Clinical Study Protocol

EU PAS Number: EUPAS41308

Title: Assessment of the Effectiveness of Updated Educational Materials on Prescribers' Knowledge and Behavior with Respect to Risks Associated with INSTANYL® Off-Label Use

Study Number: Instanyl-5002

Document Version and Date: 3.0 (21 July 2022)

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

NON-INTERVENTIONAL SAFETY STUDY

PROTOCOL
(AMENDMENT#1)

Study Title: Assessment of the Effectiveness of Updated Educational Materials on Prescribers' Knowledge and Behavior with Respect to Risks Associated with INSTANYL® Off-Label Use

Study Number: Instanyl-5002

Version Number: 3.0, 21 July 2022

Amendment: 1.0

Ethics statement: This study will be conducted in compliance with the protocol, the Declaration of Helsinki, International Society for Pharmacoepidemiology Guidelines for Good Epidemiology Practices, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Guidelines for Methodological Standards in Pharmacoepidemiology, Good Pharmacovigilance Practices, and all applicable regulatory requirements.

Signature page

Study Title: Assessment of the Effectiveness of Updated Educational Materials on Prescribers' Knowledge and Behavior with Respect to Risks Associated with INSTANYL® Off-Label Use

Study Number: Instanyl-5002

Version Number: 3.0, 21 July 2022)>

MAH (Marketing Authorization Holder):

Role	**CPASS** [redacted]	**Printed Name**	[redacted]
Signature	DocuSigned by: [redacted]	**Date (DD-MMM-YYYY)**	03-Aug-2022 | 23:16:48 JST

EU and UK QPPV:

Role	European Union (EU) Qualified Person responsible for PV (QPPV) and UK (United Kingdom) QPPV	**Printed Name**	Dr. [redacted], [redacted], Global Patient Safety Evaluation Takeda Belgium NV Leonardo da Vincilaan 7, 1930 Zaventem, Belgium
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Study Information

Title	Assessment of the Effectiveness of Updated Educational Materials on Prescribers' Knowledge and Behavior with Respect to Risks Associated with INSTANYL® Off-Label Use
Protocol Version Identifier	3.0 (Amendment 1.0)
Date of Last Version of Protocol	16 June 2021
EU PAS Register Number	EUPAS41308
Active Substance	Fentanyl (ATC code: N02AB03)
Medicinal Product	Fentanyl intranasal spray (Instanyl®)
Product Reference	EU/1/09/531/001-021
Procedure Number	EMEA/H/C/000959/MEA/29.3
Marketing Authorization Holder(s)	Takeda Pharma A/S Delta Park 45 2665 Vallensbæk Strand Denmark
Joint PASS	No
Research Question and Objectives	<u>Research questions</u> Are the updated educational materials (EMs) effective in: 1. Increasing the knowledge of prescribers about Instanyl® approved indications and the risks of off-label use, addiction, misuse, abuse, diversion, overdose, and medication errors? 2. Increasing compliance of self-reported behavior with Instanyl® label? <u>Objectives</u> The overall objective of this study is to measure the changes in understanding and self-reported behavior of Instanyl® prescribers regarding Instanyl® off-label use and the key information contained in the updated EMs. Specifically, the study objectives are: 1. To assess prescribers' awareness of the updated EMs;

	2. To assess the changes in prescribers' knowledge and understanding of the key information contained in the updated EMs, including the risks of off-label use, misuse, abuse, diversion, medication errors, addiction, overdose, and death; 3. To assess the changes in prescribers' self-reported behavior in prescribing in accordance with approved indication; 4. To assess the reasons for off-label prescription; 5. To assess whether prescribers are fully aware about the profile of patients at risk of misuse and addiction.
Country(-ies) of study	France, the Netherlands, and Poland
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Marketing Authorization Holder(s)

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LIST OF IN-TEXT TABLES

2 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ADR	Adverse drug reaction
aRMM	Additional risk minimization measure
ASOCS	Association of Opinion and Behavior in health field research companies
ATC	Anatomical therapeutic chemical
CI	Confidence interval
EM	Educational material
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
EphMRA	European Pharmaceutical Marketing Research Association
EU	European Union
EU PAS	European Union electronic Register of Post-Authorization Studies
GP	General practitioner
GVP	Good Pharmacovigilance Practices
HCP	Healthcare professional
MAH	Marketing authorization holder
PASS	Post-authorization safety study
PQI	Product quality issue
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk management plan
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SmPC	Summary of product characteristics
SOP	Standard operating procedures
SSR	Special situation report
STROBE	Strengthening the reporting of observational studies in epidemiology
QX	Question Number
Q1-Q3	First-Third quartile

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4 ABSTRACT

Title

Assessment of the Effectiveness of Updated Educational Materials on Prescribers' Knowledge and Behavior with Respect to Risks Associated with INSTANYL® Off-Label Use

Rationale and Background

Instanyl® (intranasal fentanyl) is an opioid analgesic indicated for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain, marketed throughout the European Union (EU) since 20 July 2009.

The updated Instanyl® educational materials (EMs) for prescribers will be distributed in 2022. Similar updated materials will also be available for pharmacists and patients but will not be under examination in this study. The updated EMs will emphasize the facts that Instanyl® should be prescribed for the treatment for breakthrough pain in cancer patients, explain the off-label use of Instanyl®, and highlight the serious risks of off-label use, addiction, misuse, abuse, diversion, overdose, and medication errors. The updated EMs (prescriber brochure and instructional video) will be distributed to target prescribers likely to prescribe Instanyl® in European countries where Instanyl® is marketed. The goal of the EMs is to make prescribers of Instanyl® more aware of appropriate prescribing and use of Instanyl® in order to reduce risks. Also, the prescribers should be aware of the updated EMs available for patients and pharmacists.

This post-authorization safety study (PASS) is designed to evaluate the changes in understanding and self-reported behavior of targeted prescribers regarding Instanyl® off-label use and the key information contained in the updated EMs, including the risks of off-label use, addiction, misuse, abuse, diversion, overdose, and medication errors.

Research question and objectives

Research questions:

Are the updated EMs effective in:

- Increasing the knowledge of prescribers about Instanyl® approved indications and the risks of off-label use, addiction, misuse, abuse, diversion, overdose, and medication errors?
- Increasing compliance of self-reported behavior with Instanyl® label?

Objectives:

The overall objective of this study is to measure the changes in understanding and self-reported behavior of Instanyl® prescribers regarding Instanyl® off-label use and the key information contained in the updated EMs.

Specifically, the study objectives are:

1. To assess prescribers' awareness of the updated EMs;

2. To assess the changes in prescribers' knowledge and understanding of the key information contained in the updated EMs, including the risks of off-label use, misuse, abuse, diversion, medication errors, addiction, overdose, and death;
3. To assess the changes in prescribers' self-reported behavior in prescribing in accordance with approved indication;
4. To assess the reasons for off-label prescription;
5. To assess whether prescribers are fully aware about the profile of patients at risk of misuse and addiction.

Study Design

This study will consist of two cross-sectional surveys among prescribers who are current and potential prescribers of Instanyl® in France, the Netherlands, and Poland before and after the distribution of the updated EMs. Both surveys will be self-administered via the web (i.e., Internet).

The first survey (pre-EM survey) will be conducted before the distribution of the updated EMs (pre-intervention period). Following the distribution of the updated EMs, the second survey (post-EM survey) will be conducted (post-EMs distribution).

Population

The surveys will be conducted among physicians who are current and potential prescribers of Instanyl® in France, the Netherlands and Poland. Physicians will be identified from IQVIA OneKey™ lists of physicians active in clinical practice with valid contact details, and who meets the inclusion criteria: specialists of any of those medical specialties targeted for the EMs as agreed with each national competent authority, and have prescribed Instanyl® in the past 12 months (pre-EM survey) or since the updated EMs (post-EM survey), and who intend to prescribe Instanyl® in the following months after each survey.

Variables

The survey will include a mix of multiple choice, close-ended, and open-ended questions.

The questionnaire will collect information on self-reported Instanyl® prescribing behavior in the past 6 to 12 months, knowledge about Instanyl® approved indications and the risks of off-label use, addiction, misuse, abuse, diversion, overdose, and medication errors. Awareness of the updated EMs will also be assessed in the post-EM survey.

Data Sources

Primary data collection conducted through a self-administered web-based questionnaire.

Study Size

The original protocol has a target of 384 prescribers with a sample size from five countries together, at each survey (pre-EM survey and post-EM survey), which would provide a precision

of 5% across the target population. However, due to delays in approval of the EM in Germany and Spain, these countries were withdrawn. Therefore, a final sample size of 259 prescribers was targeted for each survey. This sample size is lower than originally planned, which resulted in a lower precision around the estimate (from 5% to 6%).

Data analyses

Results will be presented as overall, per country and specialty, at the specialty level (all countries) and at the country level (all specialties), for each survey separately. The number of physicians who refused to participate, were unreachable, failed screening, completed and submitted only partial questionnaires, and completed full questionnaires will be presented. Based on these numbers, the response rate, refusal rate, contact rate, and cooperation rate will be presented as overall, by country, and specialty. Study objectives will be analyzed as follows:

- Awareness of the updated EMs: this will be applicable to the post-EM survey (final analysis) only. Success will be reached if at least 80% of the prescribers are successful for this criterion.
- Knowledge will be assessed at the aggregate level at both the interim (pre-EM survey) and final (post-EM survey) analysis. At each, success will be reached if at least 80% of the prescribers are successful for this criterion. In addition, for the final analysis, the aggregated success for the knowledge criteria will be assessed as a positive absolute change (increase) in the percentage of successful prescribers from pre-EM to post-EM survey.
- Self-reported behavior will be assessed at the aggregate level at both the interim (pre-EM survey) and final (post-EM survey) analysis. At each, success will be reached if at least 80% of the prescribers are successful for this criterion. In addition, for the final analysis, the aggregated success for the self-reported behavior criteria will be assessed as a positive absolute change (increase) in the percentage of successful prescribers from pre-EM to post-EM survey.
- Awareness of the profile of patients at risk of misuse and addiction will be assessed based on the proportion of prescribers correctly answering question 13. Success will be reached if at least 80% of the prescribers are successful in answering this question.
- In addition, the reasons for off-label prescription (pediatric patients and/or unapproved pain indication) will be described.

Milestones

Study Milestone	Estimated Date
Protocol Submission	Q2 2020
Data Collection – pre-EM survey	Q1-Q2 2022
Interim Report	Q3 2022
Distribution of Updated EMs	Q2 2022
Data Collection – post-EM survey	Q4 2022 – Q1 2023
Final Study Report to EMA	Q3 2023

Abbreviations: EM = Educational material; EMA = European Medicines Agency; Q = quarter

5 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	21 July 2022	Title page	Removed Germany and Spain from country list.	There were delays in approval of the local EMs in Germany and Spain. As such, data collection was completed in the remaining countries as it needed to be finished before the distribution of the EMs in those countries. Therefore, as agreed with the PRAC, Germany and Spain were withdrawn from the study.
2	21 July 2022	6 Milestones	Added the actual date for data collection and distribution of updated EMs.	At the time of this Protocol Amendment, data collection was completed.
3	21 July 2022	7.1 Rationale for country selection	Clarified that while the study was originally planned to be conducted in five countries, data collection was only performed in three countries (Germany and Spain were removed).	See number 1.
4	21 July 2022	9.1 Study design	Removed reference to Germany and Spain.	See number 1.
5	21 July 2022	9.2 Setting	Removed reference to Germany and Spain.	See number 1.
6	21 July 2022	9.3 Variables	Harmonized with the revised questionnaire and success criteria.	Changes were made for consistency with the final version of the questionnaire and the topics addressed in success criteria (Annex 1).
7	21 July 2022	9.2.4 Target prescribers for pre-EM and post-EM surveys	Reference to the withdrawal of Germany and Spain from the study.	See number 1.
8	21 July 2022	9.2.4 Target prescribers for pre-EM and post-EM surveys	Added that paper mail invites can be used to invite prescribers in case of difficulties achieving the sample size.	Added more details on physician recruitment (which were added in the SAP) and consolidated all information in Section 9.2.4 (instead of having it in two separate sections).
9	21 July 2022	9.5 Study size	Explained that the final sample size will be lower than originally planned,	Added details on the consequences of Germany and Spain being withdrawn.

			which will result in a lower precision around the estimate.	
10	21 July 2022	9.6.1 Data collection	Moved text to Section 9.2.4.	Consolidated the information about prescriber recruitment in a single section.
11	21 July 2022	9.6.1 Approaches for increasing the response rate	Added that paper mail invites can be used to invite prescribers in case of difficulties achieving the sample size.	See number 8.
12	21 July 2022	9.7 Data analysis (all subsections)	1. Added more details on the analysis such as the introduction of a 2-sided CI and guidance on handling questions with multiple answers. 2. Introduced the possibility that some specialties may be grouped if there are low numbers (i.e., GPs + internal medicine vs. all other specialties). 3. Added the "failed screening" prescribers to the computation of response rates. 4. Added details on the descriptive presentation of the questionnaire answers. 5. Clarified several aspects of the analysis of success, which were unclear in the original protocol version, such as: a) the success for awareness, knowledge and self-reported behavior is assessed at the aggregate level by the proportion of successful prescribers achieving a pre-defined success threshold. Other analyses will be considered complementary; b) the change of results from pre-EM to post-EM is assessed as the absolute change in the percentage of successful prescribers from pre-EM to	Harmonized the data analysis section with the SAP which introduced several clarifications on the analysis and main criterion used to assess the success of awareness, knowledge, and self-reported behavior.

			post-EM survey (at the aggregate level) instead of a change in the mean proportion (of the individual results). 6. Removed one of the sensitivity analyses which was not deemed relevant (to assess the change in the mean proportion where the mean proportion of correct answers was <80% in the pre-EM survey). 7. Clarified the analysis on the profile of unsuccessful prescribers.	
13	21 July 2022	Annex 1	1. Question verbatim was amended to reflect changes in the questionnaire that were done after pilot. 2. Definition of correctly answered questions, assessment of success was revised for consistency with the final questionnaire, and changes were made during SAP development.	Harmonization with the final version of the questionnaire and the refinement of scoring system done during SAP development.
14	21 July 2022	Annex 2	Changed the verbatim of some questions and indications of the correct/targeted answer to reflect changes made to the questionnaire between the original protocol and data collection.	Harmonization with the final version of the questionnaire used for data collection which reflected changes made to improve, clarify, and accommodate feedback from the pilot assessment.
15	21 July 2022	Annex 3	Replaced the checklist with a new version and reviewed the items.	New version of ENCePP Checklist for study protocols was implemented.

Abbreviations: CI = Confidence interval; EM = Educational materials; ENCePP= The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; GP = General practitioner; PRAC = Pharmacovigilance Risk Assessment Committee; SAP = Statistical analysis plan.

6 MILESTONES

Milestone	Planned date	Actual date	Comments
Protocol Submission	Q2 2020		
Data Collection – pre-EM survey	Q3-Q4 2021	Q1-Q2 2022	Delay in approval of local EM versions.
Interim Report	Q3 2022		
Distribution of Updated EMs	Q4 2021-Q1 2022	Q2 2022	
Data Collection – post-EM survey	Q4 2022 – Q1 2023		
Final Study Report to EMA	Q3 2023		

Abbreviations: EM = Educational material; EMA = European Medicines Agency; Q = quarter.

7 RATIONALE AND BACKGROUND

Instanyl® (intranasal fentanyl) is an opioid analgesic indicated for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain (**Error! Reference source not found.**), (1), (**Error! Reference source not found.**), (4).

- Breakthrough pain is defined as a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain;
- Patients with maintenance opioid therapy are those who are taking daily at least: 60 mg of oral morphine, 25 micrograms of transdermal fentanyl per hour, 30 mg oxycodone, 8 mg of oral hydromorphone, or an equianalgesic dose of another opioid for a week or longer;

The European Commission granted a marketing authorization valid throughout the European Union (EU) for Instanyl® on 20 July 2009.

In 2013, the marketing authorization holder (MAH) Takeda Pharma A/S updated the Instanyl® educational materials (EMs) reinforcing that Instanyl® should not be used for the treatment of acute pain other than breakthrough pain, and should only be used in patients regularly receiving an opioid treatment and reiterating the risk of off-label use. The updated EMs were approved by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) in July 2013 and subsequently reviewed and approved by local regulatory agencies. This additional risk minimization measure (aRMM) was implemented as part of the Instanyl® Risk Management Plan (RMP). The MAH subsequently conducted a prescriber knowledge survey in 2015, Post-Authorization Safety Study (PASS) Instanyl-5001, to evaluate the effectiveness of the updated EMs to ensure that prescribers who received the updated safety information had understood it and followed it when prescribing Instanyl® (PASS Instanyl-5001; The European Union electronic Register of Post-Authorization Studies [EU PAS] register number: EUPAS9924). The PASS Instanyl-5001, results were submitted by the MAH and were evaluated by the PRAC in 2016 (EMEA/H/C/000959/II/040), failed to assess the effectiveness of the EM because the study was not well-designed (absence of baseline data). Pursuant to Article 14 (**Error! Reference source not found.**), (1), (**Error! Reference source not found.**) of Regulation (EC) No. 726/2004, the MAH submitted to EMA on 12 October 2018 an application for renewal of the marketing authorization for Instanyl® (EMEA/H/C/000959/R/0049). Since off-label use has continued to be reported, and in light of the worldwide opioid crisis, the MAH was requested by EMA to expand aRMMs for Instanyl®, including an update of existing EMs with a greater emphasis on the risks of off-label use, addiction, misuse, abuse, diversion, overdose and medication errors; an improvement of digital access to EMs; and the execution of a PASS to assess the impact of the updated EMs, considering the absence of knowledge of EM impact on prescribers since the product launch. These aRMMs were included as part of the current Instanyl® RMP (v 19.6; EMEA/H/C/000959/II/0052).

To mitigate the potential risks of off-label use, addiction, misuse, abuse, diversion, overdose and medication errors, the MAH has updated the EMs, based on the key messages approved with RMP procedure EMEA/H/C/000959/II/0052, to emphasize that Instanyl® should be prescribed for the treatment of breakthrough pain in cancer patients, explain the off-label use of Instanyl®, and

highlight the risks of off-label use, addiction, misuse, abuse, diversion, overdose, and medication errors. The updated EMs (prescriber brochure and instructional video) will be distributed in 2022 to target prescribers likely to prescribe Instanyl® in European countries where Instanyl® is marketed. The goal of the EMs is to make prescribers of Instanyl® more aware of the approved indications and the appropriate use of Instanyl® and to identify and monitor patients who may be at risk of off-label use, addiction, misuse, abuse, diversion, overdose, and medication errors in order to reduce risks. Also, the prescribers should be aware of updated EMs available for patients and pharmacists.

As part of RMP (v19.6), this PASS is designed to evaluate the changes in understanding and self-reported behavior of targeted prescribers regarding Instanyl® off-label use and the key information contained in the updated EMs, including the risks of off-label use, addiction, misuse, abuse, diversion, overdose, and medication errors.

7.1 Rationale for country selection

This study was originally planned to be undertaken in five European countries – France, Germany, the Netherlands, Poland, and Spain. These five countries were selected as they had the highest volume of Instanyl® prescriptions in the EU, accounting for 91% of sales in the EU in 2018. The Instanyl® sales data in these five countries are presented in Table 7-1.

However, there were significant delays in the approval of the local EMs in Germany and Spain. Given the need to do a pre-EM survey in the countries, the MAH started the field work in France, the Netherlands, and Poland so that there would be time to complete it before the EMs were distributed in these countries. When the fieldwork was completed in these three countries, the EMs were still not approved in Germany and Spain. Therefore, the MAH proposed to the PRAC to withdraw the two countries (Germany and Spain) from the study, which was endorsed on 01 June 2022.

Table 7-1 Instanyl® Sales Data in Selected European Countries in 2018

Country	Proportion of Instanyl® Sales in EU in 2018
France	21%
Germany	8%
The Netherlands	34%
Poland	14%
Spain	14%

Abbreviation: EU = European Union

7.2 Rationale for the selection of the specialties

The survey will be distributed among prescribers whose specialty has been targeted to receive EM as agreed with each national competent authority and based on the prescribing patterns in each country according to the IQVIA database.

The foreseen specialties include oncologists, onco-radiotherapists, anesthesiologists, pain management specialists, hematologists, palliative care prescribers, internal medicine specialists/internists, and general practitioners (GPs).

8 RESEARCH QUESTION AND OBJECTIVES

8.1 Research questions

Are the updated EMs effective in:

- Increasing the knowledge of prescribers about Instanyl® approved indications and the risks of off-label use, addiction, misuse, abuse, diversion, overdose, and medication errors?
- Increasing compliance of self-reported behavior with Instanyl® label?

8.2 Objectives

The overall objective of this study is to measure the changes in understanding and self-reported behavior of Instanyl® prescribers regarding Instanyl® off-label use and the key information contained in the updated EMs.

Specifically, the study objectives are:

1. To assess prescribers' awareness of the updated EMs;
2. To assess the changes in prescribers' knowledge and understanding of the key information contained in the updated EMs, including the risks of off-label use, misuse, abuse, diversion medication errors, addiction, overdose, and death;
3. To assess the changes in prescribers' self-reported behavior in prescribing in accordance with approved indication;
4. To assess the reasons for off-label prescription;
5. To assess whether prescribers are fully aware about the profile of patients at risk of misuse and addiction.

9 RESEARCH METHODS

9.1 Study Design

This study will consist of two cross-sectional surveys among prescribers who are current and potential prescribers of Instanyl® in France, the Netherlands, and Poland before and after the distribution of the updated EMs.[1]

The first survey (pre-EM survey) will be conducted before the distribution of the updated EMs, which will be considered the baseline period (pre-EMs distribution). Approximately six months following the distribution of the updated EMs, the second survey (post-EM survey) will be conducted (post-intervention period).

Both surveys will be self-administered via the web (i.e., Internet). Pre-EM and post-EM survey will apply the same questionnaire to assess Instanyl® prescribers' knowledge and self-reported behavior with respect to off-label use, misuse, abuse, addiction, overdose, and death. The questionnaires will differ on the questions to assess awareness of the updated EMs given that pre-EM survey will be conducted before the materials are distributed. Therefore, the questionnaire applied in post-EM survey will ask only about receipt and reading of the updated EMs. Both questionnaires will ask whether the prescribers consulted other sources of information about Instanyl®.

9.2 Setting

The surveys will be conducted through a web questionnaire among prescribers who are current and potential prescribers of Instanyl® in France, the Netherlands, and Poland before and after the distribution of the updated EMs.[1]

9.2.1 Study Population

Physicians included in IQVIA OneKey™ lists, active in clinical practice, and with valid contact details who meet the inclusion criteria, as listed in Section 9.2.2, will be invited to participate in the surveys.

Respondents to survey invitation will be screened for the exclusion criteria, as listed in Section 9.2.3, to confirm their eligibility before proceeding the remainder of the survey.

9.2.2 Inclusion Criteria

- Specialists of any of those medical specialties targeted for the EMs as agreed with each national competent authority. The foreseen specialties include the following (subject to

[1] The original protocol version also included Spain and Germany but these countries were withdrawn due to delays in the approval of local EMs (see Section 7.1).

changes after the EM distribution plan is completed and agreed with national competent authorities):

- Oncologists and oncoradiologists;
- Anaesthesiologists;
- Pain management prescribers;
- Palliative care prescribers;
- Internal medicine prescribers;
- General practitioners (GPs);
- Other specialties may be locally included such as hematology. Current and potential prescribers may vary between country; thus, some countries may have modified lists of target specialties.

- Physicians who have prescribed Instanyl® in the past 12 months (pre-EM survey) or since the updated EMs (post-EM survey) and who intend to prescribe Instanyl® in the following months after each survey.

9.2.3 Exclusion criteria

The following exclusion criteria will be applied using the screening questions at the beginning of the web questionnaire:

1. Physicians who may have a conflict of interest (i.e., prescribers employed by regulatory bodies, pharmaceutical industries);
2. Inactive or retired prescribers;
3. Physicians who did not prescribe Instanyl® in the past 12 months (pre-EM survey) or since the updated EMs are distributed (post-EM survey) and do not foresee treating a patient with Instanyl® in the following 12 months, regardless of whether they have prescribed Instanyl® before.

9.2.4 Target prescribers for pre-EM survey and post-EM survey

The sampling frame will be the list of physicians from IQVIA OneKey™ Databases (see Section 9.4) on the specialties targeted by local health authorities to receive the EM. Physicians to be contacted will be randomly sampled from the lists.

A summary of the coverage of OneKey listings per universe (reference total number of physicians per specialty as reported in a published source) in each country is provided in Table 9-1 below. Of note, not all specialties are listed in national authorities' reference databases, which compile specialties on the basis of diplomas. Hence, pain management and palliative care physicians are listed as such in OneKey™ listings and do not appear in national references.

Such physicians from OneKey™ represent over 3300 physicians in France, over 9700 in Germany, over 200 in the Netherlands and over 1000 in Spain. These specialties are not available in the database for Poland. As mentioned in Section 7.1, the study was originally planned to take place

in five countries but due to the delay in approval of the EMs in Germany and Spain, these countries were withdrawn.

Table 9-1 Instanyl® Sales Data in Selected European Countries in 2018

Country	Type	Number of physicians in universe	Source	Universe Coverage by OneKey™ lists
France	General Practice	101004	ASIP (Agence des systèmes d'information partagés de santé)	91%
	Oncologists/haematologists/radiotherapists	4659		94.8%
	Anesthesiologists	19417		68%
	Internal Medicine	4036		63%
Germany	General Practice	42205	Bundesärztekammer (Generell physiciancs association)	100%
	Oncologists/hematologists	2662		100%
	Anesthesiologists	25814		81%
	Radiotherapists	8432		87%
	Internal Medicine	35082		100%
The Netherlands	General Practice	14068	BIG-register (Ministry of Health, Welfare and Sport)	82%
	Specialists	32644		78%
Poland	General Practice	23398	Eurostat	98%
	Oncologists/hematologists	2704		100%
	Anesthesiologists	5062		90%
	Radiotherapists	-		-
	Internal Medicine	14294		100%
Spain	General Practice	37.544	MINISTERIO DE SANIDAD (MoH)	100%
	Oncologists/hematologists/radiotherapists	3633		100%
	Anesthesiologists	6.351		91%
	Internal Medicine	5.027		100%

Sampling for the two surveys will be performed independently by random sampling from the list of prescribers at each timepoint.

Physicians will be invited to participate via emails or phone calls (and via paper mail in case of difficulties achieving the target sample size). The invite will not disclose the product name or protocol details but will indicate that the participants should have experience in pain management. In order to encourage participation, potential participants will be told that the results of the survey will help optimize the communication on opioid safety messages. The proposed compensation will

also be described at this stage. If they agree to participate in the survey, they will receive a link to access the survey and the instructions for completion of the web questionnaire. At least three attempts will be made until each physician is considered to be unreachable.

9.3 Variables

9.3.1 Survey Questionnaire

A copy of the questionnaire is included as Annex 2. The survey will include a mix of multiple choice, close-ended, and open-ended questions.

The questionnaire will collect information on self-reported Instanyl® prescribing behavior, knowledge about Instanyl® approved indications and the risks of off-label use, addiction, misuse, abuse, diversion, overdose, and medication errors. Awareness of the updated EMs will also be assessed in the post-EM survey).

The following variables will be collected:

- **Screening (Questionnaire Section 1, questions S1, S2 and S3):**
    - Prescribed Instanyl® in the previous 12 months [Pre-EM survey] / since [Month Year – Post-EM survey] (Yes, No)
    - Plan to prescribe Instanyl® in the following 12 months (Yes, No)
    - Is currently employed by a pharmaceutical company (e.g., Takeda) or contracted by regulatory bodies? (e.g., EMA or other) (Yes, No)
- **Prescriber characteristics (Questionnaire Section 5, questions 17, 18, 19 and 20):**
    - Age (≤30, 31-39, 40-49, 50-59, ≥60 years)
    - Primary medical specialty (anesthesiology, general practice, hematology, internal medicine, pain management, palliative care, oncology/oncoradiology, other)
    - Years of experience in specialty
    - Type of clinical setting where most time is spent practicing (hospital/clinic-based, community-based public practice, community-based private practice, or others)
- **Experience with Instanyl®(Questionnaire Section 2, questions 1 and 2):**
    - Approximate number of patients treated with Instanyl® in the past 12 months (when in pre-EM survey) or since updated EMs distribution (when in post-EM survey);

- Physician who initiated Instanyl® and/or who continued Instanyl® prescriptions initiated by another physician(only initiated Instanyl®, only continued Instanyl® prescriptions initiated by another physician, both initiated Instanyl® and continued Instanyl® prescriptions initiated by another physician).

- **Awareness of EMs/sources of information about** Instanyl® **(Questionnaire Section 4 questions 14, 15 and 16)**
  - Pre-EM survey:
    - Sources used to obtain Instanyl® information.
  - Post-EM survey:
    - Receipt/download of the updated EMs:
      - Types of updated EMs received/downloaded (Summary of Product Characteristics [SmPC], Instanyl® prescribing checklist, guide to prescribing, other).
    - Read the updated EMs:
      - Types of updated EMs read (SmPC, Instanyl® prescribing checklist, physician's guide to prescribing, other).
  - Other sources of information used to obtain Instanyl® information
  - Awareness of the pharmacist and patient's materials (Patient package information leaflet, Dosing Card, Pharmacist's guide to dispensing, Patient's guide)
- **Knowledge about key messages (Questionnaire Section 3 questions 8, 9, 10, 11, 12 and 13):**
  - Instanyl® approved indication including age, type of pain and maintenance opioid therapy
  - Instanyl® approved posology
  - Risks and consequences of Instanyl® misuse, abuse, medication errors, overdose, addiction and death
  - Responsibility to communicate risks to patients
  - Importance of reporting off-label use, misuse, abuse, addiction and overdose

- Criteria for diagnosing opioid use disorder
- Profile of patients at risk of misuse and addiction

- **Self-reported behavior (Questionnaire Section 2 questions 3, 4, 5, 6 and 7):**
  - Prescribe Instanyl® for approved or off-label indications;
  - Reasons for an off-label prescription in case the participant reports prescription for an off-label indication;
  - Considers the risks of abuse, misuse and overdose when prescribing Instanyl®;
  - Follows recommendations from the Prescriber Checklist.

Annex 1 presents the three criteria of success (awareness, knowledge, and behavior), key topics and the corresponding questions to be included in the questionnaire, respectively.

9.4 Data Sources

The source for the recruitment of healthcare professionals (HCPs) was the OneKey™ database. This data source lists information on HCPs. The databases are constructed and updated through manual and automated means from various sources, including publicly available sources. Information collected includes HCP personal information (e.g., age, gender, contact details) and professional information (e.g., year of graduation, specialities, practicing status). These lists are widely used for the recruitment of HCPs for study participation in clinical trials, observational studies and surveys (6)(10)(11).

The data source for the study-specific data collection was the HCP questionnaire. The web questionnaire completion was estimated to take approximately 15-30 minutes to complete.

Questionnaires' translation:

The translated versions of both questionnaires, from English into local language, was done using the back-and-forth method (from English into local language and then from local language into English), to ensure an accurate translation.

9.5 Study Size

The sample size formula, based on the normal approximation to the binomial distribution, is as follows:

$$n = \frac{P \cdot (1-P) \cdot \left(Z_{1-\alpha/2}\right)^2}{e^2},$$

Where P is the expected proportion, e is one half the desired width of the confidence interval (CI), and Z1–α/2 is the standard normal Z value corresponding to a cumulative probability of 1 – α/2 (e.g., if α = 0.05 then Z = 1.96).

The following Table 9-2 provides the margin of error for 95% CI based on various sample sizes and proportions of interest.

Table 9-2: Margin of Error for 95% CI Based on Various Sample Sizes and Proportions of Interest

Margin of error for 95%CI (absolute precision)					
Proportion	**6%**	**5%**	**4%**	**3%**	**2%**
10%	97	139	216	384	864
30%	225	323	504	896	2,017
50%	267	384	600	1,067	2,401
70%	225	323	504	896	2,017
90%	97	139	216	384	864

Abbreviation: CI = Confidence interval.

As the answers to the questions are not known in advance, we assume a proportion of 50% correct answers in each of the surveys (worst case scenario). Such a hypothesis yields the most conservative (i.e., the largest) sample size.

The original protocol targeted a minimum level of precision of 5%, which resulted in a sample size of at least 384 complete analyzable questionnaires for a proportion of 50%, at each survey (pre-EM and post-EM surveys). It was estimated that a total of 768 completed analyzable questionnaires would be cumulatively targeted in this study.

The original target of 384 analyzable questionnaires was to be distributed per country as presented in Table 9-3. However, due to delays in approval of the EMs in Germany and Spain, these countries were withdrawn. Therefore, a final sample size of 259 prescribers, corresponding to the sum of the remaining target per country was targeted for each survey. This sample size is lower than originally planned, which results in a lower precision around the estimate (from 5% to 6%).

The number of HCPs that need to be invited in order to reach the target number of completed and analyzable questionnaires is not known in advance. In the Instanyl-5001 study conducted in France and the Netherlands, it was necessary to invite 4,140 HCPs in France to obtain 210 complete questionnaires (5% of the HCPs invited) and 2,425 HCPs in the Netherlands to obtain 100 completed questionnaires (4% of the HCP invited). Assuming that the most conservative proportion of 4% completed questionnaires among the invited HCPs, 9,600 HCPs would have been needed to be invited in each of the surveys (pre- and post-EM surveys, respectively) in order to obtain the target 384 completed questionnaires per survey. Considering the new target of 259

completed questionnaires per survey, 6,475 HCPs (259 = 4% of HCPs invited) may need to be invited in each of the surveys (pre- and post-EM surveys, respectively).

9.5.1 Sampling Plan

For each selected country, the sample survey will include physicians identified and recruited from OneKey™ lists. A screening question in pre-EM survey will check whether the physician has prescribed Instanyl® within the previous 6 to 12 months and will continue to prescribe in the following 6 to 12 months. A screening question in post-EM survey will check whether the physician has prescribed Instanyl® since the distribution of the EMs and will continue to prescribe in the following 6 to 12 months.

Ideally, the sample of physicians should be proportionally split between the selected countries based on the number of physicians in each country and then further split among physicians based on the real proportion of each specialty and the volume of Instanyl® prescriptions they issue per country.

However, due to the expected variance of the number of physicians in the countries such a distribution is not feasible as it might yield a too small number of questionnaires in smaller countries. A pragmatic split was proposed to allocate a sufficient size to the less represented strata of the sample. The results will be weighted back according to the real proportion of physicians from OneKey™ lists to allow the representativeness of the overall sample.

As per sample size defined in the original protocol, the number of selected countries, the sales volume, and size of the country, the following country targets were considered as detailed in the column "Target number of physicians per country per the original sample size" in Table 9-3. With the withdrawal of Germany and Spain, a final target of 259 physicians is considered.

Table 9-3: Sample Size of the Physicians' Survey

Country	Target number of physicians per country per the original sample size	Total/actual number of physicians per country per the new sample size
France	94	94
Germany	50	0 (withdrawn from the study)
The Netherlands	100	100
Poland	65	65
Spain	75	0 (withdrawn from the study)
Total	**384**	**259**

As mentioned in Section 7.1, the study was originally planned to take place in five countries; but due to the delay in approval of the EMs in Germany and Spain, these countries were withdrawn. So, the initial total target of 384 physicians has been reduced to 259 physicians.

9.6 Data management

The surveys will be conducted according to the Standard Operating Procedures (SOPs) of IQVIA. Collected data will be entered and stored in a database specific to each survey wave (pre-EM and post-EM survey, respectively) and common to all countries.

Data will be checked in terms of consistency before data analysis:

- Removal of duplicates (if required);
- Data labeling and data formatting;
- Range and consistency checks for each variable to identify potential inadmissible values;
- Cross-check consistency of data for related variables (if feasible);

The study database will be locked once validated.

9.6.1 Data collection

The data collection period will last 3 to 6 months and will be conducted in parallel in the study countries.

The survey will be conducted by IQVIA. IQVIA will create a web-based survey in an online survey software to collect prescriber's answers. The lists of prescribers will be loaded into separate databases for the management of the survey.

As described previously (Section 9.2.4 Target prescribers for pre-EM and post-EM survey), prescribers will be randomly contacted.

If the questionnaire is not completed, the prescribers will be sent at least two reminders (by email, phone, or paper mail).

For each prescriber of the sample file, the number of contacts, and the date and time when he/she completed the web questionnaire will be recorded.

9.6.2 Approaches for increasing the response rate

Physicians are increasingly contacted to participate in web surveys. Their overall response rate of participation remains low according to international studies (12), (13), (14). Holbrook et al. showed that the response rate to surveys continues to decline over time, but a lower rate does not appear to reduce the representativeness of a demographic survey (14). VanGeest et al. conducted a systematic review of 66 published reports on efforts to perform for improving response rates (**Error! Reference source not found.**). Two general strategies were explored: incentives-based approaches and survey design-based approaches. Financial incentives, even little ones, were effective in improving prescriber response rates while non-monetary incentives were much less effective. These measures include the use of a short questionnaire, and questionnaires personalized, and approved by professional associations.

In order to ensure an adequate response rate, four actions will be applied to this survey:

1. A compensation fee will be proposed to prescribers for their participation in the survey;
2. All prescribers will be sent an email or contacted by experienced operators of IQVIA with extensive experience in conducting health-related surveys;
3. To maximize participation, non-responders to the initial invite will be sent at least 2 follow-up emails, where email is available, or phone calls, or in case of difficulties achieving the target sample, will be contacted via paper mail;
4. It will be explained that this study will impact risk reduction strategies for the use of opioids and their help is important for public service.

9.7 Data Analysis

The statistical analyses will be described and further detailed in a Statistical Analysis Plan (SAP). The SAP will include table shells to be populated for the clinical study report.

9.7.1 General Statistical Consideration

The statistical analysis will be conducted using the SAS® software v 9.4 on Windows™ (SAS Institute, North Carolina, USA).

All the analyses will be descriptive. Continuous variables will be described by the number of valid cases, mean, standard deviation (SD), and median, first quartile-third quartile (Q1-Q3), and minimum and maximum. A 2-sided 95% CI of mean will be presented for success criteria, when relevant. Categorical variables will be described as the total number and relative percentage per category. A 2-sided 95% CI of percentages will be presented for success criteria.

In the case of questions with multiple answers, the frequency of each option/statement ticked by the physicians will be reported in the statistical results. Free text answers (and open-ended questions) will be grouped by theme when relevant and listed according to the frequency.

The proportions of correct and appropriate answers to selected questions asked in the questionnaire will be expressed among prescribers who provided answers to those questions (the missing data will not be counted as a denominator in proportions).

An interim report will present the results from the pre-EM survey. The final report will present results of both the pre-EM and post-EM surveys.

9.7.2 Planned Analyses

Results will be presented overall, per country and specialty, at the specialty level (all countries), and at the country level (all specialties), for each survey separately. In case of lower representation of some specialties, the results for GPs and internal medicine specialists will be combined as "generalists" and the results of the other specialties will be combined as "specialists".

As a first step, no projection factor (weighting) will be applied. Consequently, "Overall - unweighted results" will show only the results observed on the overall sample and will not be generalizable of the physicians in all countries, as each stratum is not proportional to the true size

of the country and prescriber lists. As a second step, the results will be weighted according to the real proportion of HCPs in each country and specialty in order to accurately reflect the population that the survey seeks to measure. The sample adjustment will be performed following the same method adopted in von Bredow et al (**Error! Reference source not found.**).

9.7.2.1 Analysis of non-participation or refusal to participate rate

The following will be distinguished and analyzed for targeted physicians:

- Physicians who refused to participate (R): physicians who explicitly mentioned their refusal to participate;
- Unreachable physicians (U): invited but did not answer, unreachable for other reasons, wrong workplace, retired, or temporarily unavailable;
- Physicians with partial questionnaires (P): physicians who clicked the link provided in the invitation email, who began the questionnaire but never submitted it;
- Physicians with a completed questionnaire (C): physicians who completed the entire questionnaire (complete and analyzable questionnaire);
- Failed screening (F): physicians who did not meet inclusion criteria and/or who met exclusion criteria;

Based on the above, the following metrics will be computed:

- Targeted physicians: physicians to whom an email or postal mail was sent or called = C+P+R+U+F;
- Contacted physicians: physicians who were reached by phone or who received a web link to the online survey via email. For survey invitations issued via postal mail, the assumption will be that, if mail is not returned, the participant will be considered "contacted" = C+P+R+F:
- Physicians who agreed to participate: physicians willing to participate in the survey (e.g., by phone or by clicking on the link provided in the invitation email) = C+P+F;

Then, the physicians' participation in the survey will be examined in the following ways:

Response rate = C/(C + P + F + R + U)

Refusal rate = R/(C + P + F + R + U)

Contact rate = (C + P + F + R)/(C + P + F + R + U)

Cooperation rate = C/(C + P + F + R)

These data will be presented by country and specialty.

9.7.2.2 Handling of missing data

The web-based questionnaire will be programmed to prevent participants from skipping any questions. Consequently, no missing values are expected, and thus, the need for replacement or imputation of missing data is not anticipated (**Error! Reference source not found.**).

9.7.2.3 Questionnaire analysis

The general statistical considerations described above (Section 9.7.1 General statistical considerations) will be applied as stated.

Pre-EM survey assesses prescribers' knowledge and understanding of the key safety messages and self-reported behavior in prescribing according to the recommendations before the distribution of the updated EMs. Post-EM survey assesses awareness of the updated EMs, the prescribers' knowledge and understanding of the same key safety messages and self-reported behavior in prescribing according to the recommendations after the distribution of the updated EMs.

The following analyses will be performed:

- Description of the analysis population (for both pre-EM [interim analysis] and post-EM surveys [final analysis]):
  - The prescriber characteristics will be described based on Section 5 of the questionnaire (questions 17 to 20);
  - The experience of prescribers with Instanyl® will be described based on Section 2 of the questionnaire (questions 1 and 2);
  - The sources of information about Instanyl® will be described based on question 15 of Section 4 of the questionnaire;
- Description of Awareness, Knowledge, and Self-reported Behavior Questions
  - Pre-EM survey will assess:
    - Prescriber knowledge about the key EM messages (Section 3 of the questionnaire, questions 8, 9, 10, 11, 12, and 13);
    - Self-reported behavior in prescribing according to the recommendations before the distribution of the updated EMs (Section 2 of the questionnaire, questions 3, 4, 5, 6 and 7);
    - Reasons for off-label prescription (Section 2 of the questionnaire, questions 3A, 5B, 5C_1, and 5D_1) and underlying causes of pain (Section 2 of the questionnaire, questions 5C_2, and 5D_2);
    - Awareness about the profile of patients at risk of misuse and addiction (Section 3 of the questionnaire, question 13);
  - Post-EM survey will assess:

- Awareness of the updated EMs (Section 4 of the questionnaire, questions 14, 14a, 14b, and 16);
- Prescriber knowledge about the same key EM messages (Section 3 of the questionnaire, questions 8, 9, 10, 11, 12 and 13);
- Self-reported behavior in prescribing according to the recommendations after the distribution of the updated EMs (Section 2 of the questionnaire, questions 3, 4, 5, 6, and 7);
- Reasons for off-label prescription (Section 2 of the questionnaire, questions 3A, 5B, 5C_1, and 5D_1) and underlying causes of pain (questions 5C_2 and 5D_2);
- Awareness about the profile of patients at risk of misuse and addiction (Section 3 of the questionnaire, question 13).

The analysis of the questions will describe the following:

- The answers to modalities of each (sub-) question will be displayed following general statistical considerations described above (Section 9.7.1);
- In addition, for the answers to Awareness, Knowledge, and Self-reported Behavior:
  - The number and percentage of participants who answered each question correctly will be displayed;
  - The number and percentage of participants who answered all key sub-questions correctly will also be described, if applicable (e.g., those addressing each key message statement);

Both unweighted (overall, by country, and by specialty[ies]) and weighted (overall) results will be presented for all the analyses described above.

9.7.2.3.1 Assessment of success

The table presented in Section 13.1 indicates the topics included under each of the success criteria (awareness, knowledge, and behavior), their corresponding questions, the scoring system for each question, and the definition of success for each criterion.

Overall, each criterion will be assessed at an aggregate level: for all prescribers considered as a whole or a subgroup of prescribers if applicable. This is based on the proportion of prescribers successful for the criteria meeting a pre-defined threshold (e.g., success for awareness of the updated EMs will be reached if ≥80% of prescribers are successful in this criteria).

In order to determine how many prescribers were successful for a criterion, it is necessary to assess the success at the individual prescriber level, i.e., whether each prescriber was successful for the criterion. This is based on achieving a pre-defined score which results from the number of points received from answering the criterion's questions correctly. The number of points required for the criterion to be met and the number of points entitled by each question is indicated in Section 13.1.

For each of the following success criteria, both unweighted (overall, by country, and by specialty[ies]) and weighted (overall) results will be presented along with 95% CIs.

- Awareness of the updated EMs: will be applicable to the post-EM survey (final analysis) only. Success will be reached if at least 80% of the prescribers are successful for this criterion
- Knowledge will be assessed at the aggregate level at both the interim (pre-EM survey) and final (post-EM survey) analysis. At each, success will be reached if at least 80% of the prescribers are successful for this criterion. In addition, for the final analysis, the aggregated success for the knowledge criteria will be assessed as a positive absolute change (increase) in the percentage of successful prescribers from pre-EM to post-EM survey
- Self-reported behavior will be assessed at the aggregate level at both the interim (pre-EM survey) and final (post-EM survey) analysis. At each, success will be reached if at least 80% of the prescribers are successful for this criterion. In addition, for the final analysis, the aggregated success for the self-reported behavior criteria will be assessed as a positive absolute change (increase) in the percentage of successful prescribers from pre-EM to post-EM survey
- Awareness of the profile of patients at risk of misuse and addiction will be assessed based on the proportion of prescribers answering question 13 correctly. Success will be reached if at least 80% of the prescribers are successful for this question
- In addition, the reasons for off-label prescription (pediatric patients and/or unapproved pain indication) will be described

9.7.2.3.2 Complementary analysis

In addition to the analyses described above, the following analyses summarizing the prescribers' individual results will be presented as a complementary perspective of the success of prescribers:

- A quantitative analysis of the percentage of correct answers per prescriber expressed in terms of percentage of points scored on questions related to each criterion will be performed. Both unweighted and weighted results will be presented for this analysis
- An analysis based on the categorization of five knowledge levels will also be implemented for all countries and per country, with specialties combined. The number and percentage of physicians in each of the following categories will be computed and displayed in a summary table:
    - Poor level (<20% of the number of total points for the criterion)
    - Very low level (20%-40% of the number of total points for the criterion)
    - Low level (40%-60% of the number of total points for the criterion)
    - Moderate level (60%-80% of the number of total points for the criterion)
    - High level (≥80% of the number of total points for the criterion)

9.7.2.3.3 Sensitivity analysis

As described in Section 9.1, prescribers will be randomly sampled from IQVIA OneKey™ lists for the two surveys. It is possible that some prescribers might be randomly selected for both surveys. In order to quantify the potential impact on knowledge and prescribing behavior in the post-EM survey of prior participation in the pre-EM survey, a sensitivity analysis will be conducted by excluding the participants who participated in both surveys. The details are described in the SAP.

Additionally, a sensitivity analysis will be performed on the subpopulation of participants who were successful in the awareness criteria. This analysis involves comparison of the number and percentage of successful prescribers in the knowledge criteria and in the self-behavior criteria between physicians successful in the awareness criteria and those unsuccessful in the awareness criteria; this comparison was done in order to see if those successful in the awareness criteria perform better in the knowledge and self-behavior criteria.

9.7.2.3.4 Comparison between successful and unsuccessful prescribers (applicable to the final analysis only):

The profile of successful physicians and unsuccessful physicians to the three main criteria for this study (awareness of the updated EMs, knowledge, and self-reported behavior) will be compared using all available and relevant prescriber characteristics collected in the survey (i.e., country, age in classes, primary specialty, years of experience in specialization, practice setting prescribing volume, and whether prescriber initiated and/or continued Instanyl® prescriptions).

9.8 Quality control

9.8.1 Approaches for validating the questionnaire

The questionnaire will be translated from English into the local language using the back-and-forth method to ensure an accurate translation of the local versions of the questionnaire and will be validated by the MAH. Translation and back translation will be performed by IQVIA Primary Intelligence personal or an approved vendor.

9.8.2 Approaches for validating the results

The quality control for validating the results will be conducted at five levels:

1. At IQVIA Primary Intelligence management level, every effort will be undertaken to collect complete and valid data:
    - Verification of the reliability and security of the web questionnaire interface by a qualified webmaster for each country;
    - Monitoring of the quality and datasets definition by a qualified data manager. In the background of the web questionnaire, real-time checks of the answers provided by the respondents will be developed. Non-admissible answers (i.e., incorrect or unusual values, outlying values) will be detected and queries sent to the prescriber.

2. At the study database level (after merging datasets of each country), final data quality checks will be applied (beyond data management process):
    - Distribution of each variable in order to count the number of missing values and estimate the associated relative percentage;
    - Identification and count of non-analyzable questionnaires:
        - Estimation of the percentage of prescribers who do not know Instanyl®;
        - Estimation of the percentage of prescribers who do not foresee treating a patient with Instanyl® in the next 12 months;
        - Estimation of the percentage of prescribers without complete analyzable questionnaire.

Any changes in the database will be tracked and documented. The country-datasets will be stored in a dedicated database. Once the data are validated and quality checked, the database will be locked.

3. At the statistical analysis level: all data management and statistical analysis programs developed and used in the analysis will be documented. All versions generated will be dated, kept with accompanying documentation and archived. The original database will be stored. A derived database will be created for the new versions of the data in order to include recoding and computing of new variables, especially stratification of continuous variables, combination of modalities for categorical variables, calculation of composite indicators, etc.
4. At the results level, a data review will be done to ensure data integrity. A statistical analysis report including all the results will be provided for review and discussion before the interim and final reports. The final statistical report will consider the reviewers' comments;
5. At the study level, all aspects of the study will be conducted according to the SOPs of IQVIA Real-World Evidence Solutions and Primary Intelligence divisions. The study documents have been approved by people competent in medical and safety areas of IQVIA. According to the SOPs, an independent review of the survey results and report will be conducted, by a person who was not in charge of their preparation.

9.8.3 Safeguards, Security, and Traceability of Contacts

The operators of the call center specialized in health surveys, will be assigned to the project and trained on the survey methodology prior to fieldwork. The emails contacts and phone calls will be traced using the management software. All survey aspects from protocol development to the reporting of the results will be conducted according to the SOPs of IQVIA Real-World Evidence Solutions and Primary Intelligence divisions. These SOPs can be consulted on site (**Error! Reference source not found.**).

9.9 Limitations of the Research Methods

9.9.1 Possible Selection Bias due to Voluntary Participation

The potential for selection bias of prescribers participating in a survey is an inherent limitation to any study based on voluntary participation. In order to quantify any selection bias, the distribution of specialty of HCP in each country will be compared between participants and non-participants.

9.9.2 Limits Inherent to Web Surveys

The questionnaire includes general questions followed by specific ones. As the prescribers may understand the right answer in subsequent questions, it would not be possible to go back in the questionnaire and edit answers in former questions.

In such surveys, the generalization and external validity of the results is restricted to prescribers who have an active email address and willing (and able) to answer a questionnaire online. These prescribers may not be fully representative of the whole targeted population (**Error! Reference source not found.**).

Under the non-response bias category, targeted prescribers may also have activated filters in their mailbox in order to block spams and unsolicited emails. They may not even see the invitation to participate in the survey if a very strict degree of message filtering is set. Having multiple email addresses could also be a critical situation. If the one used is not the primary address or if the prescribers do not check their email box frequently, they will not receive the invitation during the recruitment period. This is one of the reasons why prescribers may be contacted by phone.

Moreover, web surveys may promote social desirability bias which refers to the tendency of prescribers to give socially desirable/expected responses instead of choosing those reflecting their current knowledge or self-reported behavior, (e.g., prescribers can copy-paste information gathered online instead of giving their own opinions) (**Error! Reference source not found.**).

Social desirability can affect the validity of survey research findings, but the use of pre-populated items in the questionnaire could/tends to reduce this bias (**Error! Reference source not found.**).

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

9.9.3 Generalization of the Survey Results to the Overall Target Population

This study will invite all potential prescribers of Instanyl® targeted for the updated EMs, in order to obtain a representative sample of current and potential prescribers across European countries. However, due to potential selection bias because of voluntary participation, the survey results may not be generalized to the target population.

10 PROTECTION OF HUMAN SUBJECTS

The survey is non-interventional and totally anonymous to the study sponsor. Data collected will remain confidential, and only aggregated data will be analyzed and communicated in a synthesis.

10.1 Regulatory and Ethics Considerations

10.1.1 Ethical Principles, Laws and Regulations

The survey will follow the regulatory and ethical requirements of each country. IQVIA will follow the European Pharmaceutical Marketing Research Association (EphMRA) code of conduct guidelines updated in February 2014 (17).

10.1.2 Physician Information

Physicians participating in the survey will be informed about the objectives of the investigation, the nature of the transmitted data, the intended use of data, recipients of these data, and their right of access and rectification to personal data, as well as their right of objection to using their data or to IQVIA keeping their data.

10.1.3 Physician Compensations

Physicians will be offered compensation in return to the time spent participating in this survey (which they may refuse). The time to complete the survey is estimated between 15 to 30 minutes.

The amount of this compensation will be determined according to the EphMRA recommendations and the Association of Opinion and Behavior in health field research companies (ASOCS) charter, and which states:

"When it is necessary to compensate a prescriber in return to the time spent during an interview or a group meeting, the compensation must not exceed the fees commonly taken by the prescriber for his/her advice or consultation and must be proportional to the time provided. The compensations should be clearly stated before the prescriber participated in the survey. They must be declared to the tax authorities in accordance with applicable laws".

10.2 Confidentiality

10.2.1 Patient Confidentiality

Not applicable: no patient's data will be collected.

10.2.2 Data Confidentiality / Data Security

Participating prescribers will access the website using an https secure link. This link is unique to each specific prescriber. The answers provided will be collected anonymously. Only aggregated data and presented as a synthesis will be transmitted to the MAH.

Data will be recorded in a central database and tracked using an audit trail. The system will enable retrieving all introduced data at any time and will include security elements to prevent others than authorized staff from accessing data. Each user will have a specific profile which will limit his/her use of the database. A security copy of the database and the application files will be made outside the server housing the web-based study. Security copies will be periodically made and stored outside this server. A copy of the data stored in the database will be transferred to MAH at the end of the study.

Description of all elements of security and traceability will be available upon request.

10.3 Record Retention

The study documentation will be stored in the Trial Master File.

The web questionnaires data will be stored on the survey server.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product 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, a new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.
Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an AE;
- A laboratory test result that requires the subject/patient to receive specific corrective therapy;
- A laboratory abnormality that leads to discontinuation of therapy;
- A laboratory abnormality that the health care provider considers to be clinically significant.

11.1.2 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded;
- In the view of the Health care provider, places the subject/patient at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused the death;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect;
- An SAE may also be any other medically important event that, in the opinion of the Healthcare provider, may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.).

11.1.3 Adverse Drug Reactions

An adverse drug reaction (ADR) is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

11.1.4 Product Quality Issues

A Product Quality Issue (PQI) refers to defects related to the safety, identity, strength, quality, or purity of the product or with the physical characteristics, packaging, labeling, or design of the product.

11.1.5 Special Situation Reports

A Special Situation Report (SSR) includes any of the following events:

- Pregnancy: Any case in which a pregnancy patient is exposed to a Takeda Product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Takeda Product. Exposure is considered either through maternal exposure or via semen following paternal exposure;
- Breastfeeding: Infant exposure from breast milk;
- Overdose: Any accidental or intentional overdose;
- Drug abuse, misuse or medication errors: Medicinal product abuse, misuse or medication errors (potential or actual);
- Suspected transmission of an infectious agent: Suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product;
- Lack of efficacy of Takeda Product;
- Accidental exposure;
- Use outside the terms of the marketing authorization, also known as "off-label";
- Use of the falsified medicinal product;
- Unintended benefit.

11.1.6 Reporting of Adverse Drug Reactions

This study is a survey to evaluate the effectiveness of EMs implemented as aRMMs. This survey does not involve data collection on clinical endpoints on individual patients. The survey does not include questions that could potentially identify an ADR, nor does it provide a free text field where study participants are requested to specify the information that may constitute an ADR.

However, it is possible that a study participant may provide information that could constitute an ADR while in conversation about the survey during a follow-up call (e.g., seeking information about the purpose of the study). If during the conduct of the study the investigator(s) or a member of the research team is spontaneously informed by an HCP or patient of an SAE), AE, ADR, SSR, or PQI where the event/issue pertains to a Takeda Product (or unbranded generic), such information should be notified to the relevant Takeda Pharmacovigilance department within one working day for fatal or life-threatening SAEs, within 4 calendar days for other SAEs, and within seven calendar days for all other events. As such reports are spontaneously notified, the causality of any AEs should be assumed unless there is evidence to the contrary.

The ADRs that are spontaneously reported will be processed as unsolicited reports according to the Good Pharmacovigilance Practices (GVP) module VI.

This survey specifically addresses off-label use, drug abuse, misuse or medication errors and overdose as it is part of the MAH strategy to understand if the aRMM that have been implemented to minimize those safety concerns were effective, or if they need to be modified or supplemented by aRMM. Therefore, the results of this survey will actively contribute to the risk management strategy for Instanyl®.

As mentioned before, no individual patient level data is expected to be reported during this survey, thus the results will likely not meet the minimum criteria for reporting. However, at the end of the questionnaire, prescribers will be encouraged to report cases of drug abuse, misuse or medication errors, overdose and off-label cases that resulted in patient harm with the occurrence of a suspected ADR (as per GVP Module VI C.2.2.12 and B.6.3) through the use of the ADR report form.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The MAH and/or designee will prepare the interim and final study reports as required by the competent authority. In addition, these data may be summarized for presentation at professional conferences and sessions, as appropriate.

The study protocol and synopsis of findings will be entered on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) register of studies (encepp.eu/encepp/studiesDatabase.jsp), and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines will be followed (18).

None of the parties involved in the management/conduct/analysis of this study may publish any study-related data without the written permission of Takeda Pharmaceutical Company Limited.

13 REFERENCES

1. Instanyl | European Medicines Agency [Internet]. [cited 2022 Jun 27]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/instanyl
2. Instanyl- EPAR- Product Information [Internet]. Available from: https://www.ema.europa.eu/en/documents/product-information/instanyl-epar-product-information_en.pdf
3. Haute Autorité de Santé - INSTANYL [Internet]. [cited 2022 Jun 27]. Available from: http://www.has-sante.fr/jcms/c_918264/en/instanyl
4. Portenoy RK, Raffaeli W, Torres LM, Sitte T, Deka AC, Herrera IG, et al. Long-term safety, tolerability, and consistency of effect of fentanyl pectin nasal spray for breakthrough cancer pain in opioid-tolerant patients. J Opioid Manag. 2010 Oct;6(5):319–28.
5. Jouaville LS, Ehrhardt C, Kürzinger ML, de Voogd H, Toussi M. Evaluation of the Effectiveness of Risk Minimisation Measures Targeting Physicians on Prescribing Practices of Thiocolchicoside Containing Medicinal Products for Systemic Use. Epidemiology (Sunnyvale) [Internet]. 9(1). Available from: https://www.omicsonline.org/open-access/evaluation-of-the-effectiveness-of-risk-minimisation-measures-targeting-physicians-on-prescribing-practices-of-thiocolch.pdf
6. Halcox JP, Banegas JR, Roy C, Dallongeville J, De Backer G, Guallar E, et al. Prevalence and treatment of atherogenic dyslipidemia in the primary prevention of cardiovascular disease in Europe: EURIKA, a cross-sectional observational study. BMC Cardiovasc Disord. 2017 Jun 17;17(1):160.
7. Le Saux O, Taylor A, Chia V, Pillas D, Kaur M, Freyer G. Cross-sectional study on comorbidities and adverse events in patients with advanced and recurrent ovarian cancer in France. Clin Epidemiol. 2015;7:431-40.
8. Curtin R, Presser S, Singer E. Changes in Telephone Survey Nonresponse over the Past Quarter Century. Public Opinion Quarterly. 2005 Jan 1;69(1):87–98.
9. Kellerman SE, Herold J. Physician response to surveys: A review of the literature. Am J Prev Med. 2001 Jan;20(1):61–7.
10. Holbrook AL, Krosnick JA, Pfent A. The Causes and Consequences of Response Rates in Surveys by the News Media and Government Contractor Survey Research Firms. In: Advances in Telephone Survey Methodology [Internet]. John Wiley & Sons, Ltd; 2007 [cited 2022 Jun 27]. p. 499–528. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/9780470173404.ch23.
11. VanGeest JB, Johnson TP, Welch VL. Methodologies for improving response rates in surveys of physicians: a systematic review. Eval Health Prof. 2007 Dec;30(4):303–21.
12. von Bredow D, Toussi M, Samad A, Kaplan S, Domahidy M, de Voogd H, et al. Evaluation of the effectiveness of risk minimization measures for trimetazidine: A cross sectional joint

PASS survey among physicians in selected European countries. Pharmacoepidemiol Drug Saf. 2018;27(12):1385-92

13. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.
14. Privacy Policy - IQVIA [Internet]. [cited 2022 Jun 27]. Available from: https://www.iqvia.com/about-us/privacy/privacy-policy
15. Wyatt JC. When to Use Web-based Surveys. J Am Med Inform Assoc. 2000;7(4):426–9.
16. Nederhof AJ. Methods of coping with social desirability bias: A review. European Journal of Social Psychology. 1985;15(3):263–80.
17. EphMRA. Code of conduct 2013 [Internet]. 2013. Available from: http://www.ephmra.org/user_uploads/code%20of%20conduct%20oct%202013.pdf
18. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008 Apr;61(4):344–9.

ANNEXES

13.1 Annex 1 – Success Criteria for Survey Assessing Effectiveness of Risk Minimization Materials

Criteria	Topic	Questions	Is the question included in the assessment of success? (Yes/No)	Definition of correctly/targeted answered question	Assessment of success
Awareness (applicable to post-EM survey only)	Accessed updated educational materials (overall)	QX(Question 14)14: Have you received or downloaded any educational materials on Instanyl® (POST-EM SURVEY: since [Month Year]?)	YES	The statement "Yes" is selected. This question will be assigned 0 points if the statements is not selected and 1 point if it is selected.	**At the individual level,** , a prescriber will be considered successful if she/he gets 4 points out of 5 ("successful prescriber in the awareness criteria"). **At an aggregated level**, success for awareness of the updated EMs will be reached if ≥80% of prescribers are successful.
	Accessed educational materials (specific)	Q14a: Please indicate which of the following educational materials you have received or downloaded.	YES	The statements "Physician's guide to prescribing" and "The Instanyl® prescribing checklist" are selected. This question will be assigned 0 points if none of those statements are selected; 1 or 2 point(s) will be assigned if 1 or 2 statements are selected.	
	Read the educational materials	Q14b: Please indicate which of the following educational materials you have read after receiving/downloading.	YES	At least the statement "Physician's guide to prescribing" or the statement "The Instanyl® prescribing checklist" is selected. This question will be assigned 0 points if none of those statements are selected and 1 point if at least one of the two statements is selected.	
	Awareness about the patient's materials	Q16: post-EM survey: Have you become aware of the following resources available for pharmacists and/or patients treated with Instanyl®?	YES	At least the statement "Dosing card" is selected. This question will be assigned 0 points if the statement is not selected and 1 point if it is selected.	

Awareness (applicable to post-EM survey only)					**At the individual level**, a prescriber will be considered successful if she/he gets 4 points out of 5 ("successful prescriber in the awareness criteria"). **At an aggregated level**, success for awareness of the updated EMs will be reached if ≥80% of prescribers are successful.
	Other sources of information	Q15: What (other ["other" should be used in Post-EM survey only]) sources of information about Instanyl® have you used?	NO, complementary question about other sources of information	Not applicable.	
Knowledge	Instanyl® approved indication	Q8: According to your knowledge, which of the following statements about Instanyl® indication are true, and which are false?	YES	The correct answer to each statement is indicated with an "X" in Annex 2. This question will be assigned 0 to 7 points depending on how many statements are correctly answered.	***For each survey evaluated separately*** *(for pre-EM and post-EM surveys):* **At the individual level**, a prescriber will be considered successful if she/he gets 23 points out of 28 ("successful prescriber in the knowledge criteria"). **At an aggregated level:** success will be reached if ≥80% of prescribers are successful. ***Change between the pre-EM and post-EM surveys*** *(final analysis only):* Assessed by the increase in the percentage of successful prescribers from pre-EM survey to post-EM survey.
	Instanyl® approved posology	Q9: According to your knowledge, what are the recommendations for Instanyl® use?	YES	The correct answer to each statement is indicated in the corresponding question box in Annex 2. This question will be assigned 0 to 3 points depending on how many statements are correctly answered.	

Knowledge					
	Risks and consequences of Instanyl® misuse, abuse, medication errors, overdose, addiction, and death	Q10: According to your knowledge, which of the following statements about Instanyl® safety profile are true, and which are false? Q11: According to your knowledge, which of the following statements about management of patients using Instanyl® are true, and which are false? Sub-questions: *Q11-2: Cancer patients already taking opioids and requiring breakthrough medication should not be assessed for opioid use disorder* and *Q11-4: Request to increase dose or early refill of prescriptions may be a sign of addiction to Instanyl®*	YES	The correct answer to each statement is indicated with an "X" in Annex 2. This question will be assigned 0 to 7 points depending on how many statements are correctly answered.	***For each survey evaluated separately*** *(for pre-EM and for post-EM surveys):* **At the individual level**, a prescriber will be considered successful if she/he gets 23 points out of 28 ("successful prescriber in the knowledge criteria"). **At an aggregated level:** success will be reached if ≥80% of prescribers are successful. ***Change between the pre-EM survey and the post-EM survey*** *(final analysis only):* Assessed by the increase in the percentage of successful prescribers from pre-EM survey to post-EM survey.
	Responsibility to communicate risks to patients	Q11: According to your knowledge, which of the following statements about management of patients using Instanyl® are true, and which are false? Sub-question: *Q11-1: It is the prescriber's responsibility to ensure that patients and caregivers are aware of the risks of misuse, addiction, and overdose to Instanyl®.*	YES	The correct answer to the statement is indicated with an "X" in Annex 2. This question will be assigned 0 or 1 point depending on whether it is answered incorrectly or correctly.	
	Importance of reporting off-label use, misuse, abuse, addiction and overdose	Q11: According to your knowledge, which of the following statements about management of patients using Instanyl® are true, and which are false? Sub-question *Q11-3: Instances of Instanyl® drug abuse, misuse, addiction, and overdose do not need to*	YES	The correct answer to the statement is indicated with an "X" in Annex 2. This question will be assigned 0 or 1 point depending on whether it is answered incorrectly or correctly.	

		be reported as they are well known risks of any opioid use.			
	Criteria for diagnosing opioid use disorder	Q12: According to your knowledge, which of the following statements about diagnostic criteria for opioid use disorder are true, and which are false?	YES	The correct answer to each statement is indicated with an "X" in Annex 2. This question will be assigned 0 to 6 points depending on how many statements are correctly answered.	
Knowledge	Prescribers are fully aware of the profile of patients at risk of misuse and addiction	Q13: According to your knowledge, which of the following patient characteristics could indicate risk of Instanyl® misuse or addiction? Please select all that apply.	YES (this question will also be used to address one of the study objectives "To assess whether prescribers are fully aware of the profile of patients at risk of misuse and addiction")	The statements "Patients with personal or family history of substance use disorder", "Patients taking psychiatric medication" and "Tobacco users" (correct statements) are selected and the statements "Patients using single-dose nasal spray", "All the above", and "None of the above" are not selected. This question will be assigned 0 points if "Patients using single-dose nasal spray" is selected without any of the three correct statements being selected, or if "all the above" (single punch) or "none of the above" (single punch) are selected. The question will be assigned 1, 2, or 3 points if 1, 2, or 3 of the correct statements are selected, irrespective of whether "Patients using single-dose nasal spray" is also selected.	***For each survey evaluated separately*** *(for pre-EM survey and for post-EM survey):* **At the individual level**, a prescriber will be considered successful if she/he gets 23 points out of 28 ("successful prescriber in the knowledge criteria"). **At an aggregated level:** success will be reached if ≥80% of prescribers are successful. ***Change between the pre-EM survey and the post-EM survey*** *(final analysis only):* Assessed by the increase in the percentage of successful prescribers from pre-EM survey to post-EM survey.

Self-reported behavior	Prescribes Instanyl® on-label (adults)	Q3: To which of the following patient groups have you prescribed Instanyl®? Please select all that apply.	YES	The statement "Pediatric (<18 years old)" is not selected irrespective of the selection of the other two statements. This question will be assigned 0 points if the statement is selected and 3 points if it is not selected.	***For each survey evaluated separately*** *(for pre-EM and for post-EM surveys):* **At the individual level**, a prescriber will be considered successful if she/he gets 14 out of 17 points (pre-EM survey) or 15 points out of 18 points (post-EM survey) ("successful prescriber in the self-reported behavior criteria"). **At an aggregated level:** success will be reached if ≥80% of prescribers are successful. ***Change between the pre-EM survey and the post-EM survey*** *(final analysis only):* Assessed by the increase in the percentage of successful prescribers from pre-EM survey to post-EM survey
	Prescribes Instanyl® on-label (already receiving maintenance opioid therapy for chronic cancer pain)	Q4: Considering the patients to whom you prescribed Instanyl®, were they all ongoing maintenance opioid therapy?	YES	The statement "Yes" is selected. This question will be assigned 0 points if the statements is not selected and 1 point if it is selected.	
	Prescribes Instanyl® on-label (breakthrough pain in cancer patients)	Q5: For which of the indications listed below have you prescribed Instanyl®? Please select all that apply.	YES	The statement A "For the management of breakthrough pain (i.e., a transitory exacerbation of pain that occurs in the background of otherwise controlled persistent pain) in cancer patients" is selected and none of the other statements are selected. This question will be assigned 0 points if any the other statement is selected and 4 points if the statement A is the only selected.	
	Risks of Instanyl® misuse, abuse, medication errors, overdose, addiction, and death	Q6: When prescribing Instanyl® to a patient, which of the following aspects do you consider? Please select all that apply.	YES	The statements "risk of overdose", "risk of misuse", and "risk of abuse" (key statements) are selected. If "none of the above" is selected (single punch), the question will be considered incorrectly answered. The selection of any of the other statements do not contribute to the assessment of success. This question will be assigned 0 points if "none of the above" is selected and 1, 2, or 3 points if 1, 2, or 3 of the above-mentioned key statements are selected.	

Self-reported behavior	Follow recommendations from prescriber checklist	Q7: How often did you provide the following information to the patients/careers? Please select all that apply.	YES	The statements "Explain how to correctly use the nasal spray in terms of dose and titration", "Explain the risks of using more than the recommended amount of Instanyl®", "Advise on the signs of Instanyl® overdose" and "[Post-EM survey ONLY] Explain how to fill in the dose-counting card" are considered correct if "always" is selected; the statements "Explain the secure storage including the need to keep Instanyl® out of reach for children", "Explain correct disposal of Instanyl®" and "Encouragement for reporting of any issue with the management of the treatment" are considered correct if "sometimes", "often", or "always" are selected. This question will be assigned 0 to 6 points for pre-EM survey and 0 to 7 points for the post-EM survey depending on how many statements are correctly answered.	***For each survey evaluated separately*** *(for pre-EM and for post-EM surveys):* **At the individual level**, a prescriber will be considered successful if she/he gets 14 out of 17 points (pre-EM survey) or 15 points out of 18 points (post-EM survey) ("successful prescriber in the self-reported behavior criteria"). **At an aggregated level:** success will be reached if ≥80% of prescribers are successful. ***Change between the pre-EM survey and the post-EM survey*** *(final analysis only):* Assessed by the increase in the percentage of successful prescribers from pre-EM survey to post-EM survey.
Reasons for Off-label prescription	Reasons for off-label prescription (if participant reports prescription for an off-label indication as answer to Q3 or Q5)	Q3A. What were the reasons for prescribing Instanyl® to pediatric patients (<18 years old)? Q5(B, C_1, D_1): What were the reasons for prescribing Instanyl® for the management of background pain (i.e., persistent baseline pain) in cancer patients?"/"What were the reasons for prescribing Instanyl® for the management of breakthrough pain (i.e., a transitory exacerbation of pain that	NO, question not used to determine success (but it addresses one of the study objectives "To assess the reasons for off-label prescription").	-	Not applicable

		occurs in the background of otherwise controlled persistent pain) in non-cancer patients?"/"What were the reasons for prescribing Instanyl® for the management of background pain (i.e., persistent baseline pain) in non-cancer patients.			

13.2 Annex 2 Instanyl® Prescriber Survey Questionnaire

Section 1: Screening

S1. Have you prescribed Instanyl® **[Pre-EM survey:** in the past 12 months?**] [Post-EM survey:** since *[Month Year]***?]**

☐ Yes

☐ No *[Not eligible for this study, TERMINATE]*

Data: single punch

[Month Year] provided by country depending on the distribution dates of EM

S2. Do you plan to prescribe Instanyl® in the next 12 months?

☐ Yes

☐ No *[Not eligible for this study, TERMINATE]*

Data: single punch

S3. Are you currently employed by a pharmaceutical company (e.g., Takeda) or contracted by regulatory bodies (e.g., EMA or [add the name of the local regulatory agency])?

☐ Yes *[Not eligible for this study, TERMINATE]*

☐ No

Data: single punch

Section 2: Instanyl® Prescribing Practice

1) Approximately how many patients have you treated with Instanyl®, in the past **[Pre-EM survey:** 12 months?**]** **[Post-EM survey:** since **[Month Year]**?**]**

|__|__|__| patients
Data: numeric, 3 digits
[Month Year] provided by country depending on the distribution dates of EM

2) Were you the physician who initiated Instanyl® and/or did you continue Instanyl® that was started by another physician?
Please select all that apply.

	Yes	No
Only initiated Instanyl®	( )	( )
Only continued Instanyl® prescriptions initiated by another physician	( )	( )
Both initiated Instanyl® and continued Instanyl® prescriptions initiated by another physician	( )	( )

Data: single punch per row

3) To which of the following patient groups have you prescribed Instanyl®?
Please select all that apply.

Pediatric (<18 years old)	(A)
Adult (>18 to 65 years old)	(B)
Elderly (>65 years old)	(C)

Data: multiple punch
B and C are the correct options

- 3A) What were the reasons for prescribing Instanyl® to pediatric patients (<18 years old)?
  Please select all that apply.

Fast relief of pain	( )
Lack of alternative therapeutic options	( )
Other routes of administration not possible	( )
Patient/Caregiver's request	( )

Local guidelines/recommendations from professional society	( )
Other (please specify)	( )

Data: multiple punch, open text for "other, please specify"
Ask only if Q3=A is selected

4) Considering the patients to whom you prescribed Instanyl®, were they all on ongoing maintenance opioid therapy?[1]

☐ Yes
☐ No

Data: single punch
'Yes' is the correct answer

5) For which of the indications listed below have you prescribed Instanyl®?
Please select all that apply.

For the management of breakthrough pain (i.e., a transitory exacerbation of pain that occurs in the background of otherwise controlled persistent pain) in cancer patients	• (A)
For the management of background pain (i.e., persistent baseline pain) in cancer patients	• (B)
For the management of breakthrough pain (i.e., a transitory exacerbation of pain that occurs in the background of otherwise controlled persistent pain) in non-cancer patients	• (C)
For the management of background pain (i.e., persistent baseline pain) in non-cancer patients	• (D)

Data: multiple punch, open text for "other, please specify"
Order of the options will be randomized.
Correct answer: A.

5B) What were the reasons for prescribing Instanyl® for the management of background pain (i.e., persistent baseline pain) in cancer patients?

Fast relief of pain	( )
Lack of alternative therapeutic options	( )

[1] Patients receiving maintenance opioid therapy are those who are taking at least 60 mg of oral morphine daily or, at least 25 micrograms of transdermal fentanyl per hour or, at least 30 mg oxycodone daily or, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily for a week or longer.

Other routes of administration not possible	( )
Patient/Caregiver's request	( )
Local guidelines/recommendations from professional society	( )
Other (please specify)	( )

Data: multiple punch, open text for "other, please specify"

Ask only if Q5=B is selected

5C_1) What were the reasons for prescribing Instanyl® for the management of breakthrough pain (i.e., a transitory exacerbation of pain that occurs in the background of otherwise controlled persistent pain) in non-cancer patients?

Fast relief of pain	( )
Lack of alternative therapeutic options	( )
Other routes of administration not possible	( )
Patient/Caregiver's request	( )
Local guidelines/recommendations from professional society	( )
Other (please specify)	( )

Data: multiple punch, open text for "other, please specify"

Ask only if Q5=C is selected

5C_2) Please specify the underlying cause of the breakthrough pain (i.e., a transitory exacerbation of pain that occurs in the background of otherwise controlled persistent pain) in non-cancer patients?

Musculoskeletal disorders pain (back pain, fibromyalgia, arthritis, etc.)	( )
Pain during care of dressings, bedsores or chronic wounds	( )
Nervous system disorders (multiple sclerosis, neuropathic pain, etc.)	( )
Other: (please specify)	( )

Data: multiple punch, open text for "other, please specify"

Ask only if Q5=C is selected

5D_1) What were the reasons for prescribing Instanyl® for the management of background pain (i.e., persistent baseline pain) in non-cancer patients?

Fast relief of pain	( )

Lack of alternative therapeutic options	( )
Other routes of administration not possible	( )
Patient/Caregiver's request	( )
Local guidelines/recommendations from professional society	( )
Other (please specify)	( )

Data: multiple punch, open text for "other, please specify".
Ask only if Q5=D is selected

5D_2) Please specify the underlying cause of the background pain (i.e., persistent baseline pain) in non-cancer patients?

Musculoskeletal disorders pain (back pain, fibromyalgia, arthritis, etc.)	( )
Pain during care of dressings, bedsores or chronic wounds	( )
Nervous system disorders (multiple sclerosis, neuropathic pain, etc.)	( )
Other: (please specify)	( )

Data: multiple punch, open text for "other, please specify"
Ask only if Q5=D is selected

6) When prescribing Instanyl® to a patient, which of the following aspects do you consider? Please select all that apply.

Quality of life	( )
Nature of the pain	( )
Alternative treatments	( )
Risk of respiratory depression	( )
Risk of overdose	(X)
Risk of misuse	(X)
Risk of abuse	(X)
Appropriateness of route of administration	( )

None of the above	( )

Data: multiple punch or single punch if "none of the above" is selected

'(X)' indicates **correct** answer and will not be included in the survey administered to prescribers. It will be used for analysis of survey responses.

7) How often did you provide the following information to the patients/caregivers who are prescribed Instanyl®? Please select all that apply.

	Never	Rarely	Sometimes	Often	Always
Explain how to correctly use the nasal spray in terms of dose and titration	( )	( )	( )	( )	(X)
Explain the risks of using more than the recommended amount of Instanyl®	( )	( )	( )	( )	(X)
Advise on the signs of Instanyl® overdose	( )	( )	( )	( )	(X)
Explain the secure storage including the need to keep Instanyl® out of reach for children	( )	( )	(X)	(X)	(X)
Explain correct disposal of Instanyl®	( )	( )	(X)	(X)	(X)
Encouragement for reporting of any issue with the management of the treatment	( )	( )	(X)	(X)	X ()
[Post-EM survey ONLY] Explain how to fill in the dose-counting card	( )	( )	( )	( )	X ()

Data: single punch per row

'(X)' indicates correct answer and will not be included in the survey administered to prescribers. It will be used for analysis of survey responses.

Section 3: Instanyl® Knowledge

8) According to your knowledge, which of the following statements about Instanyl® indication are true, and which are false?

	True	False
Instanyl® is approved for the treatment of breakthrough pain (i.e., a transitory exacerbation of pain that occurs in the background of otherwise controlled persistent pain) in cancer patients with or without other concomitant diseases	(X)	( )
Instanyl® is approved for the treatment of breakthrough pain (i.e., a transitory exacerbation of pain that occurs in the background of otherwise controlled persistent pain) in non-cancer patients with rheumatoid arthritis or other musculoskeletal disease	( )	(X)
Instanyl® is approved for the treatment of background/persistent pain in cancer patients with or without other concomitant diseases	( )	(X)
Instanyl® is approved for the treatment of background/persistent pain in non-cancer patients with rheumatoid arthritis or other musculoskeletal disease	( )	(X)
Instanyl® can be prescribed to pediatric patients (<18 years old)	( )	(X)
Instanyl® should only be prescribed to patients already receiving opioid therapy	(X)	( )
Instanyl® can be prescribed as an add-on therapy for patients undergoing non-opioid analgesic therapy	( )	(X)

Data: single punch per row

The order of the options will be randomized

'(X)' indicates correct answer and will not be included in the survey administered to prescribers. It will be used for analysis of survey responses.

9) According to your knowledge, what are the recommendations for Instanyl® use?

the initial starting strength should be one dose/puff of |__| micrograms in one nostril *(3 digits)*
treat no more than |__| breakthrough pain episodes per day *(2 digits)*
If more than one dose/puff is not sufficient to alleviate pain, another can be taken after waiting at least |__|__| minutes *(3 digits)*

Data: semi numeric

Correct answers: 50; 4; 10

10) According to your knowledge, which of the following statements about the Instanyl® safety profile are true, and which are false?

Statement	True	False
Instanyl® acts quickly to relieve pain, so it is less likely to be abused	( )	(X)
Opioid overdose can cause respiratory depression that may result in fatal outcomes	(X)	( )
Off-label use is when a prescribed drug is not used according to the labeled indication including its indication, age group, dose and route of administration	(X)	( )
Off-label use of Instanyl® increases the risk of misuse, abuse, medication error, overdose, addiction, and death	(X)	( )
Patients receiving Instanyl® may develop opioid-induced hyperalgesia	(X)	( )

Data: single punch per row

'(X)' indicates correct answer and will not be included in the survey administered to prescribers. It will be used for analysis of survey responses.

11) According to your knowledge which of the following statements about management of patients using Instanyl® are true, and which are false?

Statement	True	False
It is the prescriber's responsibility to ensure patients and caregivers are aware of the risks of misuse, addiction, and overdose to Instanyl®?	(X)	( )
Cancer patients already taking opioids and requiring breakthrough medication should not be assessed for opioid use disorder	( )	(X)
Instances of Instanyl® drug abuse, misuse, addition and overdose do not need to be reported as they are well known risks of any opioid use	( )	(X)
Request to increase dose or refill prescriptions early may be a sign of addiction to Instanyl®	(X)	( )

Data: single punch per row

'(X)' indicates correct answer and will not be included in the survey administered to prescribers. It will be used for analysis of survey responses.

12) According to your knowledge which of the following statements about diagnostic criteria for opioid use disorder, are true, and which are false?

Patient Behavior	True	False
Continued use of opioids despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of its use	(X)	( )
Taken the substance in larger amounts or over a longer period than was intended	(X)	( )
The patient develops withdrawal/physical dependence	(X)	( )
Taking opioids as prescribed and able to fulfill major obligations at work, school, or home	( )	(X)
A great deal of time and effort taken by patient to ensure continuing opioid supply, use or recover from its effects	(X)	( )
Use of the substance is recurrent in situations in which it is physically hazardous	(X)	( )

Data: single punch per row

'(X)' indicates correct answer and will not be included in the survey administered to prescribers. It will be used for analysis of survey responses.

13) According to your knowledge, which of the following patient characteristics could indicate risk of Instanyl® misuse or addiction?
Please select all that apply.

Patients with personal or family history of substance use disorder	(X)
Patients taking psychiatric medication	(X)
Tobacco users	(X)
Patients using single-dose nasal spray	(…)
All the above	(…)
None of the above	(…)

Data: multiple punch or single punch if "none of the above" or "all of the above" is selected

'(X)' indicates correct answer and will not be included in the survey administered to prescribers. It will be used for analysis of survey responses.

Section 4: Awareness of the Educational Materials

ASK SECTION 4 IN POST-EM SURVEY ONLY (EXCEPT FOR Q15)

14) Have you received or downloaded any educational materials on Instanyl® since **[Month Year]?]**

Yes	(**X**)
No	( )

Data: single punch

[Month Year] provided by country depending on the distribution dates of EM

'(X)' indicates the targeted answer and will not be included in the survey administered to prescribers. It will be used for analysis of survey responses.

a) Please indicate which of the following educational materials you have received or downloaded. Please select all that apply.

1	Instanyl® Summary of Product Characteristics	( )
2	The Instanyl® prescribing checklist	(**X**)
3	Physician's guide to prescribing	(X)
4	Other, please specify:	( )

Data: multi-punch, open text for "other, please specify"
Ask if Q14=Yes
'(X)' indicates targeted answers and will not be included in the survey administered to prescribers. It will be used for analysis of survey responses.

b) Please indicate which of the following educational materials you have read after receiving/downloading. Please select all that apply.

Instanyl® Summary of Product Characteristics	( )
The Instanyl® prescribing checklist	(X)
Physician's guide to prescribing	(X)
None of the above	( )

Data: multi-punch, single punch if "None of the above" is selected
Ask respective items 1-4 if selected in Q14a
'(X)' indicates targeted answers and will not be included in the survey administered to prescribers. It will be used for analysis of survey responses.

15) What (other **["other" should be used in Post-EM survey only])** sources of information about Instanyl® have you used?
Please select all that apply.

Drug information on Instanyl® website	( )
Drug information on other website(s)	( )
Materials provided by company representatives	( )
Professional/scientific literature or conference	( )
Communication from Health Authorities	( )
Other, please specify:	( )
None of the above	( )

Data: multi-punch, single punch if "None of the above" is selected, open text for "other, please specify"

16) Have you become aware of the following resources available for pharmacists and/or patients treated with Instanyl®?

	Yes	No
Patient Package Information Leaflet	( )	( )
Dosing Card	(X)	( )
Pharmacist's guide to dispensing	( )	( )
Patient's guide	( )	( )

Data: single punch per row

'(X)' indicates the targeted answer and will not be included in the survey administered to prescribers. It will be used for analysis of survey responses.

Section 5: Prescriber Characteristics

17) Please indicate your age group

≤30 years old	( )
31-39 years old	( )
40-49 years old	( )
50-59 years old	( )
≥60 years old	( )

Data: single punch

18) What is your primary medical specialty?

Anesthesiology	( )
General Practice	( )
Hematology	( )
Internal Medicine	( )
Pain Management	( )
Palliative Care	( )
Oncology/Oncoradiology	( )
Other specialty as defined per country	( )
Other, please specify:	( )

Data: single punch, open text for "other, please specify"

19) For how many years have you been practicing in this specialty?

|__|__| years

Data: open numeric, 2 digits, maximum value set as 60

20) In which setting do you spend the majority of your time when practicing?

Hospital/clinic-based	( )
Community-based public practice	( )
Community-based private practice	( )
Other, please specify:	( )

Data: multiple punch, open text for "other, please specify"

Thank you for your participation in the survey.

Should you be informed about an adverse event/product complaint, please follow routine Pharmacovigilance procedures or contact the MAH. You could also report an adverse event/product complaint using the attached report form.

[Complete]

13.3 Annex 3 ENCePP Checklist

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 authorization holders when submitting the protocol of a non-interventional post-authorization safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorization 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: Assessment of the Effectiveness of Updated Educational Materials on Prescribers' Knowledge and Behavior with Respect to Risks Associated with INSTANYL® Off-Label Use

EU PAS Register® number: EUPAS41308
Study reference number (if applicable): Instanyl-5002

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				

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

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)	☒	☐	☐	7.0
2.1.2 The objective(s) of the study?	☒	☐	☐	8.2
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	9.2.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

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
3.2 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))	☐	☐	☒	

[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.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
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:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.1
4.2.2 Age and sex	☐	☒	☐	
4.2.3 Country of origin	☒	☐	☐	9.1
4.2.4 Disease/indication	☒	☐	☐	9.1
4.2.5 Duration of follow-up	☒	☐	☐	9.5.1
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

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorizing 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 categorized according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g., dose, duration)	☐	☐		
5.5 Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.7.2.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.7.2.3
6.3 Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g., HRQoL, QALYs, DALYS, health care services utilization, 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)	☒	☐	☐	9.9.1
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9.2

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)	☒	☐	☐	9.7.2

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)	☒	☐	☐	9.2.4 and 9.4

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)	☒	☐	☐	9.3.1
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.1
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)	☐	☐	☒	9.3.1
9.2.2 Outcomes? (e.g., date of occurrence, multiple events, severity measures related to event)	☐	☐	☒	
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)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.1
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.4 Are stratified analyses included?	☒	☐	☐	9.7.2
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?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.2.3.3

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)	☒	☐	☐	10.3
11.2 Are methods of quality assurance described?	☒	☐	☐	9.7.2.3.3
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8.2

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?	☒	☐	☐	9.9.1
12.1.2 Information bias?	☒	☐	☐	9.9.2
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)	☒	☐	☐	9.5

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?	☒	☐	☐	10.1.1
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?	☒	☐	☐	5.0

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:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____