NOVARTIS

Global Clinical Development – General Medicine

Non-Interventional Study Protocol

CVOL458A2001

Title	Usage Patterns of Selected Systemic NSAIDs (Including Diclofenac): A Retrospective Cohort Study
Protocol version identifier	v00
Date of last version of protocol	05 August 2015
EU PAS Register number	Study not yet registered
Active substance	M01AB05 (diclofenac), M01AC06 (meloxicam), M01AE01 (ibuprofen), M01AE02 (naproxen), M01AE03 (ketoprofen), M01AH01 (celecoxib), M01AH05 (etoricoxib)
Medicinal product	Not applicable
Product reference	Not applicable
Procedure number	Not applicable
Name of Marketing authorization holder(s)	Novartis Pharma
Joint PASS	No
Research question and objectives	Conduct a retrospective cohort study to describe the usage patterns of selected systemic NSAIDs (nonsteroidal anti-inflammatory drugs) using information from selected

	population-based health care automated databases in Europe and North America. The study aims to accomplish the following: • Describe demographic characteristics, specific comorbidities, selected comedications, and selected potential indications for use among patients treated with selected systemic NSAIDs (including diclofenac). • Describe treatment patterns, including, dose, duration of treatment, and switching patterns, among patients treated with selected systemic NSAIDs (including diclofenac).
Country (-ies) of study	United Kingdom, United States of America
Author	[redacted]

Marketing authorization holder(s)

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

1 Table of contents

List of figures

List of tables

2 List of abbreviations

ATC	Anatomical Therapeutic Chemical
CCAE	Commercial Claims and Encounters Database (MarketScan)
CPRD	Clinical Practice Research Datalink
DDD	Defined Daily Dose
DMARD	Disease Modifying Antirheumatic Drug
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GOLD	Online database containing data collected in primary care practices; part of the CPRD in the United Kingdom
GP	General Practitioner
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
H2	A type of histamine receptor
HES	Hospital Episode Statistics
ICD-9-CM	The International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10	*International Statistical Classification of Diseases and Related Health Problems, 10th Revision*
IRB	Institutional Review Board
ISAC	Independent Scientific Advisory Committee
ISPE	International Society for Pharmacoepidemiology
MAH	Marketing Authorization Holder
MDCR	Medicare Supplemental and Coordination of. Benefits Database (MarketScan)
MPR	Medication Possession Ratio
MREC	Multi-centre Research Ethics Committee
NSAID	Nonsteroidal Anti-inflammatory Drug
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PSUR	Periodic Safety Update Report
Q*n*	Quarter of a Calendar Year
RTI-HS	RTI Health Solutions
SNRI	Serotonin and Noradrenaline Reuptake Inhibitors
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TNF	Tumor Necrosis Factor
UK	United Kingdom
US	United States
WHO	World Health Organization

3 Responsible parties

Table 3-1 Main responsible parties

Role	Person
Main protocol authors	[redacted]
Principal investigator (PI)	[redacted]
MAH contact person	[redacted]

4 Abstract

Title

Usage Patterns of Selected Systemic NSAIDs (including diclofenac): A Retrospective Cohort Study

Version and date

Final 0.0, 05 August 2015

Name and affiliation of main author

Elena Rivero Ferrer, MD, MPH

Director Epidemiology, RTI Health Solutions

Rationale and background

NSAIDs (nonsteroidal anti-inflammatory drugs) are widely used medications for the treatment and management of a number of painful and inflammatory conditions. Evidence accumulated on the safety profile of NSAIDs in the last decade has led to the development of guidelines and recommendations for use in recent years, which may have influenced changes in the characteristics of NSAID users and in the patterns of NSAID use.

Even though NSAIDs are widely used, there are gaps in the knowledge of utilization and treatment patterns of these medications. The influence of demographic characteristics like age and sex, comorbidities, and indications on the selection of and treatment with NSAIDs is unclear. Information on switching between doses and NSAIDs and the duration of treatment is limited.

Novartis seeks to conduct a retrospective cohort study to describe the usage pattern of selected systemic NSAIDs including diclofenac using the most recent information available from select population-based health care automated databases in Europe and North America.

Research question and objectives

The study aims to accomplish the following:

- Describe demographic characteristics, specific comorbidities, selected comedications, and selected potential indications for use among patients treated with selected systemic NSAIDs (including diclofenac)
- Describe treatment patterns, including dose, duration of treatment, and switching patterns, among patients treated with selected systemic NSAIDs (including diclofenac)

Study design

This will be a non-interventional, descriptive, retrospective drug utilization study, using a cohort design, of users of selected systemic NSAIDs.

Setting

The study will be conducted in two large populations covered through automated health care databases, the Clinical Practice Research Datalink (CPRD) in the United Kingdom (UK) and Truven Health Analytics' MarketScan Commercial Claims and Encounters Database (Commercial Database) and MarketScan Medicare Supplemental and Coordination of Benefits Database (Medicare Supplemental Database) in the United States (US).

In each database, patients aged 18 years or older receiving or filling a prescription for any of the selected systemic NSAIDs (diclofenac, meloxicam, ibuprofen, naproxen, ketoprofen, celecoxib, etoricoxib) at any time from October 1, 2012, to September 30, 2013, in the MarketScan databases and from May 1, 2013, to April 30, 2014, in the CPRD will be eligible to enter the study cohorts of *prevalent users*.

A subpopulation of *new users* of each specific NSAID will be identified among the overall population of *prevalent users*. *New users* are defined as those members of the study cohort who had no recorded prescriptions for any NSAID during the 12 months before the index date. An individual will be categorized into one of the mutually exclusive cohorts of NSAID *new users*. *New users* will be followed for 1 year.

Variables

Demographic characteristics

Age as of the index prescription and sex will be variables used to describe the populations of *prevalent* and *new* NSAIDs users.

Geographic region, payer, and health plan type will be variables used to describe *prevalent* and *new* NSAID users only in the MarketScan databases.

Lifestyle variables

Smoking will be assessed in *prevalent* and *new* NSAID users in the CPRD only. Smoking history will be categorized as current, past, and never smoked based on information as recorded by the GP.

Other lifestyle factors will be assessed in *prevalent* and *new* NSAID users based on diagnosis codes for conditions suggesting obesity, alcohol abuse or dependence, and drug abuse that are included among the specific comorbidities.

Specific comorbidities

Specific comorbid diagnoses relevant to NSAID treatment will be assessed among *prevalent* and *new users* of selected systemic NSAIDs based on historical information of inpatient and outpatient diagnosis and procedure codes available before the index date. Based on the available information on comorbidities, a modified version of the Charlson comorbidity index score will be computed as an overall summary of the patient's comorbidity.

Selected comedications

Use of selected other medications will be assessed in the year before and including the index date among *prevalent* and *new users* of selected systemic NSAIDs.

Health care resource use

The number of hospitalizations, emergency department visits, and outpatient specialist visits/referrals in the year before the index date will be ascertained among *prevalent* and *new users* of selected systemic NSAIDs

Specialty of prescribing physician

The type of prescriber of each initiating treatment with the selected NSAID will be ascertained among *prevalent* and *new users* in the MarketScan databases for the index prescription. The CPRD captures prescriptions only from general practitioners.

Selected potential indications

Selected potential indications relevant to NSAID treatment will be assessed among *new users*. All diagnosis and surgical procedure codes recorded within 2 months before and 1 month after the index date will be tabulated by rank frequency. Diagnoses found in at least 5% of NSAID users will be considered to be the potential clinical condition for which NSAIDs have been prescribed.

Dose

Among *new users* of each specific NSAID, the daily dose will be evaluated for the index and all subsequent consecutive prescriptions. The distribution of the daily prescribed dose associated with the index prescription will be described for all *new users* of selected NSAIDs.

Duration of treatment

Duration of treatment will be assessed among *new users* of selected systemic NSAIDs. For each prescription, duration of treatment will be defined by the days' supply. Duration of treatment will be estimated through the number of consecutive prescriptions or the days' supply of each prescription, as available in each database. A treatment episode is defined as consecutive prescriptions until no more prescriptions are found by the end date of the days' supply of the last prescription plus a grace period of 30 days.

Persistence and adherence

Persistence is defined as the duration of time (days) from initiation to discontinuation of NSAID treatment. It will also be assessed as the proportion of patients who continue refilling prescriptions within 30 days from the end of the previous prescription at given points in time within the 1-year of follow-up.

Medication adherence will be measured by means of the medication possession ratio and the proportion of days covered.

Use of multiple NSAIDs

Use of multiple NSAIDs will be defined as a prescription for an NSAID different from the index NSAID that was filled during the days' supply window plus the 30-day grace period of the index NSAID, provided there are consecutive prescriptions for the index NSAID.

Switching

NSAID switching will be defined as filling or receiving a subsequent prescription for a different NSAID during the calculated duration of the treatment episode of an existing NSAID prescription, plus a 30-day grace period, provided there is no other subsequent prescription for the initial NSAID.

NSAID *dose* switching will be defined as any change in the dose category defined for the specific NSAID during the first treatment episode.

Data sources

The data for this study will be retrieved from the CPRD in the UK and Truven Health Analytics' MarketScan Commercial Database and Medicare Supplemental Database in the US.

Study size

This is a descriptive study, and no formal sample size calculation has been performed. The expected number of eligible patients could range from 400,000 NSAID users in the CPRD to over 3 million in the MarketScan databases.

Data analysis

All study measures described above will be analyzed descriptively through the tabular and graphical display of mean values, medians, ranges, and standard deviations for continuous variables of interest and proportions for categorical variables (with corresponding 95% confidence intervals, as appropriate).

The following analyses will be conducted in the NSAID cohorts of *prevalent users*:

- Age- and sex-specific prevalence of use of each specific NSAID

The following analyses will be conducted and tabulated separately for each of the specific NSAID cohorts of *prevalent* and *new users*:

- Demographic characteristics at the index date
- For MarketScan databases only, the percentage distribution by the following variables:
    - Geographic region

  - Payer
  - Health plan type
  - Specialty of prescribing physician
- Number and proportion of patients according to the following characteristics:
  - Specific comorbidities and categories of Charlson comorbidity index
  - Selected comedications
  - Categories of health care resource use

The following analyses will be conducted and tabulated separately for each of the specific NSAID cohorts of *new users*:

- Rank frequency distribution of identified selected potential indications that occur in at least 5% of new users
- Total number of prescriptions and descriptive statistics for number of prescriptions per patient during the 1-year follow-up period
- Number of NSAID treatment episodes and descriptive statistics within the 1-year follow-up period
- Proportion of patients by number of treatment episodes (e.g., 1, 2, 3, ≥ 4) within the 1-year follow-up period
- Proportion of patients by daily dose category at the index prescription and descriptive statistics of daily dose
- Proportion of patients by categories of duration of the first treatment episode and descriptive statistics of duration
- Proportion of patients by categories of dose by duration of the first treatment episode
- Proportion of patients with evidence of multiple NSAID use during the first treatment episode, and proportion of each specific NSAID added on
- Proportion of patients with evidence of NSAID switch during the first treatment episode, and cross-tabulation of initial and “switched to” NSAID
- Proportion of patients with evidence of NSAID *dose* switch during the first treatment episode, and cross-tabulation of initial and “switched to” *dose*
- Descriptive statistics of the total number of days’ supply of the prescribed NSAID within the 1-year follow-up period
- Descriptive statistics of time to discontinuation of first treatment episode, time to NSAID switch, and time to NSAID dose switch
- Survival analysis will be used to describe the cumulative proportion of patients discontinuing the first NSAID treatment episode. Patient-persistence curves will be used to depict the proportion of patients who were persistent with each NSAID at any given point in time within the 1-year of follow-up period
- Descriptive statistics of the medication possession ratio and the proportion of days covered.

Milestones

- Registration in the EU PAS Register: before start of data collection
- Start of data collection: August 10, 2015 (tentative)
- End of data collection: September 25, 2015 (tentative)
- Final report of study results: March 16, 2016 (tentative)

5 Amendments and updates

None

6 Milestones

Table 6-1 PASS milestones

Milestone	Planned date
Registration in the EU PAS Register	Before start of data collection
Start of data collection[a]	August 10, 2015
End of data collection[b]	September 25, 2015
Final report of study results	March 16, 2016

[a] Start of data collection: In the case of secondary use of data, the date from which data extraction starts.

[b] End of data collection: The date from which the analytical dataset is completely available.

7 Rationale and background

NSAIDs (nonsteroidal anti-inflammatory drugs) are widely used medications for the treatment and management of a number of painful and inflammatory conditions. Evidence accumulated on the safety profile of NSAIDs in the last decade has led to the development of guidelines and recommendations for use of NSAIDs in recent years. These guidelines and recommendations may have influenced changes in characteristics of NSAID users and in the patterns of NSAID use.

Even though NSAIDs are widely used, there are gaps in the knowledge of utilization and treatment patterns of these medications. Influence of demographic characteristics like age and sex, comorbid conditions, and indications on the selection of and treatment with NSAIDs is unclear. Evidence on switching between doses and NSAIDs and the duration of treatment is limited.

This retrospective cohort study aims to answer these knowledge gaps. Novartis has voluntarily initiated this post-authorization safety study (PASS) to describe the pattern of use of selected systemic NSAIDs, including diclofenac, using the most recent information available from selected population-based health care automated databases in Europe and North America. The study is expected to contribute to a better understanding of the characteristics of systemic NSAID users and patterns of systemic NSAID use.

8 Research question and objectives

This is a retrospective cohort study that aims to describe the usage patterns of selected systemic NSAIDs (i.e., diclofenac, meloxicam, ibuprofen, naproxen, ketoprofen, celecoxib, etoricoxib) using information from selected population-based health care automated databases in Europe and North America. More specifically, the study aims to accomplish the following:

- Describe demographic characteristics, specific comorbidities, selected comedications, and selected potential indications for use among patients treated with selected systemic NSAIDs (including diclofenac)
- Describe treatment patterns, including dose, duration of treatment, and switching patterns, among patients treated with selected systemic NSAIDs (including diclofenac)

9 Research methods

9.1 Study design

This will be a non-interventional, descriptive, retrospective drug utilization study, using a cohort design, of users of selected systemic NSAIDs (including diclofenac). The study will be conducted in two large populations covered through automated health care databases, the Clinical Practice Research Datalink (CPRD) in the United Kingdom (UK) and Truven Health Analytics' MarketScan Commercial Claims and Encounter Database (Commercial Database) and Medicare Supplemental and Coordination of Benefits Database (Medicare Supplemental Database) in the United States (US). Both are large, longitudinal databases with extensive detail on medical services provided to individual patients.

9.2 Setting

In each database, patients aged 18 years or older receiving or filling a prescription for any of the selected systemic NSAIDs at any time during a period of 1 year (cohort assembly period) will be eligible to enter in the study cohorts of *prevalent users*. The selected NSAIDs are the following: diclofenac (ATC M01AB05), meloxicam (ATC M01AC06), ibuprofen (ATC M01AE01), naproxen (ATC M01AE02), ketoprofen (ATC M01AE03), celecoxib (ATC M01AH01), and etoricoxib (ATC M01AH05). Etoricoxib is not marketed in the US; therefore, users of etoricoxib will be ascertained only in the CPRD. The selected NSAIDs represent more than 80% of NSAID users in each data source.

The cohort assembly period will be the most recent 1-year period of data available in each database that allows 1 year of follow-up data after inclusion of the last patient. This period will be from October 1, 2012, to September 30, 2013, in the MarketScan databases and from May 1, 2013, to April 30, 2014, in the CPRD.

The overall study period will be from October 1, 2012, to September 30, 2014, in MarketScan databases and from May 1, 2013, to April 30, 2015, in the CPRD.

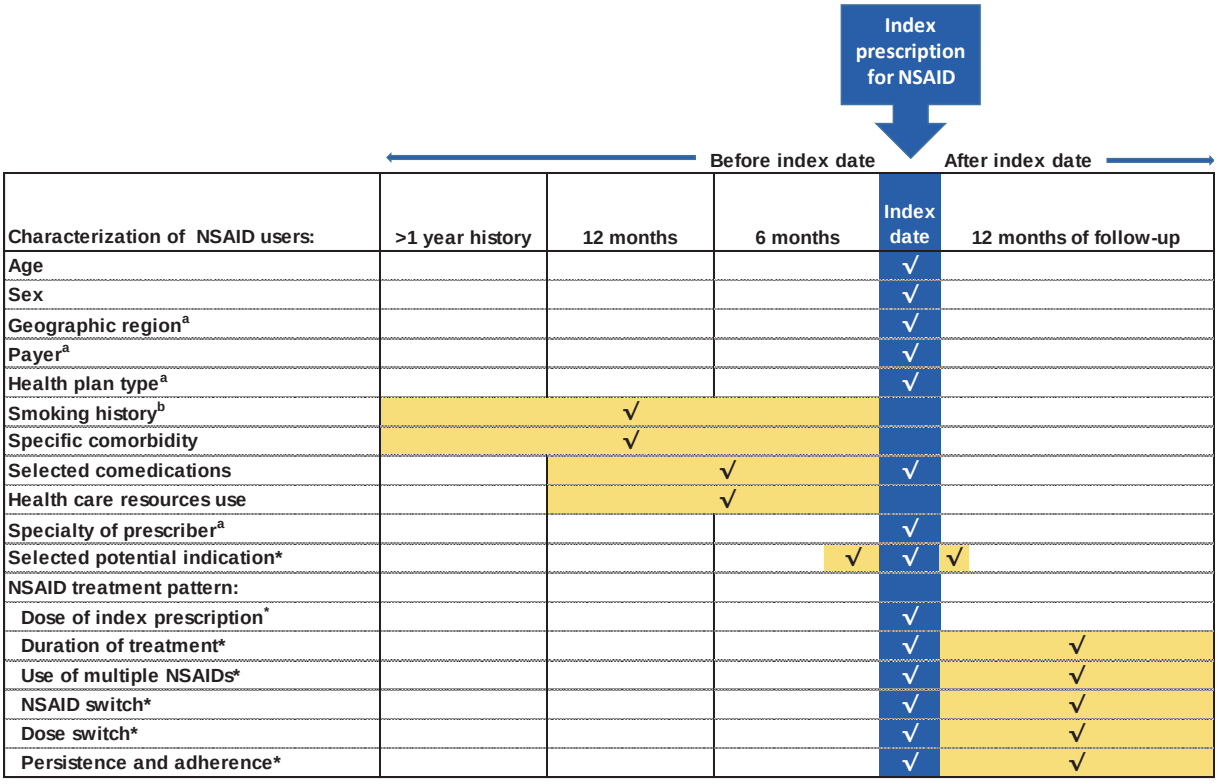
To ensure adequate time to assess patient comorbidities and prior NSAID use, patients will be required to have at least 12 months of continuous enrollment in the database before their first (index) prescription/dispensing. The index date will be defined as the date of the first captured prescription for an NSAID recorded within the cohort assembly period (with or without previous NSAID prescriptions). Patients will be assigned to a specific NSAID cohort of *prevalent users* based on the first prescription for that NSAID during the cohort assembly period. An individual patient may be assigned to more than one cohort of *prevalent users* if he/she has received or filled a prescription for more than one of the selected NSAIDs during this period.

A subpopulation of *new users* of each specific NSAID will be identified among the overall *prevalent users* population. *New users* are defined as those members of the study cohort who had no recorded prescriptions for any NSAID during the 12 months before the index date. An individual will be categorized into one of the mutually exclusive cohorts of NSAID *new users*. *New users* will be followed for 1 year. The follow-up will start on the index date and will finish at the earliest of the following dates: 1 year after the index date, death, disenrollment from the database, or end of study period.

Prevalent users of each specific NSAID will be characterized at the index date according to age, sex, prior specific comorbidities, selected comedications, and health care resource use. Geographic region, payer, health plan type, and specialty of the prescribing physician are characteristics that will be assessed only in users in the MarketScan databases.

New users of each specific NSAID will be characterized (1) at the index date according to age, sex, prior specific comorbidities, selected comedications, health care resource use, and selected potential indication; geographic region, payer, health plan type, and specialty of the prescribing physician will be assessed only in users in the MarketScan databases, and (2) during the 1-year follow-up period to assess the pattern of use of the NSAID including duration, dose, use of more than one NSAID, switching, and persistence and adherence to therapy (Figure 9-1).

Figure 9-1 Overview of study design



Characterization of NSAID users:	>1 year history	12 months	6 months	Index date	12 months of follow-up
Age				√	
Sex				√	
Geographic region[a]				√	
Payer[a]				√	
Health plan type[a]				√	
Smoking history[b]	√				
Specific comorbidity	√				
Selected comedications		√		√	
Health care resources use		√			
Specialty of prescriber[a]				√	
Selected potential indication*			√	√	√
NSAID treatment pattern:					
Dose of index prescription*				√	
Duration of treatment*				√	√
Use of multiple NSAIDs*				√	√
NSAID switch*				√	√
Dose switch*				√	√
Persistence and adherence*				√	√

NSAID = nonsteroidal anti-inflammatory drug.

[a] Characteristic to be assessed only in NSAID users in MarketScan databases.

[b] Characteristic to be assessed only in NSAID users in the CPRD.

Note: An * indicates characteristics to be assessed only in the subset of patients that qualify as *new users*.

9.3 Variables

9.3.1 Demographic variables

Age at the index prescription and sex will be variables used to describe the populations of *prevalent* and *new* NSAID users. Age will be calculated at the index date from the date of birth and will be categorized as follows: 18-44, 45-64, 65-84, and > 84 years.

Geographic region, payer, and health plan type will be variables used to describe *prevalent* and *new* NSAID users only in the MarketScan databases.

9.3.2 Lifestyle variables

Information on smoking is not available in MarketScan databases. Smoking will be assessed in *prevalent* and *new* NSAID users in the CPRD. Smoking history will be categorized as current, past, and nonsmoker based on information as recorded by the GP.

Other lifestyle factors will be assessed in *prevalent* and *new* NSAID users based on diagnosis codes for conditions suggesting obesity, alcohol abuse or dependence, and drug abuse. These are included among the specific comorbidities of interest in Section 9.3.3 (Table 9-1).

9.3.3 Specific comorbidities of interest

Specific comorbid diagnoses relevant to NSAID treatment selection will be assessed among *prevalent* and *new users* of NSAIDs based on historical information of inpatient and outpatient diagnosis or procedure codes available before the index date. The specific comorbidities include chronic conditions and conditions that may influence the decision to prescribe one or another NSAID.

To ensure that baseline health history is captured, the lookback period for comorbidity ascertainment will be up to 3 years prior to the index date in MarketScan databases, because the average duration of patient enrollment in a commercial health insurance database is typically 2 years or less.[1] In the CPRD, all available time since patient registration will be used.[2] See Table 9-1 for a list of comorbidities of interest in this study.

Table 9-1 ICD-10 codes for specific comorbid conditions

ICD-10 code	Description
Infectious diseases	
B15.x-B17.x	Acute viral hepatitis
B18.x	Chronic viral hepatitis
B19.x	Unspecified viral hepatitis
B20.x–B22.x, B24.x	(*) AIDS/HIV
Neoplasms	
C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C97.x	(*) Solid tumor without metastasis, except non-melanoma skin cancer and lymphoma
C81.x–C85.x, C88.x, C96.x, C90.0, C90.2	(*) Lymphoma
C77.x–C80.x	(*) Metastatic solid tumor
D00.x-D09.x	In situ neoplasms
D10.x-D36.x	Benign neoplasms
D37.x-D38.x	Neoplasms of uncertain or unknown behavior
Blood	
D65.x-D69.x	Coagulation defects, purpura and other haemorrhagic conditions
Endocrine	
E10-E14	Diabetes mellitus
E10.0, E10.1, E10.9, E11.0, E11.1, E11.9, E12.0, E12.1, E12.9, E13.0, E13.1, E13.9, E14.0, E14.1, E14.9	Diabetes, uncomplicated
E10.2–E10.8, E11.2–E11.8, E12.2–E12.8, E13.2–E13.8, E14.2–E14.8	(*) Diabetes, complicated
E66.x	Obesity
E78.x	Disorders of lipoprotein metabolism and other lipidemias

ICD-10 code	Description
Nervous system	
G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0–G83.4, G83.9	(*) Paralysis (hemiplegia or paraplegia)
F00.x–F03.x, F05.1, G30.x, G31.1	(*) Dementia
F20.4, F31.3–F31.5, F32.x, F33.x, F34.1, F41.2, F43.2	Depression
Circulatory system	
I10.x-I15.x	Hypertensive diseases
I20.x-I25.x	Ischaemic heart diseases
I21.x, I22.x, I25.2	Myocardial infarction
I26.x, I27.x, I28.0, I28.8, I28.9	Pulmonary circulation disorders
I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0	(*) Congestive heart failure
I44.1–I44.3, I45.6, I45.9, I47.x–I49.x, R00.0, R00.1, R00.8, T82.1, Z45.0, Z95.0	Cardiac arrhythmias
A52.0, I05.x–I08.x, I09.1, I09.8, I34.x–I39.x, Q23.0–Q23.3, Z95.2–Z95.4	Valvular disease
G45.x, G46.x, H34.0, I60-I69	Cerebrovascular diseases, including transient cerebral ischemic attacks
I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	Peripheral vascular disorders
I74	Arterial embolism and thrombosis
Respiratory system	
J40.x-J47.x	(*) Chronic lower respiratory diseases
I27.8, I27.9, J60.x–J67.x, J68.4, J70.1, J70.3	(*) Other chronic respiratory diseases
Digestive system	
K20.x-K23.x	Diseases of oesophagus
K25.x-K28.x	(*) Peptic ulcer disease
K29.x	Gastritis and duodenitis
K30.x	Functional dyspepsia
K31.x	Other diseases of stomach and duodenum
K50.x	Crohn disease [regional enteritis]
K51.x	Ulcerative colitis
K57.x	Diverticular disease of intestine
B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4	(*) Mild liver disease
I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7	(*) Moderate or severe liver disease

ICD-10 code	Description
Skin and subcutaneous tissue	
L20.x-L30.x	Dermatitis and eczema
L40.x	Psoriasis
L50.x-L54.x	Urticaria and erythema
Musculoskeletal system and connective tissue	
M05.x, M06.x,	(*) Rheumatoid arthritis
M07.x	Psoriatic and enteropathic arthropathies
M08.x	Juvenile arthritis
M10.x	Gout
M12.0, M12.3	Other specific arthropathies
M13.x	Other arthritis
M15.x–M17.x	Polyarthrosis, coxarthrosis, gonarthrosis
M30.x	Polyarteritis nodosa and related conditions
M31.5, M32.x–M34.x, M35.1, M35.3, M36.0	(*) Systemic connective tissue disorders
M40.x–M43.x	Deforming dorsopathies
M45.x	Ankylosing spondylitis
M46.1, M46.8, M46.9	Other inflammatory spondylopathies
M47.x	Spondylosis
M48.x-M49.x	Other spondylopathies
M50.0, M50.1, M51.0, M51.1	Cervical disc disorders and other intervertebral disc disorders with myelopathy or radiculopathy
M53.x	Other dorsopathies
M54.x	Dorsalgia
M54.3	Sciatica
M54.4	Lumbago with sciatica
M54.5	Low back pain
M79.7	Fibromyalgia
M80.x-M82.x	Osteoporosis
M88.x	Paget disease of bone
Genitourinary system	
N10	Acute tubulointerstitial nephritis
N11	Chronic tubulointerstitial nephritis
N12	Tubulointerstitial nephritis, not specified as acute or chronic
N17	Acute renal failure
I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2	(*) Renal disease
Other	
F10, E52, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51.x, Z50.2, Z71.4, Z72.1	Alcoholism

ICD-10 code	Description
F11.x–F16.x, F18.x, F19.x, Z71.5, Z72.2	Drug abuse

ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision.*

(*) indicates comorbid conditions in the updated version of Charlson comorbidity index

Specific comorbidities will be identified by the appropriate *International Classification of Disease, 9th Edition, Clinical Modification* (ICD-9-CM) codes in the MarketScan databases and Read and ICD-10 codes in the CPRD.

Based on the available information on comorbidities, the adapted Charlson comorbidity index by Quan et al.[3] will be used as an overall summary of the patient's comorbidity. In its original version, the Charlson comorbidity index is a clinical comorbidity weighted index of 17 comorbid diseases.[4] It has been adapted and validated in different settings for use in health care claims databases with ICD-9-CM codes.[5-8] An adapted and validated version of this index is also available for Read codes.[9]

9.3.4 Selected comedications

Use of other medications will be assessed in the year before and including the index date among *prevalent* and *new users* of each of the selected NSAIDs. The selected medications include drugs used to treat chronic conditions that are relevant to characterize the risk profile of users of NSAIDs, as well as medications that are recommended to be used along with NSAIDs (e.g., gastroprotective medications) or that may interact with NSAIDs. The relevant medications and the Anatomical Therapeutic Chemical (ATC) codes are as follows:

- Diabetes medications
  - Insulins and analogues (A10A)
  - Blood glucose–lowering drugs (A10B)
- Peptic ulcer medications
  - Proton pump inhibitors (A02BC)
  - H2-receptor antagonists (A02BA)
  - Antacids (A02A)
  - Prostaglandins (A02BB)
- Antithrombotic agents
  - Vitamin K antagonists (B01AA)
  - Heparins (B01AB)
  - Platelet aggregation inhibitors (B01AC)
  - Direct thrombin inhibitors (B01AE)
- Cardiovascular medications
  - Organic nitrates (C01DA)

  - Cardiac glycosides (C01A)
  - Antiarrhythmics (C01B)
  - Diuretics (C03)
  - Peripheral vasodilators (C04)
  - Antihypertensives (C02)
  - Beta-blocking agents (C07)
  - Calcium channel blockers (C08)
  - Angiotensin-converting enzyme inhibitors (C09A, C09B)
  - Angiotensin II receptor antagonists (C09C, C09D)
  - Renin inhibitors (C09X)
- Lipid-lowering drugs (C10)
  - Statins (C10AA)
  - Other lipid-modifying agents (C10AB, C10AC, C10AD, C10AX, C10BA)
- Systemic corticosteroids (H02)
- Trimethoprim (J01E)
- Quinolones (J01M)
- Calcineurin inhibitors (L04AD)
  - Ciclosporin (L01AD01)
  - Tacrolimus (L01AD02)
- Disease-modifying antirheumatic drugs (DMARDs)
  - Methotrexate (L04AX03)
  - Chloroquine phosphate (P01BA01)
  - Hydroxychloroquine (P01BA02)
  - Leflunomide (L04AA13)
  - Sulfasalazine (A07EC01)
- Anti-TNF (tumor necrosis factor) biologics
  - Etanercept (L04AB01)
  - Infliximab (L04AB02)
  - Adalimumab (L04AB04)
  - Certolizumab pegol (L04AB05)
  - Golimumab (L04AB06)

- Non–TNF-active biologics
  - Rituximab (L01XC02)
  - Abatacept (L04AA24)
  - Anakinra (L04AC03)
  - Tocilizumab (L04AC07)
- Antiinflammatory and antirheumatic products, nonsteroids (M01A)
- Antigout preparations (M04A)
- Bisphosphonates (M05BA)
- Opioids (N02A)
- Other analgesics and antipyretics (N02B)
  - Salicylic acid and derivatives (N02BA)
  - Pyrazolones (N02BB)
  - Anilides (N02BE)
  - Other analgesics and antipyretics (N02BG)
- Selective serotonin reuptake inhibitors (N02CC)
- Phenytoin (N03AB02)
- Lithium (N05AN)
- Serotonin and noradrenaline reuptake inhibitors (SNRIs)
  - Venlafaxine (N06AX16)
  - Milnacipran (N06AX17)
  - Duloxetine (N06AX21)
  - Desvenlafaxine (N06AX23)
- Drugs for obstructive airway diseases (R03)
  - Adrenergics, inhalants (R03A)
  - Other drugs for obstructive airway diseases, inhalants (R03B)
- CYP450C9 inhibitors

ATC codes will be mapped to National Drug Codes to identify the medication pharmacy dispensing in the MarketScan databases and to Gemscript/British National Formulary codes for identification of the medications prescribed by the general practitioners (GPs) and recorded in the CPRD.

9.3.5 Health care resource utilization

As a crude marker of illness burden, the number of hospitalizations, emergency department visits, and outpatient specialist visits/referrals in the year before the index date will be

ascertained among *prevalent* and *new users* of diclofenac and *prevalent* and *new users* of each selected NSAID.

9.3.6 Specialty of prescriber of NSAID

The type of prescriber of each selected NSAID will be ascertained among *prevalent* and *new users* in the MarketScan databases for the index prescription based on an algorithm that will consider the physician specialty of the outpatient visit for which the date is closest to the date of the filled prescription. The CPRD captures prescriptions only from general practitioners.

9.3.7 Selected potential indications

Selected potential indications relevant to NSAID treatment will be assessed among *new users*. NSAIDs can be used for a number of indications, including chronic and acute conditions associated with pain. Within the CPRD, all prescriptions are generated directly from the computer, and details of each prescription—including dosage, instructions, and quantity—are recorded electronically. In addition, the GP records the indication for each new course of drug therapy, but the degree of completeness is variable. In the MarketScan databases, indications are not recorded for prescriptions. All diagnosis and surgical procedure codes recorded within 2 months before and 1 month after the index date will be tabulated by rank frequency and those found for at least 5% of NSAID users will be considered to be the potential clinical condition for which NSAIDs have been prescribed.

The selected potential indications of interest and corresponding ICD-10 codes shown in Table 9-2 will be used as the basis of the above-mentioned rank frequency distribution.

Table 9-2 ICD-10 codes for selected potential indications

ICD-10 code	Description
Neoplasm	
C00-C76 and C81-C97	Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin
C77–C80	Metastatic solid tumor
Nervous system	
G43.9	Migraine, unspecified
G44	Other headache syndromes
Digestive system	
K00-K14	Diseases of oral cavity, salivary glands and jaws
Musculoskeletal system and connective tissue	
M00-M03	Infectious arthropathies
M05-M14	Inflammatory polyarthropathies
M15-M19	Arthrosis
M20-M25	Other joint disorders
M25.2	Cramp and spasm
M25.5	Pain in joint
M25.6	Stiffness of joint
M30-M36	Systemic connective tissue disorders

ICD-10 code	Description
M40-M43	Deforming dorsopathies
M45-M49	Spondylopathies
M50-M54	Other dorsopathies
M60-M79	Soft tissue disorders
M60-M63	Disorders of muscles
M65-M68	Disorders of synovium and tendon
M70	Soft tissue disorders related to use, overuse and pressure
M75	Shoulder lesions
M76	Enthesopathies of lower limb, excluding foot
M77	Other enthesopathies
M79.7	Fibromyalgia
M80-M94	Osteopathies and chondropathies
M95-M99	Other disorders of the musculoskeletal system and connective tissue
Genitourinary system	
N20-N23	Urolithiasis
N94	Pain and other conditions associated with female genital organs and menstrual cycle
Symptoms, signs not classified elsewhere	
R50	Fever of other and unknown origin
R51	Headache
R52	Pain, not elsewhere classified
Injury, poisoning, and certain other consequences of external causes	
S00-T14	Trauma/bone fracture
Surgical procedures	
00-0Y PCS codes	Surgical procedures

ICD-10 codes for selected potential indications will be mapped to the appropriate *International Classification of Disease, 9th Edition, Clinical Modification* (ICD-9-CM) codes in the MarketScan databases and to Read and ICD-10 codes in the CPRD.

9.3.8 Dose

Among *new users* of each specific NSAID, the daily dose will be evaluated for the index and all subsequent consecutive prescriptions. The daily dose for each treatment episode will be derived from the recorded dose or from the time between consecutive prescriptions and the prescribing information (days supplied, strength, number of units, and number of boxes), according to the available information in each database. A treatment episode of NSAID use will be based on the continuation of drug therapy or refills (see Section 9.3.9).

The distribution of the daily prescribed dose associated with the index prescription will be described for all *new users* of each specific NSAID.

The daily dose of the index prescription will be categorized in low, normal, and high categories using the World Health Organization (WHO) defined daily dose (DDD) as the normal daily dose.[10] The cut-off values for the definition based on the WHO DDD of each selected NSAID is found in Table 9-3.

Table 9-3 Cut-off values to define daily dose of NSAIDs

NSAID	Low daily dose (mg)	Normal (WHO defined daily dose)	High daily dose (mg)
Diclofenac	< 0.1 g	0.1 g	> 0.1 g
Naproxen	< 0.5 g	0.5 g	> 0.5 g
Ibuprofen	< 1.2 g	1.2 g	> 1.2 g
Meloxicam	< 15 mg	15 mg	> 15 mg
Ketoprofen	< 0.15 g	0.15 g	> 0.15 g
Celecoxib	< 0.2 g	0.2 g	> 0.2 g
Etoricoxib	< 60 mg	60 mg	> 60 mg

The daily dose of medications is recorded in the CPRD (UK). In the MarketScan databases, the daily dose will be calculated for each dispensing claim as (quantity dispensed × strength)/days.

9.3.9 Duration of treatment

Duration of treatment will be assessed for *new users*. For each prescription, duration of treatment will be defined as the day's supply. For prescriptions without a day's supply noted, treatment duration will be calculated by dividing the number of tablets dispensed by the estimated daily dosage.

Duration of use will be estimated through the number of consecutive prescriptions or the days' supply of each prescription, as available in each database. Consecutive prescriptions are defined as those with a maximum gap of 30 days from the end of the last prescription. Duration will be adjusted by days of overlap between two consecutive prescriptions. Discontinuation will be defined by gaps of more than 30 days between the end of one prescription and a subsequent prescription.

A treatment episode is defined as consecutive prescriptions until no more prescriptions are found by the end date of the days' supply of the last prescription plus a grace period of 30 days.

Duration of treatment episodes will be categorized as ≤ 2 weeks, > 2 to 4 weeks, > 4 weeks to 3 months, and > 3 to 6 months, > 6 to 9 months, and > 9 to 12 months.

The cohort of *new users* of each specific NSAID will be characterized according to duration of the first treatment episode.

9.3.10 Persistence and adherence

Persistence is defined as the duration of time (days) from initiation to discontinuation of NSAID treatment. It will also be assessed as the proportion of patients who continued refilling

prescriptions within 30 days from the end of the previous prescription at given points in time within the 1-year of follow-up. Persistence will be measured as a function of gaps between refills.

Medication adherence will be measured by means of the medication possession ratio (MPR) and the proportion of days covered. The medication possession ratio will be calculated as the number of days of medication supply divided by the number of elapsed days including the last prescription within the 1-year of follow-up. The proportion of days covered will be calculated as the percentage of the number of days' supply obtained during the 1-year follow-up observation period. The proportion of days covered will take into account overlap in prescription/refills to avoid double counting.[11,12]

9.3.11 Use of multiple NSAIDs

Use of multiple NSAIDs will be assessed in the cohort of *new users* of each specific NSAID during the first treatment episode. Prescription of multiple NSAIDs will be defined as a prescription for an NSAID different from the index NSAID that was filled during the days' supply and the 30-day grace period of the index NSAID, provided there are consecutive prescriptions for the index NSAID.

9.3.12 NSAID switching

Switching from one NSAID to another will be assessed during the first treatment episode among *new users*. Switching is defined as filling or receiving a subsequent prescription for a different NSAID during the calculated duration of the treatment episode of an existing NSAID prescription plus a 30-day grace period, provided there is no subsequent prescription for the initial NSAID. Time in days from the index date to the first NSAID switch will be calculated.

9.3.13 Dose switching

For each patient, consecutive prescriptions in the first treatment episode for a specific NSAID will be evaluated for dose switching. Dose switching is defined as any change in the dose category defined for the specific NSAID (e.g., a change in diclofenac dose from < 0.1 g/day to 0.1 g/day, or from < 0.1 g/day to > 0.1 g/day) during the calculated duration of the treatment episode of an existing NSAID prescription plus a 30-day grace period. Time in days from the index date to the first dose switch will be calculated.

9.4 Data sources

The data for this study will be retrieved from the CPRD in the UK, provided by the CPRD Group of the Medicines & Healthcare Products Regulatory Agency, and Truven Health Analytics' MarketScan Commercial Database and Medicare Supplemental Database, administrative insurance claims databases in the US provided by Truven Health Analytics, with the approval of third-party use of the data licensed by Novartis.

9.4.1 MarketScan Commercial Claims and Encounters Database and Medicare Supplemental Database

The Commercial Database primarily consists of employer-sourced and health plan–sourced data containing medical and drug utilization data for more than 66 million individuals.[13] The database encompasses employees, their spouses, and their dependents covered by employer-sponsored private health insurance. More than 100 large employers and 12 unique health plans throughout the US are represented in the database. Medical claims in the Commercial Database include complete payment and charge information, including amount of patient responsibility. Other standardized items on each medical claim include but are not limited to dates and place of service (e.g., inpatient, outpatient, emergency), diagnoses, procedures, and detailed information on hospitalizations, including admission and discharge dates. Pharmacy claims in the Commercial Database include complete outpatient prescription drug information, which consists of patient copayments, mail order drugs, injectables, drugs from specialty pharmacies, and all standardized prescription-level fields collected on a typical pharmacy claim (e.g., date of fill/refill, drug name and class, strength, quantity, and days' supply). The data include copayment information for inpatient, outpatient, and pharmacy claims. The Commercial Database also contains medical (i.e., inpatient, outpatient, physician office, and ancillary services) and pharmacy claims for Medicare-eligible retirees with employer-sponsored Medicare supplemental plans.

The sex and age distribution of individuals in the Medicare Supplemental Database is fairly consistent with the US Medicare population, and the database contains mainly data from fee-for-service health plans. For retired persons receiving Medicare supplemental coverage, the claims data capture the Medicare-covered portion of payment (represented as Coordination of Benefits Amount, or COB), the employer-paid portion, and any patient out-of-pocket expenses for health care services performed in care settings (e.g., inpatient, outpatient). Claim records in the database contain information on patient characteristics, including demographic details (e.g., age, sex, health coverage, and race), eligibility information, service and provider type, diagnoses, detailed information about hospitalizations, inpatient and outpatient physician services, prescription drug use, and cost data. Unique, encrypted enrollee identifiers in the database allow patients to be tracked longitudinally.

All claims are paid and adjudicated, and the MarketScan research databases fully comply with the Health Insurance Portability and Accountability Act of 1996.[13]

9.4.2 The Clinical Practice Research Datalink

The CPRD contains anonymized diagnostic and prescribing information recorded by GPs as part of their routine clinical practice in the UK. The database coverage is approximately 5 million active patients (between 4% and 7% of the UK population, depending on calendar year) and over 13 million active and inactive patients. These data are linkable, at least partially, with other health care data sets (e.g., hospitalization records, national mortality data, and cancer registry data) via the patient's National Health Service number, sex, date of birth, and postal code. Approximately 65% of the English practices contributing to the CPRD have consented to have their patient information linked to other health care data sets.[14]

Information on prescriptions written by GPs, including prescribed dose and duration, is automatically recorded in the database. Read codes are used to record diagnoses. Additional diagnostic and treatment information can be found in letters from specialists and hospitals, and other sources. Identifying patients who have both CPRD and Hospital Episode Statistics (HES) data enables access to the hospitalization data, including diagnosis and procedural coding. However, data on drugs prescribed or administered in the hospital setting are not available.

Several studies have compared CPRD data with physician records and external sources such as mortality and cancer registries.[15-21] Accuracy of recording diagnoses and procedures varies among medical conditions but is generally good, and the addition of external linked data sources improves the validity of case ascertainment.[16]

9.4.3 Comparison of MarketScan and CPRD data

Use of both the MarketScan and CPRD data is proposed because the two data sources have different strengths and weaknesses. Both databases are large, and they represent different populations and have thousands of patients treated with NSAIDs. For some key variables, however, the availability of data differs in the two databases, as in the following examples:

- Both databases provide details of health care (diagnoses, procedures, drugs)
    - The CPRD has more detailed data on primary care services provided by the GP but also generally has information from specialists to which patients were referred, and the linkage with HES provides information on inpatient services.
    - The Commercial Database has a more complete picture of a patient's health care experience (e.g., medications, specialists, procedures, inpatient information), as long as the service received was paid by the insurance provider.
- Demographics
    - The CPRD covers people of all ages, and the age and sex distribution of individuals resembles that of the general population in the UK.[14]
    - The Commercial Database contains data on some people aged over 65 years, the age of eligibility for Medicare, but the age distribution is more weighted toward ages younger than 65. However, the Medicare Supplemental Database includes over 5.6 million individuals aged over 65 years with sex and age distributions similar to those of the entire US Medicare population.
- Duration of observation in the data
    - Nearly everyone in the UK is covered by national health insurance, which includes registering with a GP. On average, individuals tend stay in the same practice for life unless they are transferred out (e.g., patient moves to another area).
    - The Commercial Database has a shorter average duration of per-person observation time in the database than the CPRD, since for employed people in the US, insurance often changes when a person moves from one job to another.

Table 9-4 summarizes additional features of each database. Both databases have good representation of comorbid conditions if they are recorded, and both have less information on lifestyle factors like diet, smoking, physical activity, and occupation.

Table 9-4 Availability of data in MarketScan databases and the CPRD

Variable	Market Scan	CPRD
Age	Available for all	Available for all
	Patients aged older than 65 years are underrepresented; for patients aged older than 65 years, only those with Medicare supplemental insurance included	Ages representative of the UK population
Sex	Available for all	Available for all
Comorbid conditions	ICD-9-CM codes and medications are used to define comorbidities using code algorithms	Patient's medical history and prescriptions recorded; inpatient diagnoses available through linkage with HES; Read codes and medications are used to define comorbidities using code algorithms
Medications	Available for all with pharmacy coverage, which is the vast majority; days' supply and prescription fill date available; dose data are less reliably captured	Prescriptions are recorded if written by the GP, who prescribes nearly all chronic medications; the first 30-day supply might not be recorded if prescribed by a specialist
Length of follow-up	Continuous follow-up time is generally about 2 years but tends to be slightly longer for patients with chronic diseases, e.g., 2.5 years for patients with psoriasis in a recent study[22]	Follow-up time is life-long for patients who continue with the same GP

CPRD = Clinical Practice Research Datalink; GP = general practitioner; HES = Hospital Episode Statistics; ICD-9-CM = International Classification of Disease, 9th Edition, Clinical Modification; UK = United Kingdom.

9.5 Study size

This is a descriptive study, and no formal sample size calculation has been performed.

A preliminary review of the CPRD GOLD database identified patients with at least 1 prescription for one of the selected systemic NSAIDs of interest during the period January 01, 2013, through December 31, 2013, while registered at a practice with research-quality (up-to-standard) data (see Table 9-5). Exploratory data from MarketScan databases, CCAE & MDCR,[*] in the period Q1 through Q4 2013, for systemic NSAIDs with estimated counts above 2,000 users, are also shown in Table 9-5. The NSAIDs that were selected for the study are those that are more frequently prescribed, and the estimated number of patients prescribed account for over 80% of the NSAID use in the population covered by these databases.

[*] CCAE = Commercial Claims and Encounters database; MDCR = Medicare Supplemental and Coordination of. Benefits Database.

Table 9-5 Preliminary counts of patients with acceptable data quality in the CPRD and MarketScan data sources

	Patient count	
Drug name (ATC code)	**CPRD, 2013**	**MarketScan, 2013**
Diclofenac (M01AB05)	80,362	593,663
Meloxicam (M01AC06)	11,722	851,418
Ibuprofen (M01AE01)	164,047	1,702,421
Naproxen (M01AE02)	247,727	920,698
Ketoprofen (M01AE03)	827	—
Celecoxib (M01AH01)	5,861	245,230
Etoricoxib (M01AH05)	8,524	—
Indomethacin (M01AB01)	—	156,362
Ketorolac, systemic (M01AB15)	—	2,714
One or more of the above	—	3,988,629
Any systemic NSAID	501,601	—

9.6 Data management

Routine procedures will include assessing incoming data by checking electronic files, maintaining security, and protecting data confidentiality. Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.

Appropriate data storage and archiving procedures will be followed (i.e., storage on CD-ROM or DVD), with periodic backup of files to tape. Standard procedures will be in place at each research center to restore files in the event of a hardware or software failure.

Analyses will be conducted using SAS software version 9.3 or later (Cary, North Carolina: SAS Institute, Inc.; 2011).

9.7 Data analysis

All analyses will be performed by RTI Health Solutions (RTI-HS) according to the final, approved analysis plan.

All study measures described above will be analyzed descriptively through the tabular and graphical display of mean values, medians, ranges, and standard deviations of continuous variables of interest and proportions for categorical variables (with corresponding 95% confidence intervals, as appropriate). Further stratification by baseline variables such as age may be performed and will be described in the analysis plan.

In secondary database analyses, if information on a variable such as a disease diagnosis or a medication is available in the database, patients are assumed to have the factor only if there is evidence for its presence (i.e., absence of information will be taken to mean absence of the condition or medication). Missing data will be coded in a separate category as “unknown” for

variables such as age and sex, and their frequency will be described in the tables. Additional details on handling of missing data will be addressed in the statistical analysis plan.

9.7.1 One-year period prevalence

The following estimates will be calculated for the NSAID cohorts of *prevalent users*:

- Age- and sex-specific 1-year period prevalence of use of each specific NSAID, calculated as the number of patients receiving or filling at least one prescription for a specific NSAID per 1,000 population of the same age and sex category enrolled in the database

9.7.2 Baseline data

The following analyses will be conducted and tabulated separately for each of the specific NSAID cohorts of *prevalent* and *new users*:

- Demographic characteristics at the index date, for each selected NSAID:
  - Number of users overall and percentage by age category (18-44, 45-64, 65-84, and > 84 years) and sex
  - Descriptive statistics for age
- For the CPRD only, the percentage distribution of NSAID users by categories of smoking history: never smoked, current smoker, past smoker, and missing.
- For MarketScan databases only, the percentage distribution by the following variables:
  - Geographic region; South, North Central, West, Northeast, unknown, missing
  - Payer: Commercial, Medicaid, Medicare
  - Health plan type: preferred provider organization, health management plan/health network option, point of service, other, unknown
  - Specialty of physician prescriber
- Number and proportion of patients according to the following characteristics:
  - Specific comorbidities
  - Categories of Charlson comorbidity index (e.g., 0, 1-2, ≥ 3)
  - Selected comedications
  - Number of hospitalizations in the year prior (e.g., 0, 1, 2, ≥ 3)
  - Number of emergency department visits in the year prior (e.g., 0, 1, 2, ≥ 3)
  - Number of outpatient specialist visits/referrals (e.g., 0, 1, 2, ≥ 3)

9.7.3 Follow-up

The following analyses will be conducted and tabulated separately for each of the specific NSAID cohorts of *new users*:

- Rank frequency distribution of identified selected potential indications that occur in at least 5% of *new users*
- Total number of prescriptions and descriptive statistics for number of prescriptions per patient during the 1-year follow-up period
- Number of NSAID treatment episodes and descriptive statistics within the 1-year follow-up period
- Proportion of patients by number of treatment episodes (e.g., 1, 2, 3, $\geq$ 4) within the 1-year follow-up period
- Proportion of patients by daily dose category at the index prescription of the first treatment episode and descriptive statistics for daily dose
- Proportion of patients by categories of duration of the first treatment episode and descriptive statistics for duration
- Proportion of patients by categories of dose by duration of the first treatment episode
- Proportion of patients with evidence of multiple NSAID use during the first treatment episode and proportion of each specific NSAID added on
- Proportion of patients with evidence of NSAID switch during the first treatment episode, and cross-tabulation of initial and "switched to" NSAID
- Proportion of patients with evidence of NSAID *dose* switch during the first treatment episode, and cross-tabulation of initial and "switched to" *dose*
- Descriptive statistics for the mean total number of days' supply of the prescribed NSAID within the 1-year follow-up period
- Descriptive statistics for time to discontinuation of first treatment episode, NSAID switch, and NSAID dose switch
- Survival analysis will be used to describe the cumulative proportion of patients discontinuing the first NSAID treatment episode. Patient-persistence curves will be used to depict the proportion of patients who were persistent with each NSAID at any given point in time within the 1-year of follow-up.
- Descriptive statistics for the MPR calculated as the number of days' supply divided by the number of elapsed days including the last prescription within the 1-year of follow-up
- Descriptive statistics for the proportion of days covered, calculated as a measure of persistence (number of days' supply obtained during 1-year follow-up observation period/365 days x 100).

9.8 Quality control

Standard operating procedures will be used to guide the conduct of the study. These procedures include internal quality audits; rules for secure and confidential data storage; methods to maintain and archive project documents; quality-control procedures for programming; standards for writing protocols, analysis plans, and reports; and requirements for senior scientific review.

All programming written by one study analyst will be independently reviewed by a different analyst, with oversight by a senior statistician. All key study documents, such as the analysis plan and study reports, will undergo quality-control review, senior scientific review, and editorial review.

An independent Office of Quality Assurance at RTI-HS will perform audits and assessments that involve various aspects of the project, including but not limited to education and training documentation, data entry and data transfer procedures and documentation, and institutional review board (IRB) documentation. Such audits will be conducted by the Office of Quality Assurance according to established criteria in standard operating procedures and other applicable procedures.

A quality-assurance audit of this study may be conducted by the sponsor or the sponsor's designees.

Procedures will be consistent with the International Society for Pharmacoepidemiology (ISPE) *Guidelines for Good Pharmacoepidemiology Practices*[23] and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology.*[24]

Appropriate data storage and archiving procedures will be followed (e.g., storage on CD-ROM and DVD), with periodic backup of files. Standard procedures will be in place to restore files in the event of a hardware or software failure.

9.9 Limitations of the research methods

The design of this study will obtain information from records of routine clinical practice that will characterize users of diclofenac and the selected NSAIDs in terms of age and sex, treatment indication, use of selected concurrent medications, specific comorbidities, and other aspects related to the treatment patterns, such dose and duration of treatments. Population-based automated health care databases are suitable to address many of the objectives related to the drug utilization; however, they present some weaknesses. Diagnosis codes, if recorded inaccurately, may cause misclassification of conditions of interest. Medical history may not be perfectly reflected by automated data collected during patient encounters with health care providers. For example, not every patient with a history of a specific disease may necessarily have such history recorded, so the data may underestimate the proportion of patients with a history of that particular disease. As long as underrecording occurs to the same extent in all the study cohorts, it will not bias the results.

The underestimation of actual use of the drug has to be considered in studies conducted in automated health care databases. Recording of drugs prescribed, whether in the form of prescriptions issued by physicians (CPRD) or pharmacy-dispensed prescriptions (MarketScan

databases), may not reflect actual use of the drugs. Furthermore, underestimation of use may be relevant for drugs that are available over the counter. Also, patients hospitalized during the drug supply period are unlikely to use the full medication supply.

9.10 Other aspects

This study adheres to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)*[23] and has been designed in line with the ENCePP *Guide on Methodological Standards in Pharmacoepidemiology*.[24] The ENCePP Checklist for Study Protocols[25] has been completed (see Annex 2).

This is a post-authorization safety study (PASS) voluntarily initiated by the marketing authorization holder and will comply with the definition of the non-interventional (observational) study referred to in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use tripartite guideline Pharmacovigilance Planning E2E[26] and provided in the European Medicines Agency (EMA) *Guideline on Good Pharmacovigilance Practices (GVP), Module VIII: Post-Authorisation Safety Studies*,[27] and with the 2012 European Union pharmacovigilance legislation, adopted June 19, 2012.[28]

The study will be registered in the EU PAS Register[29] before the study implementation commences.

10 Protection of human subjects

This is a non-interventional study using data from secondary health care databases and does not pose any risks for patients. All data are de-identified with no breach of confidentiality with regard to personal identifiers or health information. RTI Health Solutions will obtain approval of the study protocol from the RTI International IRB.

The CPRD group has obtained ethical approval from a Multi-centre Research Ethics Committee (MREC) for all observational research using CPRD data without patient involvement. Study protocols need to be submitted to and approved by the CPRD's Independent Scientific Advisory Committee (ISAC). ISAC is responsible for reviewing protocols for scientific quality, but may recommend that study-specific MREC approval be sought if ethical issues arise in relation to an individual study. RTI Health Solutions will obtain approval of the study protocol from the CPRD's ISAC.

This study was designed and shall be implemented and reported in accordance with the *Guidelines for Good Pharmacoepidemiology Practices (GPP)* of the International Society for Pharmacoepidemiology,[23] the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines,[30] and with the ethical principles laid down in the Declaration of Helsinki.

11 Management and reporting of adverse events/adverse reactions

As this is a study based on secondary use of data, safety monitoring and safety reporting, where there is a safety-relevant result, is provided on an aggregate level only; no reporting on an individual case level is required. In studies based on secondary use of data with a safety-relevant result, reports of adverse events/adverse reactions should be summarized in the study report, i.e., the overall association between an exposure and an outcome. Relevant findings from the study report will be included in the periodic aggregated regulatory reports submitted to Health Authorities.

12 Plans for disseminating and communicating study results

The study protocol, updated study protocol following substantial amendments (if any), study progress reports (if requested), study status, and final study report will be included in regulatory communications in line with the Risk Management Plan, Periodic Safety Update Reports (PSURs), and other regulatory reporting requirements. Study reports will be prepared using a template following the GVP Module VIII Section B.6.3.[27]

Upon study completion and finalization of the study report, the results of this non-interventional study may be submitted for publication, posted in a publicly accessible database of results, or both. Publications will comply with internal Novartis standards and recommendations of the International Committee of Medical Journal Editors.[31]

When reporting results of this study, the appropriate STROBE checklist will be followed.[30]

For an applicable non-interventional PASS (conducted in the European Union), the final manuscript will be communicated to the EMA and the competent authorities of the Member States in which the product is authorized within 2 weeks after the first acceptance for publication as per the European Medicines Agency (EMA) *Guideline on Good Pharmacovigilance Practices (GVP), Module VIII: Post-Authorisation Safety Studies.*[27]

13 References

1. Seeger J, Daniel GW. Commercial insurance databases. In: Strom BLK, Stephen E Hennessy, Sean editor. Pharmacoepidemiology, 5th edition: Wiley-Blackwell; 2012.

2. Lewis JD, Bilker WB, Weinstein RB, Strom BL. The relationship between time since registration and measured incidence rates in the General Practice Research Database. Pharmacoepidemiol Drug Saf. 2005 Jul;14(7):443-51.

3. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011 Mar 15;173(6):676-82.

4. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

5. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol. 1994 Nov;47(11):1245-51.

6. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992 Jun;45(6):613-9.

7. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005 Nov;43(11):1130-9.

8. Schneeweiss S, Maclure M. Use of comorbidity scores for control of confounding in studies using administrative databases. Int J Epidemiol. 2000 Oct;29(5):891-8.

9. Khan NF, Perera R, Harper S, Rose PW. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. BMC Fam Pract. 2010;11:1.

10. WHO. Purpose of the ATC/DDD system. Oslo: WHO Collaborating Centre for Drug Statistics Methodology; 2009. Available at: http://www.whocc.no/atc_ddd_methodology/purpose_of_the_atc_ddd_system/. Accessed 16 July 2015.

11. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. Ann Pharmacother. 2006 Jul-Aug;40(7-8):1280-88.

12. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. Pharmacoepidemiol Drug Saf. 2006 Aug;15(8):565-74; discussion 75-7.

13. Danielson E. Health research data for the real world: the MarketScan® databases. Truven Health Analytics; January 2014. Available at: http://truvenhealth.com/Portals/0/Users/031/31/31/PH_13434%200314_MarketScan_WP_web.pdf. Accessed 12 May 2015.

14. Williams T, van Staa T, Puri S, Eaton S. Recent advances in the utility and use of the General Practice Research Database as an example of a UK Primary Care Data resource. Ther Adv Drug Saf. 2012 Apr;3(2):89-99.

15. Devine S, West SL, Andrews E, Tennis P, Eaton S, Thorp J, et al. Validation of neural tube defects in the full featured—General Practice Research Database. Pharmacoepidemiol Drug Saf. 2008 May;17(5):434-44.

16. Herrett E, Shah AD, Boggon R, Denaxas S, Smeeth L, van Staa T, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. BMJ. 2013;346:f2350.

17. Jick SS, Kaye JA, Vasilakis-Scaramozza C, Garcia Rodriguez LA, Ruigomez A, Meier CR, et al. Validity of the general practice research database. Pharmacotherapy. 2003 May;23(5):686-9.

18. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. Br J Gen Pract. 2010 Mar;60(572):e128-36.

19. Lewis JD, Brensinger C, Bilker WB, Strom BL. Validity and completeness of the General Practice Research Database for studies of inflammatory bowel disease. Pharmacoepidemiol Drug Saf. 2002 Apr-May;11(3):211-8.

20. Soriano JB, Maier WC, Visick G, Pride NB. Validation of general practitioner-diagnosed COPD in the UK General Practice Research Database. Eur J Epidemiol. 2001;17(12):1075-80.

21. Van Staa TP, Abenhaim L, Cooper C, Zhang B, Leufkens HG. The use of a large pharmacoepidemiological database to study exposure to oral corticosteroids and risk of fractures: validation of study population and results. Pharmacoepidemiol Drug Saf. 2000 Sep;9(5):359-66.

22. Kimball AB, Schenfeld J, Accortt NA, Anthony MS, Rothman KJ, Pariser D. Incidence rates of malignancies and hospitalized infectious events in patients with psoriasis with or without treatment and a general population in the U.S.A.: 2005-09. Br J Dermatol. 2014 Feb;170(2):366-73.

23. ISPE. Guidelines for good pharmacoepidemiology practices (GPP). Revision 2. International Society for Pharmacoepidemiology; April 2007. Available at: http://www.pharmacoepi.org/resources/guidelines_08027.cfm. Accessed 05 January 2015.

24. ENCePP. Guide on methodological standards in pharmacoepidemiology (revision 3). EMA/95098/2010 Rev.3. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; July 2014. Available at: http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml. Accessed 06 April 2015.

25. ENCePP. ENCePP checklist for study protocols (revision 2). European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; 14 January 2013. Available at: http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml. Accessed 06 April 2015.

26. ICH. Pharmacovigilance planning. E2E. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2004. Available at: http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/pharmacovigilance-planning.html. Accessed 05 January 2015.

27. EMA. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies (EMA/813938/2011 Rev 1). European Medicines Agency; 19 April 2013. Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf. Accessed 28 April 2015.

28. European Commission. Commission implementing regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council. 20 June 2012. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF. Accessed 05 January 2015.

29. ENCePP. Electronic register of studies. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; 2015. Available at: http://www.encepp.eu/encepp/studiesDatabase.jsp. Accessed 05 January 2015.

30. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. 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.

31. ICMJE. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. International Committee of Medical Journal Editors; December 2014. Available at: http://www.icmje.org/urm_main.html. Accessed 05 January 2015.

14 Annexes

14.1 Annex 1 – List of stand-alone documents

None

14.2 Annex 2 – ENCePP checklist for study protocols

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMEA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

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

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

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

Study title:
Usage patterns of selected systemic NSAIDs (including diclofenac): a retrospective cohort study

Study reference number:
VOL458A/Voltaren/CVOL458A2001

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[2]	☒	☐	☐	12
1.1.2 End of data collection[3]	☒	☐	☐	12
1.1.3 Study progress report(s)	☐	☒	☐	
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS Register	☒	☐	☐	12
1.1.6 Final report of study results	☒	☐	☐	12

Comments:

The protocol will be registered prior to start of data collection.

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)	☒	☐	☐	12
2.1.2 The objectives of the study?	☒	☐	☐	12-13
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	13
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 if applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

This is a drug utilization study; no hypotheses will be tested.

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)	☒	☐	☐	13
3.2 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:

This is a drug utilization study; no effect will be measured.

[2] 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.

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

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	13
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	13
4.2.2 Age and sex?	☒	☐	☐	13
4.2.3 Country of origin?	☒	☐	☐	13
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)	☒	☐	☐	13

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)	☒	☐	☐	13
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:

This is a drug utilization study; no biological effect will be measured, and validity testing of exposure will not be performed.

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 of validation sub-study)	☐	☐	☒	

Comments:

This is a drug utilization study; no endpoints will be assessed.

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:

This is a drug utilization study; no effects will be measured, and confounding will not be assessed.

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.)	☒	☐	☐	25-28
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?	☒	☐	☐	25-28
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)	☒	☐	☐	25-28
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.)	☒	☐	☐	25-28
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	25-28
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☒	☐	☐	25-28
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	25-28
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

This is a drug utilization study with secondary use of health care databases.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	28

Comments:

This is a drug utilization study with secondary data collection.

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?	☒	☐	☐	29
10.3 Are descriptive analyses included?	☒	☐	☐	29
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:

This is a drug utilization study; no effects or effect modification will be measured, and confounding will not be assessed.

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?	☒	☐	☐	29
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	29-29
11.3 Are methods of quality assurance described?	☒	☐	☐	32
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	32
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

This is a drug utilization study with secondary data.

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)	☒	☐	☐	28
12.3 Does the protocol address other limitations?	☒	☐	☐	32-33

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?	☒	☐	☐	33
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	33
13.3 Have data protection requirements been described?	☒	☐	☐	33

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?	☒	☐	☐	12

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)?	☒	☐	☐	34
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	34

Comments:

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

Date: [redacted]

Signature: [redacted]