PASS INFORMATION

Study title	**Evaluation of the Effectiveness of Risk Minimisation Measures: A Survey among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of Instanyl® in France and the Netherlands** **Study Number: Instanyl-5001**
Protocol Version identifier	Version 5
Date of last version of protocol	06 February 2015
EU PAS Register number	
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
Marketing authorization holder (MAH) or sponsor company	Takeda (United Kingdom)
Joint PASS	No
Research question and objectives	Research question: Was the updated educational materials effective in: - Increasing the knowledge of physicians about safe use of Instanyl®, - Influencing their attitude when prescribing Instanyl®. Objective: To measure the proportion of targeted physicians who received, understood and followed the safety information about Instanyl® provided in the educational materials.
Countries of study	France and the Netherlands
Author	Dr Massoud Toussi, Medical Director, RWES/HEOR, IMS Health, Tour Ariane, 5-7 Place de la Pyramide, 92088 La Défense Cedex, France. Email: mtoussi@fr.imshealth.com
MAH(s)	Takeda Pharma A/S Denmark
MAH contact person	Dr Paul Dolin, Head of Pharmacoepidemiology Takeda Development Centre Europe Ltd 61 Aldwych, London WC2B 4AE, United Kingdom

Field Code Changed

1. TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ANNEXES

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
AR	Adverse reaction
ASOCS	Association of Opinion and Behaviour in health field research companies
CI	Confidence interval
EMA	European Medicines Agency
EphMRA	European Pharmaceutical Marketing Research Association
GVP	Good pharmacovigilance practices
GP	General practitioner
HCP	Health care professional
PASS	Post-authorization safety study
PIL	Patient information leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
RMM	Risk minimization measures
RMP	Risk minimization plan
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SOP	Standard operating procedures
SPC	Summary of product characteristics
STROBE	Strengthening the reporting of observational studies in epidemiology

3. RESPONSIBLE PARTIES

Sponsor:

Takeda Development Centre Europe Ltd

Contact person: Dr Paul Dolin, Head of Pharmacoepidemiology, Takeda Development Centre Europe Ltd, United Kingdom.

Subcontractor:

IMS Health

Contact person: Dr Massoud Toussi, Principal, Medical Director, IMS RWES, France.

4. ABSTRACT

4.1 Title:

Evaluation of the Effectiveness of Risk Minimisation Measures: A Survey among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of Instanyl® in France and the Netherlands

Version n°5: 6th February 2015

Main author: Massoud Toussi, Medical Director, HEOR, IMS Health,
Tour Ariane, 5-7 Place de la Pyramide, 92088 La Défense Cedex, France.
E-mail address: mtoussi@fr.imshealth.com

4.2 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 (1,2,3), marketed throughout the European Union since July 2009.

Educational materials were updated in late 2013 and aimed at reiterating safe use and minimizing off label use of Instanyl®. They focused on the fact that Instanyl® should not be used for the treatment of acute pain other than breakthrough pain, should only be used in patients receiving an opioid treatment, and reiterating the risk of off-label use.

As part of a risk minimization activity, the education materials are being distributed to healthcare professionals (HCPs) in Europe in the countries where the drug is marketed.

This post-authorization safety study (PASS) is designed to evaluate the process and outcome indicators to ensure that physicians received the updated safety information, understood it and follow it when prescribing Instanyl®.

4.3 Research question and objectives

Research question:

Was the updated educational materials effective in:

- Increasing the knowledge of physicians about safe use of Instanyl®,
- Influencing their attitude when prescribing Instanyl®.

Objective:
To measure the proportion of targeted physicians who received, understood and followed the safety information about Instanyl®.

4.4 Study design

An anonymous, cross sectional and non-interventional survey of a sample of physicians in France and the Netherlands who are likely to prescribe Instanyl®.

4.5 Population

Inclusion criteria:

- Physicians prescribers, or potential prescribers, of Instanyl®,
- Specialists of any of those targeted for the educational materials:
  - Oncolologists,
  - Anesthesiologists,
  - Radiologists,
  - Hospital-based General practitioners (GPs).

Exclusion criteria:

- Physicians who do not treat patients or who may have a conflict of interest (i.e. physicians employed by regulatory bodies, pharmaceutical industries),
- Physicians who do not know Instanyl®.

4.6 Variables

The collected information includes: demographics, type of practice, awareness and knowledge about safe use of Instanyl® presented in the updated educational materials, and the physician' consideration of the safety warnings.

The proportion of correct and appropriate answers about safe use of Instanyl® given by the physicians will be assessed overall, by country and among subgroups of specialties.

4.7 Data sources

The survey is a primary data collection conducted through a web questionnaire.

4.8 Study size

The sample survey will include physicians from the following sources:

- Takeda's lists of physicians targeted for the educational materials,
- IMS Medical Radar reference files,

The sample size calculation is based on the survey objective, *i.e*. to evaluate the prescribers and potential prescriber awareness and knowledge about safe use of Instanyl® as updated in the educational materials.

Since the expected proportion of physicians knowledgeable about safe use of Instanyl®, is not known and there is no evidence supporting it, the worst case hypothesis will assume a proportion of 50%. For a confidence interval of 95% and a precision of 6%, a total of 267 analysable web questionnaires will be needed for the overall sample, 178 in France and 89 in the Netherlands.

4.9 Data analysis

The statistical analysis will be conducted using the SAS® softwareV9.3 on Windows™ (SAS Institute, North Carolina, USA).

Results will be presented, overall, and at country level per specialty.

Continuous variables will be described by the number of valid cases and missing data, mean, standard deviation, median, Q1, Q3, minimum, and maximum. No missing data will be replaced. Categorical variables will be described as the total number and relative percentage per category. Confidence intervals of 95% will be calculated when relevant.

Calculations will first be performed on raw data per specialty, and weighted according to the real proportion of targeted physicians in each country to accurately reflect the population the survey seeks to measure.

Possible selection bias will be assessed by comparing the distributions of available characteristics (e.g. region, age, gender, type of practice and specialty) between respondent and non-respondent physicians.

4.10 Milestones

- Start of data collection - Fieldwork: Mar-April 2015
- End of data collection - Fieldwork: End October 2015
- Submission of study report to EMA: End of March 2016.

5. AMENDMENTS AND UPDATES:

Number	Date	Section of study protocol	Amendment or update	Reason
1	14 Jan 2015	§4.1 Milestones	Update of the date and version number	Revised protocol
2	14 Jan 2015	§9.5.2 Study size calculation	Addition of a table including the study sample size considering also a precision of 5 and 10%, and update of the text accordingly.	Requested by PRAC
3	14 Jan 2015	§9.6.1 Data collection	Addition of a specification about reminders and recruitments by phone if the number of needed response is not reached	Requested by PRAC
4	06 Feb 2015	§4.10 Milestones	Update of the study milestones	Revised protocol
5	06 Feb 2015	§6 Milestones	Update of the study milestones	Revised protocol

6. MILESTONES

- Start of data collection: Mar-April 2015
- End of data collection: End-October 2015
- Submission of study report to EMA: End of March 2016

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 (1,2,3).

- 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, at 8 mg of oral hydromorphone, or an equianalgesic dose of another opioid for a week or longer.

The European Commission granted a marketing authorisation valid throughout the European Union for Instanyl® on 20 July 2009.

Due to the opioid nature of Instanyl®, which contains fentanyl, there is a potential risk of off-label use, abuse and misuse.
Takeda has updated educational materials focusing on the fact that Instanyl® should not be used for the treatment of acute pain other than breakthrough pain, and be used in patients receiving an opioid treatment, and reiterating the risk of off-label use.
The updated materials were approved by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) in July 2013. The MAH is sending the updated educational materials for reiterating the safe use of the drug to the healthcare professionals (HCPs) during 2014 in the countries where the drug is marketed. This risk minimization measure (RMM) was implemented as part of the Instanyl® risk management plan (RMP).

This post-authorization safety study (PASS) is designed to evaluate the process and outcome indicators to ensure that physicians received the updated safety information, understood it and follow it when prescribing Instanyl®.

7.1 RATIONALE FOR COUNTRY SELECTION

This study is being undertaken in France and The Netherlands, the two countries with the highest volume of Instanyl® prescribing in the EU. All other countries have minimal prescribing by comparison and therefore were not considered appropriate for conduct of this survey.

7.2 RATIONALE FOR THE SELECTION OF THE SPECIALTIES

Takeda distributed the educational materials to physicians who were likely to prescribe Instanyl®:

- Oncologists,
- Anesthesiologists,
- Radiologists,
- Hospital-based general practitioners (GPs) likely to be involved in management of cancer patients.

In France and Netherlands, market research shows little prescribing of Instanyl® in primary care setting.

8. RESEARCH QUESTION AND OBJECTIVES

8.1 RESEARCH QUESTION

Was the updated educational materials effective in:

- Increasing the knowledge of physicians about safe use of Instanyl®,
- Influencing their attitude when prescribing Instanyl®.

8.2 OBJECTIVE

The objective of the survey is to measure the proportion of targeted physicians who received, understood and followed the safety information about Instanyl® provided in the updated educational materials.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This survey will be cross-sectional, multinational, non-interventional and conducted in an anonymous way.

9.2 SETTING

The survey will be conducted through a web questionnaire among prescribers, or potential prescribers, of Instanyl® in settings of two European countries (France and the Netherlands).

9.2.1 Inclusion criteria

The survey will be conducted among physicians meeting the following inclusion criteria:

- Prescribers, or potential prescribers, of Instanyl®, i.e. physicians who know the drug,
- Specialists of any of those targeted for the educational material:
  - Oncologists,
  - Anesthesiologists,
  - Radiologists,
  - Hospital-based GPs likely to be involved in management of cancer patients.

9.2.2 Exlusion criteria

Inactive and retired physicians (when evidence is available to identify them) will be deleted from the contact lists before randomisation.

The following exclusion criteria will be checked at the beginning of the web questionnaire:

- Physicians who do not treat patients or who may have conflicts of interest with the survey (i.e. physicians employed by regulatory bodies, pharmaceutical industries),
- Physicians who do not know Instanyl®.

9.3 VARIABLES

The collected information from each physician will include demographics, type of practice and potential prescription of the drug.
The awareness and knowledge of the safety information included in the educational materials regarding Instanyl® sent to the HCPs, the sources of communication and the intention of the physician to consider the updated safety warnings will also be collected.

The proportions of correct and appropriate answers to selected questions asked in the questionnaire will be expressed among physicians with complete analysable web questionnaires. The endpoint will be assessed overall, by country and among subgroups of physicians' specialty.

9.4 DATA SOURCES

The survey is a primary data collection conducted through a web questionnaire.
The questionnaire will be developed and tested among 5-6 physicians (2-3 per country) for its comprehensibility, consistency and the appropriateness of medical terms. Physicians' comments will be implemented in the final version. The local translated versions of the questionnaire from English into French and Dutch will be done using the back and forth method to ensure an accurate translation.
The web questionnaire completion is estimated to take 10 to 15 minutes.

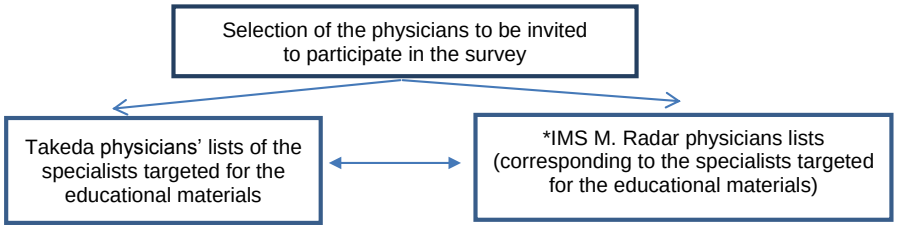
9.5 STUDY SIZE

9.5.1 Sampling plan

The statistical unit is the physician. For each selected country, the sample survey will include physicians identified and recruited from two sources:

- Takeda's lists of physicians who were targeted for the educational material,
- IMS Medical Radar's reference lists of required specialists.

Figure 9.5-1: Physicians selected to be invited in the survey



* IMS lists may potentially include physicians who were not sent the educational material, if these physicians were added into IMS lists recently, after the date of distribution of the educational material.

These lists will be restricted to the targeted specialists' population, i.e. selected specialists who are currently active and not retired in 2014 at the time of the survey. The use of IMS Medical Radar's lists will be needed for France and the Netherlands if Takeda cannot transfer the lists to IMS due to local data protection laws, or if Takeda's lists do not contain sufficient information on targeted physicians (e.g. lack of email addresses/phone numbers). In the latter case, a match-merge of these two data sources will be done, with Takeda's lists as the master source and IMS Medical Radar's lists as an additional source used to compensate the potential shortcomings.

As per sample size defined below and the number of selected countries and specialities, physicians will be stratified only by country and specialty. Other criteria such as region, age and gender of the prescriber are less relevant than country and specialty, since they may not be available in all countries or not be a determinant as important as country or specialty. The use of more strata would have needed a larger sample size.

A random stratified sampling method will be applied. As a first step, all lists will be merged, and then the eligible physicians will be divided into homogeneous groups, called strata, which are mutually exclusive (a physician can only belong to one stratum). This stratification will be done based on the following criteria:

- Country: 2 possibilities,
- Specialty: 4 possibilities.

Thus, 2 x 4 = 8 strata will be formed.

Table 9.5.1-1: Strata definition

Stratum ID	Country	Specialty
1	France	Oncologists
2	France	Anesthesiologists
3	France	Radiologists
4	France	Hospital based GPs
5	The Netherlands	Oncologists
6	The Netherlands	Anesthesiologists
7	The Netherlands	Radiologists
8	The Netherlands	Hospital based GPs

The physicians' allocation to a stratum is explained in the section below (Study size calculation). However, eligible physicians are not evenly distributed across these 4 specialties. Thus, hospital-based GPs are much more prevalent. As a consequence, specialties could be aggregated into two categories if needed.

9.5.2 Study size calculation

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

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

where P is the expected proportion, e is one half the desired width of the confidence interval, and $Z_{1-\alpha/2}$ is the standard normal Z value corresponding to a cumulative probability of 1 – α/2. The following table provides the margin of error for 95% confidence interval based on various sample sizes and proportions of interest (Table 9.5.2-3~~Table 9.5.2-3~~).

Table 9.5.2-1: Sample size obtained for various precisions and various proportions

	Margin of error for 95% CI		
Proportion	**10%**	**6%**	**5%**
10%	35	97	139
30%	81	225	323
50%	97	**267**	384
70%	81	225	323
90%	35	97	139

Since the proportion of physicians informed about the updated safety information and recommendations for safe use of Instanyl® is not known and there is no evidence supporting

the expected proportion, the worst case hypothesis will be assumed considering that 50% of physicians will be knowledgeable about the safety information distributed recently. This assumption yields the largest sample size.

Considering this hypothesis and in order to achieve a confidence interval (CI) of 95% with a half-width of 6%, a total of 267 analysable physician questionnaires will be needed for the overall sample. Considering a margin of error of 5% instead of 6%, the required sample size would be 384 analysable physician questionnaires for the overall sample.

Based on IMS Medical Radar experience from previous similar surveys and estimates and the evaluation of the survey feasibility, the sample size of 267 is considered for this study. It is estimated that about 10-15% of physicians will not complete the questionnaire or not be analysable (i.e. physicians who respond to questions regarding their knowledge on the updated safety concerns of Instanyl®). Taking into account these respondent physicians without analysable questionnaires, the overall sample size of **307** participating physicians will be required to reach 267 analysable questionnaires.

This overall sample size can be further divided into two sample for each country. For the conduct of survey, ideally 307 participating physicians (267 analysable physicians respectively) should proportionally be split between the two countries, based on the number of physicians employed in a hospital setting in each country, which was estimated at 160,314 in France and 21,541 in the Netherlands in 2009[1] in the last available information on Eurostat (European Commission). Thus the suggested sample size split is 88% for France and 12% for the Netherlands, i.e. 271 participating physicians in France and 36 in the Netherlands (235 analysable physicians in France and 32 in the Netherlands respectively).

However, this sample size will not be sufficient for the Netherlands. Usually, to ensure the robustness of statistical estimations at a wished level of analysis (e.g. specialty or aggregated specialties per country), the sample size should not be lower than a threshold of 40 statistical units in each entity of this level.

To comply with this constraint, an arbitrary split of 2:1 will be implemented: **205** participating physicians in France and **102** in the Netherlands are required to provide 178 analysable physicians in France and **89** in the Netherlands. For this last country, the less common specialties need likely to be grouped.

With such sample it will be necessary to weight back the study results according to the real proportion of physicians in order to allow the representativeness of the overall sample.

In web surveys, the number of physicians to be contacted in order to reach the required number of physicians with analysable questionnaires is usually around ten times more than the expected final number.

Table 9.5.2-2: Sample size per country and overall

	France	The Netherlands	Overall
*Arbitrary allocation of the sample 2:1 between France and The Netherlands **	*66.7%*	*33.3%*	*100%*
Number of participating physicians required	205	102	307
Number of participating physicians with complete analysable questionnaire expected	178	89	267

** Note: The country-distributions of the 'Number of participating physicians required' and the 'Number of participating physicians with complete analysable questionnaire expected' are the same, since the second*

[1] http://epp.eurostat.ec.europa.eu/portal/page/portal/health/health_care/data/database

one is deducted from the first one through the application of a 15% inflation rate due to physicians who will not complete the questionnaire.

At each country level, the sample size will be further divided into the selected groups of specialties. Takeda's detailed counts of distributed educational material per country were used to estimate the real breakdown of targeted specialists (Table 9.5.2-3~~Table 9.5.2-3~~).

Table 9.5.2-3: Physicians who received the educational material by country

	France	The Netherlands	Overall
Physicians employed in a hospital setting*	160,374	21,541	181,915
Weight of each country	88.2%	11.8%	100%
Distributed educational material (# of packs)**	±3,000	±2,900	±7,900
Components by specialty**:			
General practitioners, n (vertical %)	1,500 (50.0%)	2,204 (76.0%)	
Oncologists, n (vertical %)	600 (20.0%)	464 (16.0%)	
Anesthesiologists, n (vertical %)	200 (6.7%)	116 (4.0%)	
Radiologists, n (vertical %)	700 (23.3%)	116 (4.0%)	
Components by aggregated specialties**:			
General practitioners, n (vertical %)	1,500 (50.0%)	2,204 (76.0%)	
Other specialties, n (vertical %)	1,500 (50.0%)	696 (24.0%)	

** Source: EuroStat*
*** Source: Takeda*

Building a sample proportionally distributed by number of specialists would yield very small numbers for less frequent specialties, mainly in the Netherlands.

As a consequence, an over-sampling in Netherlands will be applied in order to provide a sufficient number of analysable specialties while preserving the number of analysable hospital-based GPs (Table 9.5.2-4~~Table 9.5.2-4~~):

- For France where the sample size is large enough: a minimal number of 50 is assigned to the GPs category and the remaining number is proportionally distributed between the 3 other specialties.
- For The Netherlands: a minimal number of 40 is assigned to the hospital-based GPs category and the remaining number is equally distributed between the 3 smallest specialties.

This allocation is applied to the number of analysable questionnaires. Then, the number of required participating physicians is deducted taking into account 15% of respondents without analysable questionnaires. The same methodology cannot be applied to both countries due to feasibility concerns (i.e. it is better that the sampling rate (number of required participating physician / number of physicians in Takeda's list) at specialty level does not exceed 10%).

Table 9.5.2-4: Sample size per country and per specialty

n (vertical % per country)*	France	The Netherlands	Overall
Number of participating physicians required	**205**	**102**	**307**
General practitioners, n (vertical %)	70 (34.1%)	46 (45.1%)	
Oncologists, n (vertical %)	55 (26.8%)	20 (19.6%)	
Anesthesiologists, n (vertical %)	17 (8.3%)	18 (17.6%)	
Radiologists, n (vertical %)	63 (30.7%)	18 (17.6%)	
Sub-total of non-GP specialties	135 (65.9%)	56 (54.9%)	
Number of physicians with an analysable questionnaire	**178**	**89**	**267**
General practitioners, n (vertical %)	60 (33.7%)	40 (44.9%)	
Oncologists, n (vertical %)	48 (27.0%)	17 (19.1%)	
Anesthesiologists, n (vertical %)	15 (8.4%)	16 (18.0%)	
Radiologists, n (vertical %)	55 (30.9%)	16 (18.0%)	
Sub-total of non-GP specialties	118 (66.3%)	49 (55.1%)	

** To be aligned with the n by country, numbers n per specialty have been rounded to the superior integer for the oncologists, otherwise to the inferior integer.*

Note that the determined quotas for anesthesiologists and radiologists, especially in The Netherlands may be difficult to achieve due to the few physicians in the available list (less than 200), and a usual expectable response rate of 10% to this kind of web survey. In the event that this goal would not be reached, then additional GPs or oncologists will be recruited to compensate and preserve the sample size at country level.

Sample adjustment:

Since the relative weight of each country and of each specialty in the sampling plan is different from its real relative weight in the target lists

A sample adjustment will be performed. The survey results will be weighted to reflect the real proportion of the two countries and within each country to reflect the real proportion of each specialty in order to extend the survey results to the overall target population. Both unweighted (i.e. raw data) and weighted results will be presented in the report.
A weight variable will be applied to each statistical unit (i.e. the analysable physician) during the results calculation in order to correct the over-sampling of the Netherlands, for oncologists, anaesthesiologists and radiologists, and the under-sampling of France for GPs. This variable will indicate how many unit(s) of the population of interest an observation counts in a statistical procedure. Its value will change per country and per specialty. The weights will be normalized to obtain their sum equal to the sample size.

In order to fill-in each stratum of the sample survey from Takeda's files and/or the IMS Medical Radar reference files, an independent sample will be selected per stratum through a simple random sampling without replacement.

In each specific stratum, physicians will be contacted according to the order of draw in this stratum. If a physician does not want to participate in the survey, the next one in order of draw will be contacted, and so on until the required number of physicians is met. If the target for a stratum is not achieved after the end of the initial list, an additional randomly sampled list will be prepared and the physicians contacted until the goal is reached or no names are

left in that stratum. If both the Takeda list and IMS Medical Radar file have been exhausted in any particular stratum, a strategy will be determined to adjust the sample size within stratum with associated weighting.

It is to be noted that this sample is calculated to be representative as a whole, not per country or specialty. Thus the subgroup analyses will not guarantee the same confidence intervals as the whole sample.

9.6 DATA MANAGEMENT

The survey will be conducted according to the Standard Operating Procedures (SOPs) of IMS Medical Radar and IMS Real World Evidence Solutions.

Collected data will be entered and stored in a database specific to the survey and the country. A study database will be created by merging of databases of each country.

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 non admissible values,
- cross-check the 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 five to six weeks, and will be conducted in parallel in the two countries.

The survey will be conducted by IMS Medical Radar, a division of IMS Health specialized in the conduct of phone and web surveys for more than 20 years. IMS Medical Radar will create a web-based instance survey. Physicians' answers/data will be collected through a web questionnaire. The lists of physicians will be loaded into separate databases for the management of the survey.

As described previously (§9.5.1~~9.5.1~~: Sampling plan and §9.5.2~~9.5.2~~: Study size calculation), physicians will be randomly contacted, mainly by email and also by phone when needed, according to their stratum by the IMS Medical Radar team. Their recruitment will be done as follows:

- Physicians will be invited to participate in the survey (via emails/mails or phone calls). The survey background and objectives, the contact information for questions, and the proposed compensation will be explained to the physicians at this step. If they agree to participate in the survey, they will receive a link to access the survey and the instructions for the web questionnaire completion.
- If the questionnaire is not completed and sent to IMS Medical Radar, the physicians will be sent a reminder by email one week after the start of the survey.
- If the target is not achieved in the stratum, a reminder by phone will be conducted 1.5 week after the start of the survey.
- If the questionnaire is still not completed and sent to IMS Medical Radar, the physicians will be sent a last reminder by email two weeks after the start of the survey.

If necessary, if the minimum number of needed responders is still not reached, the recruitment will be performed by phone to achieve the target in a specific stratum.

A physician will be considered as contacted if he/she has:

- refused to participate,

Formatted: Font: (Default) Arial, 10.5 pt, (Asian) Japanese (Japan), (Other) English (United Kingdom)

Formatted: Font: (Default) Arial, 10.5 pt, (Asian) Japanese (Japan), (Other) English (United Kingdom)

- been contacted at least 3 times and up to 5 times,
- been sent the survey, completed and sent it back to IMS Medical Radar.

Moreover, a physician will be considered as unreachable if he/she has been contacted between three and five times without any answer.

For each physician of the sample file, the number of contacts, and the date and time when he/she completed the web questionnaire will be recorded. The recruitments in each stratum will be stopped when the target is reached. If both Takeda's list and IMS file have been exhausted in any particular stratum, the recruitments in this stratum will be prematurely ended and a strategy will be determined to adjust the sample size with associated weighting.

9.6.2 Approaches for increasing the response rate

Physicians are increasingly contacted to participate in web or phone surveys. Their overall response rate of participation remains low according to international studies (5)(6)(7). 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 (7). VanGeest et al. conducted a systematic review of 66 published reports on efforts to perform for improving response rates (8). Two general strategies were explored: incentives-based approaches and survey design-based approaches. Financial incentives, even little ones, were effective in improving physician 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 increase the response rate, three actions will be applied to this survey:

1) A compensation fee will be proposed to physicians for their participation in the survey.
2) All physicians will be sent an email or contacted by experienced operators of IMS Medical Radar with extensive experience in conducting health related surveys.
3) Each physician will be emailed or called up to 3-5 times before being considered as "not reachable", and reminders will be sent by email if IMS Medical Radar does not receive the web questionnaire.

9.7 DATA ANALYSIS

9.7.1 General statistical consideration

The statistical analysis will be conducted using the SAS® softwareV9.3 on Windows™ (SAS Institute, North Carolina, USA).

The statistical results of the two countries will be presented in the same report, overall, by country and per physician's specialty.

Table 9.7.1-1: Mock table to implement in the statistical and study reports

			Question 1…			
Country	**General practitioners**	**Oncologists**	**Anesthesio -logists**	**Radiologists**	**Sub-total non-GP specialties**	**All**
France	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xxx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Netherlands	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Overall - unweighted results	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xxx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Overall - weighted results	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xxx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: the table structure may be adjusted in the final study report.

Continuous variables will be described by their number (of valid cases, of missing values), mean, standard deviation, and median, Q1, Q3, minimum and maximum.

Categorical variables will be described as the total number and relative percentage per category. These will be the percentage per category.

Confidence intervals of 95% will be calculated, when relevant.

In a first step, calculations will be performed on raw data. No projection factor will be applied to generalize the results to the entire prescribers' universe. As a consequence, the line "Overall – unweighted results" will show only the results observed on the overall sample, and will not reflect the countries' universe since this sample is not proportional to the size of Takeda's lists or IMS Medical Radar reference files in each country.

In a second step, the results will be weighted according to the real proportion of physicians in each country in order to accurately reflect the population that the survey seeks to measure.

For each country, the results will be reported according to the prescribers' specialty distributed proportionally to their weight within Takeda or IMS reference lists.

9.7.2 Analysis of non-participation or refusal to participate rate

As often required by the Authorities, the following different cases of total non-response will be distinguished and analysed:

- Targeted physicians: Physicians reached to whom an email or mail has been sent, or have been called.
- Contacted physicians: Physicians who have been reached out by phone or have opened their email (if the score is technically available in their country).
- 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 recruitment email).
- Physicians with complete questionnaire: Physicians who actually completed the questionnaire until its end**.**

The physicians' participation in the survey will be examined via different ratios:

- Contact rate = contacted physicians / targeted physicians
- Response rate = Physicians who agreed to participate/ contacted physicians
- Cooperation rate = Physicians with complete questionnaire / Physicians who agreed to participate
- Refusal rate = (contacted physicians-physicians who agreed to participate) / Physicians reached

The reasons for non-response will be sought, especially from all observed variables. This will ensure that missing data are reported with enough detail to strengthen the results validity, as recommended by the STROBE guidelines (9).

9.7.3 Questionnaire analysis

The general statistical considerations described above (§9.7.1~~9.7.1~~) will be applied for quantitative and qualitative variables. The number of missing data will be indicated. Missing values are expected to be few and distributed at random. Since there is no applicable method unanimously accepted, there will be no replacement or imputation of missing data (10).

Formatted: Font: (Default) Arial, 10.5 pt, (Asian) Japanese (Japan)

Confidence intervals of 95% will be calculated for endpoint.

Physicians' answers will be analysed by subgroups of physician's specialty per country, and on the overall dataset.

9.8 QUALITY CONTROL

9.8.1 Approaches for validating the questionnaire

The questionnaire will be tested among 5-6 physicians for its comprehensibility, consistency and the appropriateness of medical terms. The local translated versions of the questionnaire from English into French and Dutch will be done using the back and forth method to ensure an accurate translation.

9.8.2 Approaches for validating the results

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

1) At IMS Medical Radar management level, every efforts will be undertaken to collect complete and valid data:
   - Verification of the reliability and security of the web questionnaire interface by a qualified web-master 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 physician.
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-analysable questionnaires:
     - estimation of the percentage of physicians who do not know Instanyl®,
     - estimation of the percentage of physicians without complete analysable questionnaire.

Any changes in the database will be tracked and documented. The country-datasets will be stored in a dedicated database. Once data 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. The final statistical report will take into account the reviewers' comments.

5) At the study level, all aspects of the study will be conducted according the standard operating procedures (SOPs) of IMS Real World Evidence Solutions and Medical Radar divisions. The study documents have been approved by people competent in medical and safety areas of IMS. 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 data management and preparation.

9.8.3 Safeguards, security and traceability of contacts

The operators of the call centre specialised 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 IMS Real World Evidence Solutions and Medical Radar divisions. These SOPs can be consulted on site (11).

9.9 LIMITATIONS OF THE RESEARCH METHODS

9.9.1 Possible selection bias due to voluntary participation

The potential for selection bias of physicians participating in a survey is an inherent limitation to any study based on volunteer participation. In order to quantify any selection bias, the distribution of each stratification criterion of healthcare professional (country and specialty) 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 physicians 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 generalisation and external validity of the results is restricted to physicians who have an active email address and willing (and able) to answer a questionnaire online. These physicians may not be fully representative of the whole targeted population (12).

Among non-response bias, targeted physicians may also have activated filters in their mail box 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 physicians do not check their email box frequently they will not receive the invitation during the recruitment period. This is one of the reasons why the physicians will also be contacted by phone.

Moreover, web surveys may promote social desirability bias which refers to the tendency of physicians to give socially desirable/expected responses instead of choosing those reflecting their current knowledge or behaviour, e.g. physicians can copy-paste information gathered online instead of giving their own opinions (12).

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 (13).

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 with adjustment

As the study design presents an over-sampling in the Netherlands, of oncologists, anaesthesiologists and radiologists and an under-sampling in France and of GPs, the raw survey results will not be generalized to the overall target population, except if a sample adjustment is applied. For more transparency and accuracy, both unweighted (i.e. raw data) and weighted results will be presented in the report. Since the IMS list may identify a limited number of physicians who were not targeted with the educational material, the results may be impacted.

9.10 OTHER ASPECTS

None

10. PROTECTION OF HUMAN SUBJECTS

The survey is non-interventional and totally anonymous to the study sponsor. Data collected will remain absolutely confidential, and only aggregated data will be analysed 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. IMS will follow the European Pharmaceutical Marketing Research Association (EphMRA) code of conduct guidelines updated in February 2014 (14) for both countries, and specific local requirements will be applied as follows:

- In France:
  The LOI Bertrand (“Sunshine Act”), the law of 29 December 2011 on the reinforcement of the safety of medicines and health products (the “Act”), supplemented by a decree dated 21 May 2013 (the “Decree”), regarding transparency of the relations between healthcare companies and, notably, French-registered healthcare professionals will be followed.

  The Act states that companies which manufacture, market, or provide health products or services in relation to health products intended for human use must disclose the existence of the agreements they enter with players in the health sector, as well as any benefits that they grant to the same persons (13,15).

- In the Netherlands:
  The Dutch CGR (Code Geneesmiddelen Reclame) i.e. code for pharmaceutical advertising, regarding transparency of the relations between healthcare companies will be followed. The CGR Act states that a Dutch healthcare professional who entered into a financial relationship with a pharmaceutical company based abroad, have the obligation to register [the earnings] which lies with the healthcare professional.
  Moreover, the Dutch tax laws make necessary to store the confirmation of receipt of incentives, for the length of time required by law.

10.2 PHYSICIANS INFORMATION

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

10.2.1 Physicians compensations

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

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

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

10.3 CONFIDENTIALITY

10.3.1 Patient confidentiality

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

10.3.2 Data confidentiality / Data security

Participating physicians will access the website using an https secure link. This link is unique to each specific physician. The answers provided will be collected in an anonymous way, 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.

10.4 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/ADVERSE REACTIONS

11.1 ADVERSE EVENT COLLECTION

If an adverse event (AE) / adverse reaction (ARs) is detected in the survey or reported by the physician, it will be collected on a IMS Medical Radar (or Takeda) AE/PC collection form through the IMS Medical Radar AE electronic system, and forwarded by email to the sponsor within 24 hours after awareness.

The study operators will record the information related to Takeda drug under evaluation as defined in this protocol, regardless of whether there is an associated serious or non-serious AE:

Instruct investigators/study personnel to forward the following information for Takeda drug under evaluation in the study protocol to Takeda if the investigator/study personnel become aware of it, regardless of whether an associated serious adverse event (SAE) / serious adverse reaction (SAR) or non-serious adverse event/reaction exists:

- pregnancy exposures
- suspected transmission of infectious agent
- breast-feeding exposures
- overdoses
- misuse
- abuse
- off-label use
- medication error
- lack of drug effect

Takeda collects product complaints on investigational products and drug delivery systems used in medical research studies in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING SURVEY RESULTS

The survey will be registered in EU-PAS register (currently the ENCePP e-register of studies) by Takeda.

A survey report including the results of the two countries will be written in English, using Takeda or IMS Health template and following STROBE recommendations in MS Word format (9). It is planned to submit an abstract for consideration to the 2015 International Conference of Pharmaoepidemiology.

13. REFERENCES

1. Instanyl: Summary of Product Characteristics [Internet]. Available from: www.ema.europa.eu/...Product.../WC500033141.pdf
2. Instanyl: EPAR - Summary for the public [Internet]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000959/human_med_000838.jsp&mid=WC0b01ac058001d124
3. Haute Autorité de Santé. Instanyl – Transparency Committee opinion [Internet]. 2010 Jan. Report No.: CT 7206. Available from: http://www.has-sante.fr/portail/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. Curtin R, Presser S, Singer E. Changes in Telephone Survey Nonresponse over the Past Quarter Century. Public Opin Q. 2005 Mar 20;69(1):87–98.
6. Kellerman SE, Herold J. Physician response to surveys: A review of the literature. American Journal of Preventive Medicine. 2001 Jan;20(1):61–7.
7. 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. Advances in telephone survey methodology. 2007;499–528.
8. 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.
9. 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.
10. 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.
11. IMS data privacy obligations [Internet]. Available from: http://www.imshealth.com/portal/site/ims/menuitem.edb2b81823f67dab41d84b903208c22a/?vgnextoid=450e54de3ef51410VgnVCM10000076192ca2RCRD&vgnextfmt=default
12. Wyatt JC. When to Use Web-based Surveys. J Am Med Inform Assoc. 2000;7(4):426–9.
13. Nederhof AJ. Methods of coping with social desirability bias: A review. European Journal of Social Psychology. 1985;15(3):263–80.
14. EphMRA. Code of conduct 2013 [Internet]. 2013. Available from: http://www.ephmra.org/user_uploads/code%20of%20conduct%20oct%202013.pdf
15. LOI n° 2011-2012 du 29 décembre 2011 relative au renforcement de la sécurité sanitaire du médicament et des produits de santé. 2011-2012 décembre, 2011.

14. ANNEXES

Annex 1: List of stand-alone documents

Number	Document reference number	Date	Title
1-Protocol	Version 1	July 2014	Evaluation of the Effectiveness of Risk Minimisation Measures: A Survey among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of Instanyl® in France and the Netherlands
2-Questionnaire	Version 1	July 2014	Evaluation of the Effectiveness of Risk Minimisation Measures: A Survey among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of Instanyl® in France and the Netherlands
3-Educational material	Version X	July 2013	Educational material including: - nasal spray leaflet, - physician's guide to prescribing, - pharmacist guide to dispensing, - checklists (for prescribing and dispensing).
4-Updated SPC	Version X	May 2014	Summary of product characteristics

Annex 2: ENCePP checklist for study protocol

Study title:

Study reference number:

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

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

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☐	☐	☐	
2.1.2 The objective(s) of the study?	☐	☐	☐	
2.2.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☐	☐	☐	
2.2.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☐	
2.2.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☐	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☐	☐	☐	
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☐	☐	
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☐	

Comments:

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

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☐	☐	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☐	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☐	☐	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use	☐	☐	☐	

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
of validation sub-study)				

Comments:

Section 7: Confounders and Effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☐	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☐	

Comments:

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	☐	☐	☐	
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc.)	☐	☐	☐	
8.1.3 Covariates?	☐	☐	☐	
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☐	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☐	
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☐	
8.3 Is the coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☐	☐	☐	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☐	

Comments:

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☐	☐	☐	

Comments:

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☐	☐	☐	
10.2 Is the choice of statistical techniques described?	☐	☐	☐	
10.3 Are descriptive analyses included?	☐	☐	☐	
10.4 Are stratified analyses included?	☐	☐	☐	
10.5 Does the plan describe the methods for adjusting for confounding?	☐	☐	☐	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☐	

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	☐	☐	☐	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☐	☐	
11.3 Are methods of quality assurance described?	☐	☐	☐	
11.4 Does the protocol describe quality issues related to the data source(s)?	☐	☐	☐	
10.5 Is there a system in place for independent review of study results?	☐	☐	☐	

Comments:

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss: 12.1.1 Selection biases? 12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐ ☐	☐ ☐	☐ ☐	

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☐	
12.2 Does the protocol address other limitations?	☐	☐	☐	

Comments:

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

Comments:

Section 14: amendments and deviations	Yes	No	N/A	Page Number(s)
14.1 Does the protocol include a section to document future amendments and deviations?	☐	☐	☐	

Comments:

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

Comments:

Name of principle investigator: _____

Date: / / [DD/MM/YYYY]

Signature:

Annex 3: Additional information

1) Survey questionnaire