Post Authorization Safety Study (PASS) Information

Acronym/Title	Risk of anaphylactoid reactions of Iopromide after intra-arterial administration (UVIA Study)
Protocol version and date	v1.0 / 19 July 2018
IMPACT study number	19677
Study type / Study phase	PASS / Phase IV
EU PAS register number	Not yet registered
Active substance	Radiological / Low Osmolar non-ionic Contrast Medium (LOCM), (V08AB05) Iopromide
Medicinal product	Iopromide
Product reference	Not applicable
Procedure number	Not applicable
Study Initiator and Funder	Bayer AG
Research question and objectives	To describe the risk of anaphylactoid reactions of Iopromide after intra-arterial administration and to put these results into perspective to intra-venous administration.
Country(-ies) of study	Not applicable
Author	[redacted]

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG
MAH contact person	[redacted]

The study will be conducted in compliance with the protocol

and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

1. Table of contents

2. List of abbreviations

AE	Adverse Event
ADR	Adverse Drug Reaction
CI	Confidence Interval
CRF	Case Report Form
DMR	Data Management Report
HEOR	Health Economics and Outcomes Research
i.a.	intra-arterial
i.v.	intra-venous
IRB	Institutional Review Board
LOCM	Low Osmolar non-ionic Contrast Medium
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
OS	Observational Study
PASS	Post-Authorization Safety Study
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
QPPV	Qualified Person Responsible For Pharmacovigilance

3. Responsible parties

3.1 Study initiator and funder

Role: [redacted]
Name: [redacted]

Role: [redacted]
Name: [redacted]

Role: [redacted]
Name: [redacted]

Role: [redacted]
Name: [redacted]

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Role: [redacted]
Name: [redacted]

Role: [redacted]
Name: [redacted]

Contributing Medical Experts [redacted]

Contact details of the responsible parties at Bayer AG are available upon request.

3.2 Collaborator(s)/External partner(s)/Committee(s)

[redacted]

4. Abstract

Acronym/Title	Risk of anaphylactoid reactions of Iopromide after intra-arterial administration (UVIA Study)
Study type / Study phase	PASS / Phase IV
Authors	[redacted]
Rationale and background	Iopromide is on the market for >30 years and has been applied for >250 million times. While the safety profile, including risk of anaphylactoid reactions, after intra-venous administration has been widely investigated, rare data are available on the risk of anaphylactoid reactions after intra-arterial administration. The risk for anaphylactoid reactions after intra-arterial injections is assumed to be lower than after intra-venous injections as the mast cells in the lung might have a stimulating effect on immune reactions.
Research question and objectives	To describe the risk of anaphylactoid reactions of Iopromide after intra-arterial administration and to put these results into perspective to intra-venous administration.
Study design	Nested Case Control Analysis in a pooled cohort of 4 non-interventional studies with Iopromide
Population	Patients undergoing contrast enhanced CT scan for various reasons who received Iopromide by intra-arterial or intra-venous administration.
Variables	Number and proportion of anaphylactoid reactions
Data sources	Four company sponsored non-interventional studies with Iopromide
Study size	~120,000 records of patients with intravenous and ~ 30,000 with intra-arterial administration
Data analysis	Cases of anaphylactoid reactions will be identified following a preset case definition. Controls are patients without any ADR after the contrast administration. The exposure variable is defined as i.a. administration vs. i.v. administration of Iopromide. A crude case-control analysis will be conducted followed by a logistic regression model taking into account available confounder information (e.g. age, sex, history of allergy, premedication etc.) The entire planned analysis will be described in a statistical analysis plan. It will be finalized

	before the analysis starts.

5. Amendments

None

6. Milestones

Table 1: Milestones

Milestone	Planned date
Start of data collection	31 August 2010
End of data collection	30 September 2011
Registration in the EU PAS register	30 July 2018
Final report of study results	30 March 2019

7. Rationale and background

Iopromide (Ultravist) is a low osmolar non-ionic contrast medium (LOCM) with the active ingredient iodine (1, 2). Iopromide is on the market for more than 30 years and has cumulated >250 million applications. It is currently used in more than108 countries and administered to >15 million patients per year.

The overall safety, including rare anaphylactoid reactions, has been shown in numerous studies (3-6). For example, Kopp et al. reported 11 serious ADRs considered as anaphylactoid reactions to Iopromide in a post-marketing surveillance study in 74,717 patients (3). Mortele et al. prospectively recorded all adverse events (AEs) in a cohort of 29,508 consecutive patients in a hospital setting over 2 years (4). The overall incidence of AEs was 0.7%, with 161 cases of urticaria, 13 cases of facial or laryngeal edema and 13 cases of bronchospasm (4). Palkowitsch et al. analyzed the safety and diagnostic image quality of Iopromide in a large non-interventional observational study of European and Asian patients (IMAGE Study) in 44,835 patients showing and overall ADR rate of 2.8% including 243 patients (0.54%) suffering from urticaria, erythema, and/or rash (5). A specific focus on pediatric patients was the study concept of Dillman et al. Acute allergic-like reactions to the contrast material were documented in 20 (0.18%) of the patients (6). Three other publications raise the question of different safety profiles of different brands, at least in Asian population (7-9). This is a topic that is still in discussion.

All author teams concluded that adverse events (AEs) and adverse drug reactions, (ADRs), including anaphylactoid reactions are rare.

Eventually, a recent publication by Zhang et al. summarized the knowledge about incidence, classification and management of acute AEs to two low osmolar iodinated contrast media, Isovue and Iopromide in contrast-enhanced computed tomography by leveraging data from 137,473 patients (9).

However, despite the fact that the safety profile of Iopromide and all other iodinated contrast media is well understood, there is a continuous discussion pertaining to the nature of anaphylactoid reactions which are unpredictable and which can be very severe or even potentially lethal.

While the safety profile of Iopromide and the LOCM class is well established the majority of data is on procedures with intra-venous contrast administration. However, there is some evidence pointing to the fact that intra-venous and intra-arterial administration might lead to slightly different safety profiles specifically with respect to anaphylactoid reactions potentially caused by the lung passage after intra-venous administration. (3, 9, 10). The lung passage might have some - so far not-well understood - impact on immune reactions (11). However, this new aspect has not thoroughly been investigated yet and more conclusive evidence is needed.

Since anaphylactoid reactions are rare only a retrospective analysis on a large database bears the potential of answering this scientific question. Bayer has an ethical obligation to do so as only Bayer is in the possession of this large data set comprising this unique set of patients. Thus, the study presented here aims to investigate the risk of anaphylactoid reactions of Iopromide after intra-arterial administration and to put these results into perspective to data after intra-venous administration by analyzing the database consisting of four company sponsored non-interventional studies.

8. Research questions and objectives

8.1 Primary objective

The primary objective is to evaluate the risk of anaphylactoid reactions of Iopromide after intra-arterial administration compared to intravenous administration. This includes the evaluation of specific patient group with higher or lower risk.

8.2 Secondary objective(s)

The following research questions are secondary objectives:

1. Assess the proportion of patients with anaphylactoid reactions after intra-arterial administration of Iopromide
2. Assess the proportion of patients with anaphylactoid reactions after intra-venous administration of Iopromide
3. Assess the impact of pretreatment with histamines and/or corticosteroids
4. Evaluate the general ADR profile in the analysis population.

9. Research methods

9.1 Study design

The aim of the study is to investigate the anaphylactoid reactions of Iopromide after intra-arterial versus intra-venous administration. It is hypothesized that the lung passage might have some - so far not well understood - impact on immune reactions. This new aspect has not thoroughly been investigated yet and Bayer possesses the data and the capacities to elucidate this question.

The study will be an exploratory integrated pooled analysis of four company sponsored non-interventional studies with Iopromide. About 30,000 records of patients with intra-arterial and about 120,000 with intravenous administration will be analyzed. All studies have been published.

9.2 Setting

In this integrated analysis the data of four company sponsored non-interventional studies with Iopromide in contrast-enhanced X-ray examination will be pooled. The pool will consist of studies 'PMS I', 'Ultravist in CT', 'IMAGE', and 'TRUST'. In the year 2010, the three studies 'PMS I', 'Ultravist in CT' and 'IMAGE' were pooled and the general ADR profile was analyzed (12). The 'TRUST' study will be added to the existing pool to enrich the intra-arterial administration group.

The four studies were all sponsored by Bayer or Schering. They comprise all available prospective observational studies with primary data collection performed with Iopromide

These are:

- 'PMS I' was conducted in contrast-enhanced X-ray examination between June 1999 and November 2003 in 27 countries in Europe, Africa and Asia and comprised 74,717 patients (3) of which 65,452 patients received intra-venous and 8,368 patients intra-arterial administration.
- 'Ultravist in CT' was performed with focus on contrast-enhanced CT examination (intra-venous application) between November 2006 and December 2008 and included 15,168 patients in Germany, Iran, Romania and Saudi Arabia. (12)
- 'IMAGE' consists of 44,835 patients with contrast-enhanced X-ray examination and was conducted in 21 European and Asian countries from February 2008 to September 2009 (5), 41,703 patients received intra-venous administration, and 2,782 patients with intra-arterial administration.
- 'TRUST' assessed the safety and tolerability of Iopromide in patients undergoing cardiac catheterization (intra-arterial administration). It was conducted from August 2010 to September 2011 in China and included 17,513 patients (13).

In total, the data pool will consist of 152,233 patients. Table 2 shows the number of patients observed in the 4 studies.

Table 2: Number of patients observed in studies

	Number of patients		
Study	**Total**	**Intra-venous administration**	**Intra-arterial administration**
PMS I (3)	74,717	65,452	8,368
Ultravist in CT (12)	15,168	15,168	-
IMAGE (5)	44,835	41,703	2,782
TRUST (13)	17,513	-	17,513
Study total	152,233	122,323	28,663
Studies with iv and ia administration	119,552	107,155	11,150

9.2.1 Study population

The study population consists of patients who received a contrast enhanced x-ray based examination with Iopromide for various clinical reasons. Iopromide was administered either intra-venously or intra-arterially.

9.2.2 Study time frame

All 4 observational studies were finalized and reported. The study data will be pooled. Results and report are expected by 31 December 2018. No additional data will be collected.

9.2.3 Selection criteria

The four studies were all sponsored by Bayer or Schering. They comprise all available prospective observational studies with primary data collection. No further studies are available.

9.2.4 Representativeness

This analysis will not include new and not yet published data. Its representativeness depends on sampling and recruiting of the underlying studies. In total, about 150,000 patients of all age groups, both sexes, multiple ethnicities and a large variety of diseases/indications from 37 countries world-wide were documented. Large unselected patient populations were enrolled in Europe (mostly in Germany and Spain), Asia (mostly in China and Korea) and North America (mostly in USA) in daily routine settings which should result in high representativeness for these geographical regions. The risk of selection bias is considered as low. Thus, the population included in the four studies (see table 2) is considered to be broadly representative of patients receiving Iopromide in the respective indications.

9.3 Variables

The primary variables to answer the study objectives are the number and percentage of anaphylactoid reactions which were documented in the observational studies. Drug-relatedness was assessed by the health care professionals.

During the mapping of the four studies, categories of variables will be harmonized. For example, categories which describe the same concomitant disease but with different terms will be mapped to the same category (see section 9.6).

9.3.1 Exposure definition

The integrated analysis will evaluate those patients who have received Iopromide (iodine concentrations of 300 mg/mL or 370 mg/mL) either intra-venously or intra-arterially. The investigators were asked to comply with the local package insert. During the study period there were no major relevant label changes in any country affecting the study population (age, indications) or dosing.

9.3.2 Outcomes definition

For the nested case-control analysis cases and controls are defined as follows:

Cases: Patients with a typical and unequivocal anaphylactoid, i.e., allergy-like reaction: Anaphylactoid shock, angioedema, asthma, bronchospasm, conjunctivitis, cough, dysphagia,

dyspnea, edema mucosal, erythema/exanthema/rash, hoarseness, lacrimation, laryngeal/pharyngeal/face edema, laryngeal/pharyngeal spasm, nasal stuffiness, pruritus/itching, respiratory arrest, rhinitis, sneezing, stridor, swelling (eyes/face), throat irritation, tongue edema, urticaria/hives/blisters, wheezing.

Control group: Patients without any reported AE

9.3.3 Covariate definition

In this study covariates of interest are:

- patient characteristics (age, sex, race, geographic region)
- concomitant diseases (risk factors)
- pre-treatment (corticosteroids, H1/H2 blocker)
- administration of Iopromide, e.g. dose and iodine concentration

9.4 Data sources

The study will be conducted by pooling data of four company sponsored non-interventional studies with iopromide (see section 9.2).

9.5 Study size

About 122,000 records of patients with intra-venous and approx. 28,000 patients with intra-arterial administration are expected for evaluation. The sample size is determined by the available data from the four studies that will be analyzed.

In the previous pooled analysis of three non-interventional studies with Iopromide (12) the incidence of drug-related erythema, urticarial and rash was 0.3%. Using this result as the assumption for this integrated analysis the 95% confidence interval of this specific ADR in the entire pool of about 150,000 patients is [0.27%; 0.33%]. Assuming an equal incidence rate for the two sub-populations, the 95% CI would be [0.27%; 0.33%] for patients with intra-venous administration, and [0.24%; 0.37%] for patients with intra-arterial administration which would be considered sufficiently precise.

9.6 Data management

A pool of three of the four studies were prepared in 2010 (12). It contains the studies 'PMS I', 'Ultravist in CT' and 'IMAGE'. The 'TRUST' study will be added to the existing pool. Variables will be mapped to the corresponding variables in the existing pool. Categories (technically displayed in code lists) will be modified if necessary. A Data Management Report (DMR) will be prepared which describes rules and decisions which were made during the preparation of the mapping. No data correction will be performed.

During data integration, the MedDRA coding of adverse event will be updated to the same most current MedDRA version.

Procedures for the anonymization of the database will be implemented e.g. patient identifies from the original studies will be replaced by randomly generated identifiers, birth dates will be replaced by year only, patient initials, investigator site identifiers and verbatim texts for adverse events will

be eliminated. The data changes can be listed in a self-evident correction list that will be attached to the Data Management Report.

9.7 Data analysis

Statistical analyses will be of exploratory and descriptive nature only. No confirmatory hypothesis tests will be performed. In case that statistical test is performed p-values will be interpreted as a metric for uncertainty thus no adjustment for multiplicity is necessary.

All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum / median / maximum quantiles). Continuous variables will be described by absolute value and as change from baseline, if applicable. Results will be presented by the type of Iopromide administration.

The analysis population will consist of all patients of the study pool which received an injection (intra-arterial or intra-venous) with Iopromide of the iodine concentrations of 300 mg/mL or 370 mg/mL at the discretion of the Radiologist. A disposition table will be prepared to describe the number of patients which were not valid for analysis.

Records which contain missing data in variables needed for the analysis will be excluded. No imputation will be done.

All statistical details including calculated variables and proposed format and content of tables, listings and figures will be detailed in the Statistical Analysis Plan (SAP). The SAP will be finalized before the analysis starts.

9.7.1 Analysis of population characteristics

All background data such as subject demographics, specific concomitant diseases, specific risk factors like previous moderate or severe acute reaction to an iodine-base contrast agent, unstable asthma, atopy requiring medical treatment, pre-medication, examination region, type of examination and indication for the application of Iopromide will be described with summary statistics.

Concentration of Iopromide will be summarized and total dose of Iopromide applied will be calculated for each patient (ml and g iodine).

9.7.2 Analysis for the primary objective

Cases of anaphylactoid reactions will be identified following a preset case definition. Controls are patients without any ADR after the contrast administration. The exposure variable of interest is defined as i.a. administration vs. i.v. administration of Iopromide. A crude odds ratio with 95 % CI of the risk of anaphylactoid reactions for i.a. vs. i.v. administration will be calculated in the case-control analysis. Furthermore, unconditional, univariate logistic regression models will be computed to identify relevant covariates (e.g. history of allergy, premedication etc.) and potential confounder. A covariate is considered as important when its effect, represented by a descriptive p-value, is below 0.1. Age and sex will always be included as a covariate. Subsequently, the covariates identified in the univariate regression models will be brought together in a multivariate logistic regression model in order to identify the individual effect on the occurrence of anaphylactoid reactions. No matching on confounders will be performed in the case-control analysis.

9.7.3 Analysis for the secondary objectives

The topic of the secondary objectives will be addressed by means of frequency and summary tables. For example, incidence tables about the incidence of anaphylactoid reactions and the corresponding preferred terms by type of administration.

9.8 Quality control

Data quality relies on the source data of the integrated observational studies. The data in these studies were captured by paper or electronic CRFs. No checks for multiple documented patients will be done because multiple documentation is unlikely given the different years and regions where the studies were conducted.

9.9 Limitations of the research methods

This is an integrated analysis on pooled data from four non-controlled, multi-center, observational cohort studies. The four studies were conducted in different years and in different countries and geographic regions all over the world. Nearly 45% of the pooled patients were enrolled in Europe and a group of 45% of the observed patients were enrolled in China. Geographical and cultural differences in the reporting of adverse events are possible.

Since i.a. administrations of contrast agents can result in procedure related adverse reactions (e.g. blood pressure drop, arrhythmia, dizziness, nausea) some of which can also be symptoms of anaphylactoid reactions, the case definition in the present study is restricted to typical and unequivocal cases of anaphylactoid reactions which cannot be caused by the catheterization procedure. This restriction to typical anaphylactoid reactions removes confounding by indication and should yield a valid odds ratio estimate in the nested case-control analysis.

Statistical adjustment for country / geographic region may be limited by the fact that more than half of exposures in i.a. administration stems from one study only conducted in one country (China).

Since the observation time of the patients in the observational studies used in this analysis was 30-60 minutes after the procedure, late-onset anaphylactoid reactions occurring hours or days after injection are not captured.

10. Protection of human subjects

The data involved in the UVIA study may involve special categories of personal data according to Art. 9 General Data Protection Regulation (Regulation (EU) 2016/679) (GDPR).

The UVIA study will investigate the safety profile of Iopromide and it supports ensuring high standards of quality and safety of health care and of medicinal products. Accordingly, the processing of the data in the context of the UVIA study should be based on Art. 9(2)(i) GDPR and on Section 22(1)(1c) of the German Act to Adapt Data Protection Law to Regulation (EU) 2016/679 and to Implement Directive (EU) 2016/680 (DSAnpUG-EU).

Furthermore, the UVIA study is a research study that aims at answering scientific questions. The processing is necessary for scientific purposes therefore can also be justified based on Art. 9(2)(j) GDPR in connection with Section 27 DSAnpUG-EU. Additional safeguards will be applied as described under section 9.6.

11. Management and reporting of adverse events/adverse reactions

As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products), for non-interventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required. Reports of adverse events/reactions will be summarized in the study report (European Medicines Agency 2012).

12. Plans for disseminating and communicating study results

Study results will be presented in a study report following the STROBE checklist. The study results will be published in an international peer-reviewed journal, e.g. Acta Radiologica, Clinical Radiology or European Journal of Radiology.

13. References

1. Krause W MH, Kollenkirchen U, Heimann G. Physicochemical Parameters of X-Ray Contrast Media. Invest Radiol. 1994;29(1):72-80.

2. Goldstein HA JG, Wiggins JR. New Clinical Trial Experience with Ultravist. Invest Radiol. 1994;29(Supplement 2):208-10.

3. Kopp AF, Mortele KJ, Cho YD, Palkowitsch P, Bettmann MA, Claussen CD. Prevalence of acute reactions to Ultravist: postmarketing surveillance study of 74,717 patients. Acta Radiol. 2008 Oct;49(8):902-11.

4. Mortele KJ, Oliva MR, Ondategui S, Ros PR, Silverman SG. Universal use of nonionic iodinated contrast medium for CT: evaluation of safety in a large urban teaching hospital. AJR Am J Roentgenol. 2005 Jan;184(1):31-4.

5. Palkowitsch P, Lengsfeld P, Stauch K, Heinsohn C, Kwon ST, Zhang SX, et al. Safety and diagnostic image quality of Ultravist: results of a large non-interventional observational study of European and Asian patients (IMAGE). Acta Radiol. 2012 Mar 01;53(2):179-86.

6. Dillman JR, Strouse PJ, Ellis JH, Cohan RH, Jan SC. Incidence and severity of acute allergic-like reactions to i.v. nonionic iodinated contrast material in children. AJR Am J Roentgenol. 2007 Jun;188(6):1643-7.

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8. Kim SR, Lee JH, Park KH, Park HJ, Park JW. Varied incidence of immediate adverse reactions to low-osmolar non-ionic iodide radiocontrast media used in computed tomography. Clin Exp Allergy. 2017 Jan;47(1):106-12.

9. Zhang B, Dong Y, Liang L, Lian Z, Liu J, Luo X, et al. The Incidence, Classification, and Management of Acute Adverse Reactions to the Low-Osmolar Iodinated Contrast Media Isovue and Ultravist in Contrast-Enhanced Computed Tomography Scanning. Medicine (Baltimore). 2016 Mar;95(12):e3170.

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11. Schild H. CM to See or not to See. Schering Diagnositics 1994. ISBN 3-921817-56-0.

12. Palkowitsch PK, Bostelmann S, Lengsfeld P. Safety and tolerability of Ultravist intravascular use: a pooled analysis of three non-interventional studies in 132,012 patients. Acta Radiol. 2014 Jul;55(6):707-14.

13. Chen JY, Liu Y, Zhou YL, Tan N, Zhang B, Chen PY, et al. Safety and tolerability of Ultravist in patients undergoing cardiac catheterization: real-world multicenter experience with 17,513 patients from the TRUST trial. Int J Cardiovasc Imaging. 2015 Oct;31(7):1281-91.

Annex 1: List of stand-alone documents

Table 3: List of stand-alone documents

Document Name	**Final version and date (if available)***
SAP (*tf*)	*< dd MMM yyyy >*
DMP (tf)	*< dd MMM yyyy >*

* Draft versions are indicated by <draft> in brackets and date. “tbd” indicates documents that are not available at the time of protocol creation, but will be issued at a later stage

Annex 2: ENCePP checklist for post-authorization safety study (PASS) protocols

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

Study title: Safety profile of Iopromide after intra-arterial administration (UVIA Study)

Study reference number: 19677

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]	X	☐	☐	9
1.1.2 End of data collection[2]	X	☐	☐	9
1.1.3 Study progress report(s)	☐	☐	X	
1.1.4 Interim progress report(s)	☐	☐	X	
1.1.5 Registration in the EU PAS register	X	☐	☐	9
1.1.6 Final report of study results.	X	☐	☐	9

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)	X	☐	☐	9
2.1.2 The objective(s) of the study?	X	☐	☐	9
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	X	☐	☐	9
2.1.4 Which formal hypothesis (-es) is (are) to be tested?	X	☐	☐	9
2.1.5 If applicable, that there is no *a priori* hypothesis?	X	☐	☐	9

[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 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**

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, new or alternative design)	X	☐	☐	10
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	X	☐	☐	10
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	X	☐	☐	9
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	X	☐	☐	9
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)	X	☐	☐	16

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	X	☐	☐	10
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	X	☐	☐	10
4.2.2 Age and sex?	X	☐	☐	10
4.2.3 Country of origin?	X	☐	☐	10
4.2.4 Disease/indication?	X	☐	☐	10
4.2.5 Duration of follow-up?	X	☐	☐	10
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	X	☐	☐	

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	X	☐	☐	12

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
categorizing 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)	X	☐	☐	12
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	X	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the product?	X	☐	☐	12

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?	X	☐	☐	12
6.2 Does the protocol describe how the outcomes are defined and measured?	X	☐	☐	12
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	X	☐	☐	12
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	X	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	X	☐	☐	12
7.1.1. Does the protocol address confounding by indication if applicable?	X	☐	☐	12
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	X	☐	☐	12
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☐	X	
7.3 Does the protocol address the validity of the study covariates?	X	☐	☐	12

Comments:

Section 8: Effect 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)	X	☐	☐	12

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)	X	☐	☐	12
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	X	☐	☐	12
9.1.3 Covariates?	X	☐	☐	13
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)	X	☐	☐	12
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	X	☐	☐	12
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	X	☐	☐	13
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	X	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	X	☐	☐	13
9.3.3 Covariates?	☐	☐	X	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	X	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	X	☐	☐	14
10.2 Are descriptive analyses included?	X	☐	☐	14
10.3 Are stratified analyses included?	X	☐	☐	14
10.4 Does the plan describe methods for adjusting for confounding?	X	☐	☐	14

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.5 Does the plan describe methods for handling missing data?	X	☐	☐	14
10.6 Is sample size and/or statistical power estimated?	X	☐	☐	14

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)	X	☐	☐	13
11.2 Are methods of quality assurance described?	X	☐	☐	13
11.3 Is there a system in place for independent review of study results?	X	☐	☐	13

Comments:

DMR would provide information on section 11.

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?	☐	☐	X	
12.1.2 Information bias?	☐	☐	X	
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)	☐	☐	X	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	X	☐	☐	12

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?	☐	☐	X	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	X	
13.3 Have data protection requirements been described?	X	☐	☐	15

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?	X	☐	☐	9

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)?	X	☐	☐	16
15.2 Are plans described for disseminating study results externally, including publication?	X	☐	☐	16

Comments:

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

Date: / /

Signature: _____

Annex 3: Additional information

None

Annex 4: Signature pages