any noxious and unintended response associated with the use of a drug in humans, at any dose, where a causal relationship (drug-event) is at least a reasonable possibility'.

11.2.3 Definitions of Serious Adverse Events (SAEs)

An adverse event is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Results in death,
- Is life threatening (an adverse event is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death),
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- Results in congenital anomaly, or birth defect,

- Requires inpatient hospitalisation or leads to prolongation of hospitalisation (hospitalisation for treatment/observation/examination caused by AE is to be considered as serious), or
- Other medically important events.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

The Sponsor has a list of events that they classify as “always serious” events. If an adverse event is reported that is considered to be an event per this classification as “always serious”, additional information on the event may be requested.

11.3 Criteria for Causal Relationship to the (Study) Drug

Not applicable. This survey does not involve patient-specific data collection, does not involve exposure to a study drug, and does not include questions that could potential identify an AE report.

Nevertheless, should an HCP report an AE to study personnel associated with the use of ENJAYMO™, study personnel should assume there is a reasonable possibility that the event may have been caused by ENJAYMO™.

11.4 Procedure in Case of Pregnancy

This direct-to-HCP survey does not involve patient-specific data collection and does not involve exposure to a study drug. In this survey, HCPs are the research subjects and will complete an online survey via a secure website. The online survey does not include questions that could potentially identify a pregnancy.

Nevertheless, should a HCP report a female patient, or partner of a male patient, becoming pregnant who was exposed to ENJAYMO™, study personnel must report the pregnancy as if it is an AE according to the timelines specified in Section 11.5.

11.5 Notification of Adverse Drug Reactions (Serious and Non-serious) by Study Personnel to Sponsor

This survey does not involve patient-specific data collection and does not include questions that could potential identify an AE. HCPs who participate in the survey are not study

investigators; they are research subjects. Therefore, HCPs are not requested nor expected to report AEs.

Nevertheless, should a HCP report an AE to study personnel, study personnel must report SAEs immediately (within 24 hours of awareness), while non-serious AEs should be reported within 30 days of awareness.

For reporting to Global Pharmacovigilance –
Fax: [redacted]
Email: [redacted]

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this study will be summarised in a study report that, after review and approval by Sanofi, will be communicated to the applicable health authorities within the agreed timeframe. Protocol details and an abstract of results will be posted as per guidelines for studies meeting the criteria for PASS. A scientific publication may be considered. Authorship of any publications resulting from this study will be determined based on the International Committee of Medical Journal Editors Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals.

13 REFERENCES

1. Roth A, Barcellini W, D'Sa S, Miyakawa Y, Broome CM, Michel M, et al. Sutimlimab in Cold Agglutinin Disease. N Engl J Med. 2021;384(14):1323-34. 10.1056/NEJMoa2027760
2. Sanofi. ENJAYMO Physician's Guide Global Template. 2020.
3. Agency EM. Guideline on good pharmacovigilance practices (GVP): Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2). 2017.
4. Artime E, Qizilbash N, Garrido-Estepa M, Vora P, Soriano-Gabarro M, Asiimwe A, et al. Are risk minimization measures for approved drugs in Europe effective? A systematic review. Expert Opin Drug Saf. 2019;18(5):443-54. 10.1080/14740338.2019.1612875
5. Mazzaglia G, Straus SMJ, Arlett P, da Silva D, Janssen H, Raine J, et al. Study Design and Evaluation of Risk Minimization Measures: A Review of Studies Submitted to the European Medicines Agency for Cardiovascular, Endocrinology, and Metabolic Drugs. Drug Saf. 2018;41(2):191-202. 10.1007/s40264-017-0604-4
6. van der Sar JM dVS, Mol PGM, on behalf of SCOPE work package 6. European healthcare professionals' familiarity with and perceived usefulness of safety communications on medicines.
7. Agency EM. Regulatory initiatives for measuring the impact of risk minimisation measures. 2016.

14 ANNEXES

Annex 1: List of stand-alone documents

Number	Document reference number	Date	Title*
1	N/A	N/A	ENJAYMO™ Physician's Guide

Annex 2: Survey invitation letter

Healthcare Professional's Survey for ENJAYMO™ (sutimlimab)

Unique Code to Access the Survey:

On behalf of Genzyme Europe BV (Sanofi), ICON Plc (ICON) is inviting you to participate in a survey being conducted among healthcare professionals who treat patients with cold agglutinin disease (CAD) in selected EU countries to evaluate their knowledge about the important potential risks of serious infections and meningococcal infections and recommendations associated with ENJAYMO™ (sutimlimab). **Sanofi is required to perform this survey in line with the requirements of the European Risk Management Plan for ENJAYMO™.** The overall goal of this study is to evaluate the effectiveness of the ENJAYMO™ additional risk minimization measures **("ENJAYMO™ Physician's Guide")** to promote safe use of ENJAYMO™. Your participation is highly valued, and your responses may help provide important information about ENJAYMO™ to healthcare professionals like yourself in the future. Participation in this survey is voluntary.

This survey will take approximately 20 minutes to complete. The survey is recommended to complete during one sitting. You will receive an honorarium of €50 in consideration of your time and valuable input.

In the course of conducting this survey, ICON will process your personal information, including your name, contact information, and bank details if the honoraria payment is made via electronic transfer. Your individual survey responses will not be linked with your personal information in any data shared with Sanofi. Your survey responses will be processed such that you will not be able to be identified without the use of additional information that is kept separate and secure by ICON (this is known as 'pseudonymisation'). If required by local legal requirements or by Sanofi, your identity will only be disclosed to comply with requirements regarding reporting of payments made to healthcare professionals. ICON may process your personal information outside the European Economic Area and/or European Union. ICON will treat your data with care and sensitivity in accordance with data protection legislation, and the detailed Privacy Information Notice at https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy.

This survey is not designed to collect adverse event or pregnancy information. To report information on potential adverse events, pregnancies, and/or quality issues (from Sanofi medication), please notify Sanofi at https://cscontactus.sanofi.us/adverseEvent.aspx or report in accordance with your national legislation via the national reporting system.

To access the survey, go to: [PLACEHOLDER FOR SURVEY LINK]
To complete the survey, you will need to enter the Unique Code printed at the top of this invitation. If you are having trouble accessing the survey, please contact ICON at Enjaymo-HCP-Survey@iconplc.com.

Annex 3: Survey questionnaire

Please enter your Unique ID to participate in the survey. Your Unique ID was provided in your survey invitation.
Unique ID: ➔ **IF ENTERED, PROCEED TO COUNTRY AND LANGUAGE SELECTION, OTHERWISE, TERMINATE SURVEY**

The above section will only appear for respondents who did not receive their invitation directly by email from the Confirmit survey software.

Surveys invitations will include a unique ID for each HCP which will need to be entered to access the survey.

Include a % Completed Bar at the top of the survey for respondents.

Correct responses are ticked as ✓and will be removed for the actual survey.

Please select your country and language from the list below: □ Austria (German) ➔ **PROCEED TO SURVEY INTRODUCTION** □ Germany (German) ➔ **PROCEED TO SURVEY INTRODUCTION** □ Italy (Italian) ➔ **PROCEED TO SURVEY INTRODUCTION** □ The Netherlands (Dutch) ➔ **PROCEED TO SURVEY INTRODUCTION** □ My country is not listed ➔ **THANK AND TERMINATE**
[Termination Language for Non-Qualified Candidates:] Thank you for your interest in participating in this survey. However, we are required to limit participation to healthcare professionals who are from 1 of the 4 listed countries. We look forward to your potential participation in a future survey.

Survey Introduction

On behalf of Genzyme Europe BV (Sanofi), ICON is conducting a survey among healthcare professionals who prescribe ENJAYMO™ (sutimlimab). **Sanofi is required to perform this survey as mandated by the European Medicines Agency (EMA) in line with the ENJAYMO™ (sutimlimab) Risk Management Plan for Europe.** The overall goal of this study is to evaluate the effectiveness of the **"ENJAYMO™ Physician's Guide."** Participation in this survey is voluntary and will not affect your ability to prescribe ENJAYMO™.

The survey is expected to take up to 20 minutes to complete and is recommended to be completed in one sitting.

To complete the survey, you must meet study eligibility criteria. Please be assured that your individual answers will be held confidential. This study will summarise aggregated results provided by all participating healthcare professionals in order to protect the confidentiality of your individual answers.

By participating, you agree that ICON may contact you only in reference to this survey. You may withdraw from the survey at any time, in which case the information you have already provided will not be used in the final study report.

Please click on the NEXT button to verify that you qualify for this survey and to complete the required documentation for participation.

[BEGIN SURVEY SCREENING QUESTIONS]

S1. Does your practice include patients with cold agglutinin disease?

□ Yes ➔ **PROCEED TO S2**

□ No ➔ **PROVIDE A POP-UP THAT STATES** "Based on your answer, you are not eligible to take this survey. Please click "Next" to confirm your answer is correct, or click "Back" to review your answer". **IF THE USER CLICKS ON 'BACK' THEN THE QUESTION WILL BE DISPLAYED AND THE RESPONSE CAN BE**

CHANGED. IF THE USER CLICKS ON 'NEXT' THEN THANK AND TERMINATE.

S2. Do you provide your permission to share your anonymized survey responses, aggregated with all other survey responses, with the European Medicines Agency or national competent authorities?

□ Yes ➔ **PROCEED TO S3**

□ No ➔ **PROVIDE A POP-UP THAT STATES** "Based on your answer, you are not eligible to take this survey. Please click "Next" to confirm your answer is correct, or click "Back" to review your answer". **IF THE USER CLICKS ON 'BACK' THEN THE QUESTION WILL BE DISPLAYED AND THE RESPONSE CAN BE CHANGED. IF THE USER CLICKS ON 'NEXT' THEN THANK AND TERMINATE.**

S3. Are you or have you been a direct employee of Sanofi, ICON, the European Medicines Agency, or other European-based National Competent Authorities within the past 5 years?

□ Yes ➔ **PROVIDE A POP-UP THAT STATES** "Based on your answer, you are not eligible to take this survey. Please click "Next" to confirm your answer is correct, or click "Back" to review your answer". **IF THE USER CLICKS ON 'BACK' THEN THE QUESTION WILL BE DISPLAYED AND THE RESPONSE CAN BE CHANGED. IF THE USER CLICKS ON 'NEXT' THEN THANK AND TERMINATE.**

□ No ➔ **PROCEED TO MAIN SURVEY**

[Termination Language for Non-Qualified Candidates:]

Thank you for your interest in participating in this survey. However, we are required to limit participation to healthcare professionals who meet the survey eligibility requirements. We look forward to your potential participation in a future survey.

[Language for Qualified Candidates:]

Thank you for your responses. You qualify for this survey, and we look forward to your participation. Once you enter the main survey, you will only be able to move forward through the questions.

[END SURVEY SCREENING QUESTIONS]

MAIN SURVEY

[Preamble 1]: These questions are about the risks of serious infections and meningococcal infections associated with ENJAYMO™ (sutimlimab). Please be sure to review all response choices for each question before answering each question. Please note that you will only be able to move forward in the survey as you complete each question.

CORRECT RESPONSES ARE CHECKED ✓

1. Did you receive the **"ENJAYMO™ Physician's Guide"** that provides information to minimise the risks of serious infections and meningococcal infections associated with product use?

   ✓Yes
   □ No
   □ I don't know/am not sure

2. Did you read the **"ENJAYMO™ Physician's Guide"** that provides information to minimise the risks of serious infections and meningococcal infections associated with product use?

   ✓Yes
   □ No
   □ I don't know/am not sure

3. ENJAYMO™ (sutimlimab) is indicated in adult patients with cold agglutinin disease (CAD) for the treatment of (Check all that apply) **RANDOMIZE ORDER OF THE FIRST 5 RESPONSES**

   ✓Hemolytic anaemia
   □ Jaundice
   □ Cardiac arrhythmia
   □ Nausea and vomiting
   □ Cold agglutinin syndrome
   □ I don't know/am not sure

4. ENJAYMO™ (sutimlimab) should only be prescribed to patients who have received appropriate vaccinations, especially against encapsulated bacteria.

   ✓True
   □ False
   □ I don't know/am not sure

5. Are you familiar with current local guidelines or recommendations in patients with persistent complement deficiencies for meningococcal conjugate vaccine(s), meningococcal serogroup B vaccine(s), and pneumococcal vaccine(s)?

   ✓Yes
   □ No
   □ I don't know/am not sure

6. According to the ENJAYMO™ (sutimlimab) **Summary of Product Characteristics** and the **"ENJAYMO™ Physician's Guide"**, which of the following warrant specific caution when using ENJAYMO™ (sutimlimab)? Please select all that apply.

   ✓*Neisseria meningitides* infection
   ✓*Hemophilus influenza* infection
   ✓*Streptococcus pneumoniae* infection
   ✓Urinary tract infection
   ✓All of the above
   □ I don't know/am not sure

7. According to the **"ENJAYMO™ Physician's Guide"**, which of the following are important activities that are necessary when using ENJAYMO™ (sutimlimab):

		Yes, needs to be monitored	**No, does not need to be monitored**	**I don't know/am not sure**
A	Monitor patients for kidney damage	□	✓	□
B	Monitor patients for signs and symptoms of serious infections	✓	□	□
C	Take caution when prescribing ENJAYMO™ to patients who have chronic infections such as Hepatitis B, Hepatitis C or HIV	✓	□	□
D	Counsel patients about the risks of serious infection including meningitis	✓	□	□
E	Monitor patients for thyroid function	□	✓	□
F	Counsel patients about the risks of abnormal heart function	□	✓	□

8. According to recommendations in the **"ENJAYMO™ Physician's Guide,"** you should counsel patients to seek immediate medical attention if they experience symptoms associated with risks of serious infections or meningococcal infections associated with ENJAYMO™ (sutimlimab). Please answer "True", "False" or "I don't know/am not sure" to the following symptoms:

		True	False	I don't know/am not sure
A	Headache with stiff neck or back or confusion	✓	□	□
B	Fever, chills and rash	✓	□	□
C	Loss of appetite	□	✓	□
D	Muscle aches with flu-like symptoms	✓	□	□
E	Swelling in legs, ankles and feet	□	✓	□
F	Polyuria, dry mouth and blurred vision	□	✓	□

9. What is (are) the **primary source(s)** you use to learn about the appropriate indication, precautions for use, and potential risks for ENJAYMO™ (sutimlimab)? Please select all that apply. There are no correct/incorrect answers: **SELECT ALL THAT APPLY ANSWER – NO CORRECT RESPONSE.**

□ Summary of Product Characteristics
□ ENJAYMO™ Physician's Guide
□ Professional Society or Congress
□ The European Medicines Agency website
□ Via specific discussions with Sanofi MSL
□ Clinical practice guidelines; specify: _____
□ Other (not listed above); specify: _____

[ON-LINE SURVEY - PROGRAMMER: RANDOMISE THE ORDER OF THE FIRST 5 RESPONSE OPTIONS]

HCP CHARACTERISTICS

[Preamble 2]: Below are 7 additional questions to help us combine your answers with other answers we have received, and to help us interpret the survey results. THERE ARE NO CORRECT RESPONSES TO QUESTIONS 10, 11, 19, and 20. DISPLAY QUESTIONS 12-18 ON THE SAME PAGE.

10. Approximately how many years have you been practicing as a physician?

    □ <5 years
    □ 5 to <10 years
    □ 10 to <15 years
    □ ≥15 years
    □ Prefer not to answer

11. Approximately how many patients have you treated with ENJAYMO™ (sutimlimab)?

    □ None ➔ **PROCEED TO QUESTION 20**
    □ < 5 patients ➔ **PROCEED TO QUESTION 12**
    □ 5-10 patients ➔ **PROCEED TO QUESTION 12**
    □ >10 patients ➔ **PROCEED TO QUESTION 12**
    □ Prefer not to answer ➔ **PROCEED TO QUESTION 20**

12. For the most recent patient you prescribed ENJAYMO™ (sutimlimab), did you provide the patient with a copy of the ENJAYMO™ Patient Guide?

    ✓Yes ➔ **PROCEED TO QUESTION 13**

    □ No ➔ **PROCEED TO QUESTION 13**

    □ I don't know/am not sure ➔ **PROCEED TO QUESTION 13**

13. For the most recent patient you prescribed ENJAYMO™ (sutimlimab), did you confirm that their vaccination status is up-to-date according to local guidelines or recommendations for patients with persistent complement deficiencies?

    ✓Yes ➔ **PROCEED TO QUESTION 14**

    □ No ➔ **PROCEED TO QUESTION 19**

    □ I don't know/am not sure ➔ **PROCEED TO QUESTION 19**

14. For the most recent patient you prescribed ENJAYMO™ (sutimlimab), which vaccines did you check the status of? Please select all that apply.

    ✓Meningococcal conjugate vaccine(s)

    ✓Meningococcal serogroup B vaccine(s)

    ✓Pneumococcal vaccine(s)

    □ Other (not listed above); specify: _____

    □ I don't know/am not sure

15. For the most recent patient you prescribed ENJAYMO™ (sutimlimab), was the patient up-to-date on their vaccinations?

    ✓Yes ➔ **PROCEED TO QUESTION 19**

    □ No ➔ **PROCEED TO QUESTION 16**

    □ I don't know/am not sure ➔ **PROCEED TO QUESTION 19**

16. For the most recent patient you prescribed ENJAYMO™ (sutimlimab), did you administer or prescribe vaccines to the patient?

    ✓Yes ➔ **PROCEED TO QUESTION 18**

    □ No ➔ **PROCEED TO QUESTION 17**

    □ I don't know/am not sure ➔ **PROCEED TO QUESTION 19**

17. For the most recent patient you prescribed ENJAYMO™ (sutimlimab), what was the reason you did not provide vaccination?

    □ The patient refused vaccination ➔ **PROCEED TO QUESTION 19**

    ✓The patient received vaccination elsewhere ➔ **PROCEED TO QUESTION 18**

    □ I don't know/am not sure ➔ **PROCEED TO QUESTION 19**

18. For the most recent patient you prescribed ENJAYMO™ (sutimlimab), when were vaccinations administered relative to starting of ENJAYMO™ (sutimlimab)?

    □ At the same time ENJAYMO™ treatment was started

    □ Less than two weeks before ENJAYMO™ treatment was started

    ✓Two weeks before ENJAYMO™ treatment was started

    □ I don't know/am not sure

19. For the most recent patient you prescribed ENJAYMO™ (sutimlimab), did you counsel them to seek immediate medical attention if they experience symptoms associated with risks of serious infections or meningococcal infections associated with ENJAYMO™ (sutimlimab)?

    ✓Yes

    □ No

    □ I don't know/am not sure

20. Have you previously participated as an investigator of a clinical trial assessing ENJAYMO™ (sutimlimab) treatment?

    □ Yes
    □ No
    □ Prefer not to answer

21. Are you involved in the CADENCE patient registry for Cold Agglutinin Disease and Cold Agglutinin Syndrome?

    □ Yes
    □ No
    □ Prefer not to answer

CLOSING

Thank you for taking the time to complete this survey.

You may now close this browser.

Annex 4 ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

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

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: A Survey of Healthcare Professionals in Europe to Evaluate the Effectiveness of the ENJAYMO™ Physician's Guide

EU PAS Register® number: To be assigned when study is registered
Study reference number (if applicable): CEF-0205

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				6
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	

[1] 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.
[2] Date from which the analytical dataset is completely available.

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.4
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	8

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)	☒	☐	☐	9.3
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1, 9.8
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)	☒	☐	☐	11

Comments:

Measures of occurrence are levels of knowledge, expressed as the percentages of respondents with correct answers to questions regarding knowledge of information included in the ENJAYMO™ Physician's Guide.

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.1.1, 9.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.1.1, 9.3
	4.2.2 Age and sex	☐	☐	☒	
	4.2.3 Country of origin	☒	☐	☐	9.1.1, 9.3
	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)	☒	☐	☐	9.1.1, 9.4, 9.7

Comments:

This is a cross-sectional study of HCPs, who treat patients diagnosed with CAD, and who can prescribe ENJAYMO™. Age, sex, disease, and duration of follow-up are all not applicable.

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)	☐	☐	☒	
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:

This is a non-interventional study that aims to test knowledge related to risk minimisation for ENJAYMO™. Although the ENJAYMO™ Physcian's Guide may be considered an educational intervention, exposure to it/use of it is not specifically required in order to participate in this study.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8, 9.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.2
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)	☒	☐	☐	9.1, 9.2, 9.7, 9.11
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)	☒	☐	☐	9.9.2.2
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.11
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.1.2

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)	☒	☐	☐	9.9.2.2

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)	☐	☐	☒	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.1.1, 9.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.6
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)	☒	☐	☐	9.1.1, 9.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.6
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.9
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.7, 9.9.1
10.3 Are descriptive analyses included?	☒	☐	☐	9.9
10.4 Are stratified analyses included?	☒	☐	☐	9.9
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.9
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.9.1.2
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.9.1.2

Comments:

An independent statistical analysis plan will be developed to provide further details.

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, 9.10
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Results will be communicated to applicable health authorities within the agreed timeframe.

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?	☒	☐	☐	9.11
12.1.2 Information bias?	☐	☒	☐	
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)	☒	☐	☐	9.1.1, 9.3, 9.7, 9.9.1, 9.11

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

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
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Annex 5 Protocol - Signatures of Approval

_____ Date: _____

[redacted]

_____ Date: _____

[redacted]

_____ Date: _____

[redacted]