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TITLE:

A Nested Case-control Post-authorization Safety Study of Etoricoxib and Other Non-steroidal Anti-inflammatory Therapies in a Cohort of Patients with Ankylosing Spondylitis (AS) in the UK, France and Germany

PRINCIPAL INVESTIGATOR:

Not applicable

CONTACT INFORMATION:

Not applicable

SITES:

Not applicable

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LIST OF ABBREVIATIONS

AE	Adverse experience
AS	Ankylosing Spondylitis
ACE	Acetyl cholinesterase
BNF	British National Formulary
CHMP	Committee Human Medicinal Products
CI	Confidence interval
COX-2	Cyclooxygenase-2
CPRD	Clinical Practice Research Datalink
DBP	Diastolic blood pressure
DVT	Deep venous thrombosis
EDGE	Etoricoxib vs. Diclofenac Sodium GI Tolerability and Effectiveness study
EMEA	European Medicines Evaluation Agency
EPIC	Epidemiology and Pharmacology Information Core (company)
GI	Gastrointestinal
GP	General Practitioner
GPRD	General Practice Research Database
H2-receptor	Histamine 2-receptor
ISEAC	Independent Scientific and Ethics Advisory Committee
MEDAL	Multinational Etoricoxib and Diclofenac Arthritis Long-term Program
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Myocardial infarction
Mg	Milligrams
mmHg	Millimeters of mercury
NHS	National Health Service
NSAIDs	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
PASS	Post-authorization safety study
PE	Pulmonary embolism
PUBs	Perforations, ulcers or bleedings
RA	Rheumatoid arthritis
SBP	Systolic blood pressure

SPC	Summary of product characteristics
THIN	The Health Improvement Network
UK	United Kingdom

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SUMMARY OF CHANGES TO PROTOCOL

The following changes have been made to the protocol since the previous update (V1.4, 28 Jul 2014). Details are found in the relevant sections of the protocol:

- Extended the study period (for follow-up of patients) by 1.5 years to 30 June 2014, to add more follow-up time to the analysis (**Section IV Methods, C. Study Period**).
- Extended the period of time for including exposures to prescriptions for the study drugs of interest through 30June2013 (one year before the end of the study period). This allows at least one year of follow-up of patients for outcomes following exposure to one of the study drugs of interest.
- Included all of the patients who have ever been included in the study population. During preparation for the report, it was noted that for several of the databases, many "historical" patients had been dropped during annual data updates by the data vendors. This attrition was largely attributable to practices that stopped providing data to the vendor or patients who changed primary care physicians over the course of the study. In order to keep the study consistent over time and maximize the study sample size for the final report, we identified all of the patients who were ever in the analysis since 2010 and included them in the current study cohorts.
- The reader should be reminded that there have been significant changes to the British National Formulary and Anatomical Therapeutic Chemical (ATC) Classification System relative to 5 years ago when the study was first designed and conducted. To maximize completeness and accuracy, all drug code lists were manually updated after thorough reviews for the 2014 report. A few drug products were included based on substance/brand names in addition to BNF and ATC chapters. Patients therefore may now have exposures to drugs that they did not previously appear to have taken and vice versa. In particular, the number of patients who are exposed to diclofenac increased substantially due to the revised drug code list and the number of patients who were previously in the "other NSAID" exposure group and multiple NSAID group were reduced accordingly,
- Comparison of some results from this analysis to those of the original and first update to this analysis should be done very cautiously because a significant number of additional patients and follow-up time has been added to the analysis. Changes in GP practice patterns and changes in the characteristics of the patient population prescribed NSAIDs and COX-2 inhibitors over time along with the database changes noted above makes comparisons of these results to those of the prior analyses difficult.

BACKGROUND AND RATIONALE

Etoricoxib (ARCOXIA)

Etoricoxib (MK-0663; ARCOXIA) is a selective inhibitor of COX-2 which was licensed in the UK in 2002 and has subsequently been licensed across Europe through the Mutual Recognition Procedure with UK as the Reference Member State.

Etoricoxib is indicated in the symptomatic relief of osteoarthritis (OA, 30-60mg once daily), RA (90mg once daily) and the pain and signs of inflammation associated with acute gouty arthritis (120mg once daily). Following evaluation of the benefit-risk balance of etoricoxib by the CHMP in referral EMEA/H/A/31/907 and EMEA/H/A/6(12)/906, etoricoxib was also approved in June 2008 for the treatment of ankylosing spondylitis (AS, 90mg once daily). The SPC for etoricoxib which was agreed during these referral procedures is included in Appendix 1.

During the referral procedures, Merck & Co., Inc. agreed to provide a number of Follow-up Measures including a post-authorization safety study (PASS) in patients with AS taking etoricoxib.

Background

The safety and efficacy of etoricoxib has been studied in patients with AS in a single Phase III Clinical Trial (MK-0663 Protocol 032) titled “A Double-Blind, Placebo- and Active-Comparator-Controlled, Parallel-Group Study to Assess the Safety and Efficacy of MK-0663 in Ankylosing Spondylitis (AS)”. [P032 CSR] MK-0663 Protocol 032 was a double-blind, placebo- and active-comparator-controlled, parallel-group safety and efficacy study performed at 44 sites with 300 AS patients. The primary objective of the study was to demonstrate superior clinical efficacy with etoricoxib 90 mg and 120 mg administered once daily compared with placebo, in the treatment of ankylosing spondylitis over a 6-week period.

The study was done in 2-parts. Part I was a 6-week, double-blind, placebo- and active comparator-controlled treatment period, conducted under in-house blinding. Part II was a double-blind, active-comparator-controlled, continuation period, conducted under in-house blinding, to evaluate the long-term safety and maintenance of clinical effects of MK-0663 and naproxen for up to 52 weeks. In Part II, all patients who received placebo in Part I were reassigned to 1 of 3 active treatments (etoricoxib 90 mg, etoricoxib 120 mg, or naproxen 500 mg twice daily). Patients who received MK-0663 90 mg or 120 mg or naproxen 500 mg twice daily in Part I continued on the same therapy in Part II.

In Protocol 032, compared with placebo over the 6-week treatment period (Part 1), etoricoxib 90 mg and 120 mg showed statistically significant greater improvement in all 3 primary endpoints: 1) patient assessment of spine pain, 2) patient global assessment of disease activity, and 3) Bath Ankylosing Spondylitis functional index. The combined etoricoxib group demonstrated statistically significant greater improvement compared to naproxen for all 3 primary endpoints. In addition, each individual etoricoxib treatment group showed either statistical or numerical improvement compared to naproxen for the 3 primary

endpoints. There were no statistically significant differences between etoricoxib 90-mg and 120-mg groups.

With respect to overall safety in Part I of Protocol 032 there were no significant differences between the placebo and etoricoxib 90-mg and 120-mg treatment groups in the overall incidence of clinical and laboratory adverse experiences and prespecified adverse experiences including those considered drug related and/or serious, or those that led to discontinuation from study drug. With respect to overall safety in Part II of Protocol 032, there were no significant differences between treatment groups based on 95% CIs for treatment differences excluding 0.

Based on the results of MK-0663 Protocol 032 the following conclusions can be made:

Once-daily treatment with etoricoxib (90 mg and 120 mg) is superior to placebo in the treatment of AS over a 6-week period.

Once-daily treatment with etoricoxib (90 mg and 120 mg) is superior to naproxen 500 mg twice daily in the treatment of AS on all primary endpoints over 6 weeks and 1 year (for combined doses at 6 weeks, and both individual and combined doses over 1 year).

The treatment effects of etoricoxib 90 mg compared with 120 mg daily in AS are similar over 1-year treatment period.

The safety profile of etoricoxib 90 and 120 mg is similar to that of naproxen 500 mg twice daily

Because MK-0663 Protocol 032 was relatively small it was not able to provide definitive data on the safety profile of etoricoxib with respect to the incidence of GI clinical events (ulcers, gastrointestinal bleeding), thrombotic cardiovascular clinical events, congestive heart failure, or renovascular effects (hypertension, acute renal impairment / failure) in the treatment of patients with AS.

The long term cardiovascular safety data for etoricoxib was assessed in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) program. The primary purpose of the MEDAL program was to further assess the thrombotic cardiovascular safety profile of etoricoxib using a non-inferiority study design to compare to the traditional NSAID diclofenac. The MEDAL Program (including the Etoricoxib vs. Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness (EDGE), EDGE II and MEDAL studies) evaluated more than 34,000 patients with RA and OA on etoricoxib 60 or 90 mg or on diclofenac 150 mg. There was no difference between treatment groups in the cumulative incidence of confirmed thrombotic events after an average treatment duration of 18 months, including those 12,854 patients who took etoricoxib or diclofenac for more than 24 months. The results were consistent across the per-protocol, modified-intention-to-treat and intention-to-treat analyses. There were no discernible differences in thrombotic event rates between etoricoxib and diclofenac for individual types of thrombotic events or across all subgroups analyzed, including patient categories across a range of baseline cardiovascular risk.

As with other drugs in the same class, the SPC for etoricoxib which was agreed during the referral procedures in June 2008 (Appendix 1) includes special warnings and precautions for use regarding:

- Upper gastrointestinal (GI) complications [perforations, ulcers or bleedings (PUBs)]
- Thrombotic events (especially myocardial infarction (MI) and stroke), relative to placebo and some NSAIDs.
- Impairment of renal function.
- Risk of fluid retention, edema and hypertension
- Risk of cardiac failure / left ventricular dysfunction

Study Rationale

This study is being conducted by Merck & Co. Inc. as a post-licensure commitment to the European Medicines Agency (EMEA). The purpose of this study is to describe the use of etoricoxib, and to monitor and further characterize the safety profile of etoricoxib, with respect to specific clinical outcomes of interest, in European patients with AS.

OBJECTIVES

The objectives have been developed in association with the EMEA. The objectives of this study, in European patients with AS, are to:

- Describe the use of etoricoxib
- Describe the characteristics of those who use etoricoxib
- Assess the safety profile of etoricoxib and other anti-inflammatory therapies with respect to specific clinical outcomes of interest (including upper GI, cardiovascular, cerebrovascular, and renovascular events - see IV. G. Clinical Outcomes of Interest):
- Relative to non-use of these medications
- Relative to each other

HYPOTHESES

This study is for estimation purposes. The clinical outcomes of interest as stated in the primary objective above are known to be associated with anti-inflammatory treatments (non-selective NSAIDs and COX-2 selective inhibitors) and are described in drug class labeling. This study will estimate the odds of current and recent exposure to etoricoxib, and to various other anti-inflammatory treatments, compared with non-exposure to any such treatments, for the clinical outcomes of interest.

METHODS

Study Design

This study is a population-based, nested case-control study of the association of etoricoxib and other anti-inflammatory treatments with clinical outcomes within an inception cohort of patients with a diagnosis of AS who meet the study inclusion criteria.

Study Procedures

Study Accrual

Since this study is designed as a retrospective analysis of patient level data using several electronic medical databases there will be no active enrollment or follow-up of patients, and no data will be collected directly from patients.

Patients will be assigned to groups based on coded prescriptions and dispensed according to the database. Assumptions concerning the actual use of the prescriptions dispensed apply (See section **I.D.6 Exposures of Interest and Definition of Exposure**)

Informed Consent and Institutional Review Board

Prior to being finalized this protocol will be reviewed by the CHMP of the EMEA, and will undergo review and approval by the Independent Scientific Advisory Committee of the GPRD, the scientific protocol review committee (SPRC) for the EPIC (Epidemiology and Pharmacology Information Core) company, and the Independent Scientific and Ethics Advisory Committee for .IMS.

Follow-up and Safety Analysis

There will be no active follow-up data collection.

Safety Review Committee

This study will not have an external Safety Review Committee

Databases

Note: The General Practice Research Database (GPRD) is now known as the Clinical Practice Research Datalink (CPRD); but since the original protocol was written several years ago, the original terminology has been retained.

This study will use the combination of the General Practice Research Database (GPRD) in the UK, The Health Improvement Network (THIN) database in the UK, and the IMS Disease Analyzer Database (Disease Analyzer) in the UK, France and Germany.

Some general medical practices in the UK are included in both the GPRD and THIN databases, thus there are some patient records that are duplicated when both databases are combined for analysis. Because the practices that are common to both databases are not

publicly known, Merck has developed an algorithm for this study to identify the common practices (Appendix 2). For those practices that are identified as contributing to both databases, the data from the GPRD database will be used. Validation of the algorithm will be performed prior to finalizing the protocol and performing the analysis for this study.

Data for the GPRD ("GOLD" version) database are collected from the UK general practitioner (GP) practices using the practice management software. The database includes 3.5 million currently active patients with research quality data and over 10 million persons with research usable data from over 560 practices, and 39 million person years of research quality data. The database (5.5% of the UK population) is generally representative of UK general population. The data elements include demographics, medical diagnosis, all prescriptions, referrals to hospitals, hospital discharge reports, and miscellaneous patient care information, such as smoking status, height, weight, immunizations, and lab results. The GPRD database is managed by MHRA. Recently, GPRD has the capability to link the records to other NHS datasets.

The THIN database also includes computerized, anonymous, longitudinal patient medical records retrieved from GPs in the UK. THIN contains data from 6.9 million patients in 390 practices, and is also demographically representative of the UK population. The data available to researchers consist of demographic, medical and prescription information at individual patient level. In addition, there is information on referral to specialists, diagnostics and laboratory results, some lifestyle characteristics and other measurements taken in the GP practice. At the patients' postal code level socioeconomic (Townsend) and area of living (rural/urban) information is also available. EPIC is the company that administrates THIN and EPIC does not have access to any personal identifiable information (such as patient/GP names, addresses, postal codes or full date of birth) from participation practices or patients.

The Disease Analyzer database has been collated by IMS Health Ltd. since 1989. The database contains anonymous primary care records for over 9 million patients from approximately 2150 contributing GPs in Germany, France, and the UK. IMS has a statistically designed national sampling system for each country; practices / doctors are recruited based upon national sampling of practice size, region, doctor age and sex and year qualified. For each country, the patients who visit the included practices are generally representative of the entire country population. Data collected include patient demography, some patient lifestyle factors, comorbidity, medical diagnoses, prescriptions, medical tests, referrals and hospitalizations. Disease Analyzer is subject to internal validation and quality checks at IMS

Reporting

No reporting of adverse experiences to regulatory agencies is planned as part of this retrospective observational study. The data being analyzed do not contain any assessments of causality for clinical events in individual patients. The data being used for this study are anonymized at both the patient level and the GP level. The analysis results will be at the group (aggregate) level. The study results will be included in a report at the end of study and

submitted to the CHMP in a timely manner. The final results will also be included to regulatory agencies in Periodic Safety Update Reports when available.

Study Period

The study period will start within each database with data from the earliest eligible patient according to the inclusion / exclusion criteria as described below. The study period will end on 31 Dec. 2013.Note: although COX-2 inhibitors have been available In Europe only since 1999, the study includes earlier time periods in order to maximize the study sample size. Calendar time of patient entry into the cohort, and stratification of analysis by time before and after the 2005 CHMP urgent safety restriction for COX-2 inhibitors, will be used to control for possible differences in treatment of AS over time during the study period.

AS Cohort Inclusion / Exclusion Criteria

To be eligible for inclusion in the cohort the patient record must satisfy all (1 – 4) of the following:

- A recorded AS diagnosis in the database, as documented by one or more of the following READ codes. Corresponding ICD-10 codes will be identified during the analysis using existing mapping dictionaries:

7124B	Marie-Strumpell Spondylitis
7124BA	Arthritis Marie-Strumpell Spine
7124C	Ankylosing Spondylitis
7124CA	Spondylitis Ankylopoietica
7124D	Spondylitis Ossificans Ligamentosa
N100.00	Ankylosing Spondylitis
N100.11	Marie- Strumpell Spondylitis
N0450	Juvenile Ankylosing Spondylitis
2377.00	O/E - ankyl.spondyl.chest def.
388p.00	Bath Ankylosing spondylitis
N10z.00	Spondylitis NOS

- A recorded AS diagnosis following the applicable “acceptable data quality” date for the database that contains the patient’s records, as follows:

  For GPRD, the Up-to-Standard date for the practice

  For THIN, the Acceptable Mortality Reporting date for the practice

  For Disease Analyzer, the earliest of the above GPRD Up-to-Standard date or THIN Acceptable Mortality Reporting dates will be applied to all practices in the databases.

- At least 6 months (183 days) of registered medical records in the database after the applicable "acceptable data quality" date as described above, and prior to the recorded AS diagnosis. (Note: In Germany and France patients do not need to register with a GP; the date of first medical event (clinical or therapy) will be used as the registration date)

Those patients whose first recorded AS diagnosis precedes their meeting conditions 1, 2, and 3 above will be labelled "prevalent AS patients". Those patients whose first recorded AS diagnosis is the same one that meets conditions 1, 2 and 3 above will be labelled "incident AS patients".

- Complete information on gender and birth year.

AS Cohort Entry and Follow-up

The date of the first recorded AS diagnosis in an eligible patient will define the patient's entry into the cohort (cohort entry date). Each patient will be followed starting with the cohort entry date and ending with the earliest of:

- Date transferred out of the practice (In Germany and France patients do not need to register with a GP; the date of last medical event (clinical or therapy) will be used)
- Date of the last data collection from the practice
- Date of clinical event (since multiple outcomes are being evaluated, this date will vary within each patient by outcome)
- The end of the study period
- Date of death

Exposures of Interest and Definition of Exposure

Oral formulations of the following drugs during the study period through 30June2013 (one year before the end of the study period - this allows at least one year of follow-up of patients for outcomes following exposure to one of the study drugs of interest) will each be examined as exposures of interest:

Cox-2 inhibitors: etoricoxib, rofecoxib, celecoxib, valdecoxib, lumiracoxib listed in the British National Formulary (BNF) chapter 10.1.1

Non-selective NSAIDs: meloxicam, etodolac, diclofenac, ibuprofen, naproxen, indomethacin, or "other non-selective NSAIDs" (excluding salicylates) listed in the British National Formulary (BNF) chapter 10.1.1 as a group (including aceclofenac, acemetacin, azapropazone, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, feprazone, flurbiprofen, ketoprofen, lornoxicam, mefenamic acid, nabumetone, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, tolfenamic acid, and tolmetin).

As of the 2015 report, there have been significant changes to the British National Formulary and Anatomical Therapeutic Chemical (ATC) Classification System relative to 5 years ago when the study was first designed and conducted. To maximize completeness and accuracy, all drug code lists were manually updated after thorough reviews. A few drug products were included based on substance/brand names in addition to BNF and ATC chapters. Patients therefore may now have exposures to drugs that they did not previously appear to have taken and vice versa. Because of the length and complexity of the drug code lists (each drug category for each database, drug code lists have not been included in the protocol. They are available upon request.

Although some of the listed drugs are no longer available (rofecoxib, valdecoxib, lumiracoxib) they are included in the study because excluding them could potentially bias the results if their use was related to subsequent use of another included product and also to the risk of a clinical outcome of interest.

The association between the exposures of interest and clinical outcomes will be assessed during follow-up. For the case-control analysis, exposure will be classified as follows:

'Current' when the most recent exposure (calculated duration of the most recent prescription + 14 days) overlaps the 'index' date.

'Recent' when the most recent exposure (calculated duration of the most recent prescription + 14 days) **ended on a date 1 to 60 days prior to** the 'index' date (does not overlap index date).

'Prior' when the most recent exposure (calculated duration of the most recent prescription + 14 days) **ended on a date 61 to 180 days prior** to the 'index' date (does not overlap index date).

'Non-exposure' when none of the above applies. In other words the most recent exposure (calculated duration of the most recent prescription + 14 days) **ended on a date 181 or more days prior to the 'index' date, OR when the patient did not have any prescriptions during his/her follow-up in the study.**

The prescription duration will be calculated using the date the prescription was written, the amount prescribed and the daily dose. For example, a prescription written for 28 tablets of etoricoxib 60mg with instructions to take 1 tab daily will be assumed to have duration of 28 days starting with the date the prescription was written. Any prescriptions for any of the study drugs of interest for which a period of current exposure cannot be calculated will be assumed to have duration of 28 days. Fourteen days will be added to the calculated duration for each prescription for any of the study drugs of interest to account for imperfect compliance (missed doses) with the prescription instructions. Thus in the example above the patient's etoricoxib prescription duration will be a total of 42 (28+14) days.

If the patient receives a refill for the same drug while 'currently exposed' the patient will be considered to be continuing therapy and his/her 'currently exposed' status will be extended, starting on the date of the new prescription, for the duration of the new prescription according to the above rules. If the patient receives a prescription for a different drug of interest while "currently exposed" the exposure to the first drug will end the day before the

new prescription and the patient will be considered exposed to the new prescription according to the above rules. If no refills for the same drug or prescriptions for a new drug are written before the duration of the last prescription ends, then the patient's exposure will end on the last day of the last prescription duration. Periods of follow-up that are not classified as 'currently exposed' will be classified as non-exposed. A patient may have multiple periods of 'current exposure' to one or more of the study drugs of interest, and multiple periods of non-exposure, during his/her follow-up.

Patients provided more than one prescription for a COX-2 inhibitor or NSAID on the same day will be counted as being exposed to each drug simultaneously per the above rules and will be flagged as having multiple exposures during the period of overlap of the prescriptions. These patients will be treated as a special exposure category in the case-control analysis.

A sensitivity analysis will be done adding 28 days (instead of 14 days as indicated above for the primary analysis) to the calculated duration for each of the study drugs of interest.

Clinical Outcomes of Interest

The incidence rates (first diagnosis during follow-up for a given outcome or grouping of outcomes, as defined by diagnosis and BNF codes recorded in patients' electronic medical records) of the following will be estimated (note that some of the same diagnosis codes to be used for the outcomes of interest will also be used for purposes of documenting baseline medical history. Others will be used only for purposes of documenting baseline history, as indicated in the appendices):

Gastrointestinal clinical event (ulcer, perforation or bleeding) (**Appendix 3**)

Ischemic / thrombotic cardiac events: fatal and non-fatal acute myocardial infarction (**Appendix 4**), unstable angina pectoris (**Appendix 5**)

Ischemic / thrombotic cerebrovascular events: fatal and non-fatal ischemic (or not otherwise specified as hemorrhagic) stroke (**Appendices 7 & 8**), or transient ischemic attack (**Appendix 9**).

Hemorrhagic cerebrovascular events: fatal and non-fatal hemorrhagic stroke (**Appendix 10**),

Thromboembolic peripheral vascular events: deep venous thrombosis (DVT) (**Appendix 11**), pulmonary embolism (PE) (**Appendix 12**), or peripheral arterial embolism / thrombosis (**Appendix 19**)

Acute Renal impairment or failure (**Appendix 29**),

Hypertension (based on the combination of a code that qualifies as a hypertension outcome diagnosis in **Appendix 14**, and a prescription within 90 days of the diagnosis date for antihypertensive medication: including diuretic [BNF chapter 2.2], beta-blocker [BNF chapter 2.4], angiotensin-converting enzyme (ACE) inhibitor; BNF chapter 2.5.5.1], angiotensin-II receptor antagonist [BNF chapter 2.5.5.2], or calcium-channel blocker [BNF chapter 2.6.2]). N.B. It has been shown that to identify patients with hypertension in a claims

database a selection rule using both a diagnosis and prescription claim has greater sensitivity and specificity than a rule using a diagnosis claim only. (Bullano 2006)

Congestive heart failure / left ventricular dysfunction (**Appendix 15**),

Sudden / unexplained death (**Appendix 16**)

The combination of 2, 3, 4, 5 and 9 above.

The date of a clinical outcome is defined as the date assigned to the diagnosis in the medical record. Clinical outcomes and the dates assigned to them will not be validated by chart abstraction / review or any other method.

A patient will be considered at risk of a clinical outcome from the date they enter the cohort until the earlier of the end of follow-up or with the occurrence of the specific outcome.

Analysis

The analysis will be both descriptive and comparative. Descriptive analyses will be done with the cohort data to address the objectives related to the use of etoricoxib and the characteristics of patients who use it. The comparative analyses will address the objective related to the association of etoricoxib and the other drugs of interest to the clinical outcomes using a nested case-control approach.

Based on the current size of this study, the numbers of events for some of the clinical outcomes are expected to be relatively small. Thus the power to detect a minimal clinically meaningful increase in the risk of these events with exposure to etoricoxib given the present study size will be very limited. (see section **V. Sample Size Considerations**), and interpretation of results will be difficult. Therefore a "stepped approach" is planned for the comparative analysis of clinical outcomes. For each clinical outcome, the case-control analysis and estimates of the association of the drugs of interest will be undertaken when there are at least 700 events (in the entire cohort) for analysis. This minimal number of events will provide 80% power to detect a 2.5-fold increase in the risk of the event with etoricoxib compared with non-exposure given this study design. In the event that the minimum required 700 events are not available, counts and listings of events will be provided as described in section **IV. H. 1. e. Incidence of Clinical Outcomes.** Future cumulative updates to this analysis are planned; thus all outcomes will likely eventually reach the minimum 700 events needed for analysis.

Descriptive analyses of the AS cohort

A number of descriptive analyses will be done to characterize the patients who qualify for the AS cohort, their follow-up during the study period, their use of anti-inflammatory treatments during follow-up, and the crude incidence of the clinical outcomes of interest during follow-up.

Patient baseline characteristics (at entry into the AS cohort)

The following baseline characteristics will be measured at entry into the cohort for purposes of cohort description. These characteristics will be determined by 1) data in the patient record during the 6 months prior to the date of cohort entry, and 2) data in the patient record during the period 6-12 months prior to entry into the cohort for patients with at least one year of medical records.

Age (in years as a continuous variable and categorized as <65, ≥65)

Gender (categorized as male/female)

Smoking status (most recent indication, using all available patient medical record prior to the date of cohort entry) categorized as non-smoker, current smoker, ex-smoker, missing)

Body mass index (most recent measurement, using all available patient medical record prior to the date of cohort entry), kg/m^2 as a continuous variable)

Alcohol use (using all available patient medical record prior to the date of cohort entry)

Calendar year of entry into the cohort (as a continuous variable)

Date of entry into cohort [categorized as before or after the COX-2 urgent safety restriction (i.e., <17Feb05 vs. ≥17Feb05)]

Total number of prior health care encounters (total number of visits to GP and referrals to specialists as a continuous variable)

Referral to Rheumatologist (yes, no)

X-ray of the sacrum or spine (yes, no)

Most recent systolic blood pressure (SBP) (in mmHg as a continuous variable and categorized as <120, 120-139, ≥140). Patients who do not have at least one valid blood pressure measurement recorded during the 183 days prior to the date of cohort entry will be categorized as having 'missing data' in the analysis.

Most recent diastolic blood pressure (DBP) (in mmHg as a continuous variable and categorized as <80, 80-89, or ≥90). Patients who do not have at least one valid blood pressure measurement recorded during the 183 days prior to the date of cohort entry will be categorized as having 'missing data' in the analysis.

Prior use of COX-2 selective drugs (overall, by each drug, and by dose of each drug; etoricoxib, rofecoxib, celecoxib, valdecoxib, lumiracoxib) [BNF chapter 10.1.1]

Prior use of non-selective NSAIDs (overall, by each drug, and by dose of each drug; meloxicam, etodolac, diclofenac, ibuprofen, naproxen, indomethacin aceclofenac, acemetacin, azapropazone, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, feprazone, flufenamic acid, flurbiprofen, ketoprofen, lornoxicam, mefenamic acid, nabumetone, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, tolfenamic acid, and tolmetin) [BNF chapter 10.1.1]

Prior use of narcotic pain medications (yes, no) [BNF chapter 4.7.2]

Prior use of prescription aspirin (≥300-mg/tablet formulations of aspirin, benorilate, and co-codaprin) (yes, no) [BNF chapters 4.7.1 or 10.1.1]

Prior use of disease-modifying anti-rheumatic drugs (sodium aurothiomalate, auranofin, penicillamine, chloroquine, hydroxycloroquine, azathioprine, ciclosporin, leflunomide, sulfasalazine, methotrexate (yes, no) [BNF chapter 10.1.3]

Prior use of TNF inhibitors (abatacept, adalimumab, anakinra, etanercept and infliximab) (yes, no) [BNF chapter 10.1.3]

Prior use of immune suppressants (ciclosporin, sirolimus, and tacrolimus) (yes, no) [BNF chapter 8.2.2]

Prior use of oral corticosteroids (yes, no) [any oral formulation in BNF chapter 6.3.2]

Prior use of local and parenteral injectable steroids forms (yes, no) [any oral formulation in BNF chapter 10.1.2.2]

Prior use of gastroprotective agents

H2-receptor antagonists (yes, no) [BNF chapter 1.3.1]

Prostaglandin analogues (misoprostol) and any product that combined misoprostol with an NSAID (yes, no) [BNF chapter 1.3.4.]

Proton pump inhibitors (yes, no) [BNF chapter 1.3.5]

Other ulcer-healing drugs (yes, no) [BNF chapter 1.3.6]

Prior use of cardiovascular or lipid-modifying medications:

Cardiac glycosides (yes, no) [BNF chapter 2.1.1]

Diuretics (yes, no) [BNF chapter 2.2]

Beta-blockers (yes, no) [BNF chapter 2.4]

Angiotensin-converting enzyme (ACE) inhibitors (yes, no) [BNF chapter 2.5.5.1]

Angiotensin-II receptor antagonists (yes, no) [BNF chapter 2.5.5.2]

Nitrates (yes, no) [BNF chapter 2.6.1]

Calcium-channel blockers (yes, no) [BNF chapter 2.6.2]

Oral anticoagulants (acenocoumarol, coumarin, dabigatran etexilate, phenidone, and warfarin) (yes, no) [BNF chapter 2.8.2]

Oral antiplatelet drugs (75-mg dosage forms of aspirin, clopidogrel, dipyridamole and ticlopidine) (yes, no) [BNF chapter 2.9]

Anion-exchange resins (yes, no) [BNF chapter 2.12.1]

Ezetimibe (yes, no) [BNF chapter 2.12.2]

Fibrates (yes, no) [BNF chapter 2.12.3]

Statins (yes, no) [BNF chapter 2.12.4]

Nicotinic acid (yes, no) [BNF chapter 2.12.5]

Prior use of estrogen replacement therapy (yes, no) [BNF chapter 6.4.1.1]

Prior use of contraceptives (yes, no) [BNF chapter 7.3]

History of GI Clinical Event (ulcer, perforation or bleeding) (Appendix **3**)

History of MI (**Appendix 4**)

History of unstable angina pectoris (**Appendix 5**)

History of acute or subacute coronary heart disease other than MI or unstable angina pectoris (**Appendix 6**)

History of ischemic cerebral infarction (**Appendix 7**)

History of Cerebrovascular Accident – Not Otherwise Specified (**Appendix 8**)

History of TIA (**Appendix 9**)

History of hemorrhagic cerebrovascular disease (**Appendix 10**)

History of DVT or PE (**Appendix 11 or 12**)

History of kidney disease (**Appendix 13**)

History of hypertension (**Appendix 14**)

History of heart failure or left ventricular dysfunction (**Appendix 15**)

History of rheumatoid arthritis (**Appendix 17**)

History of inflammatory bowel disease (Crohn's disease or ulcerative colitis) (**Appendix 18**)

History of peripheral arterial disease (arterial embolism / thrombosis, intermittent claudication, or peripheral vascular disease) (**Appendices 19, 20, and 21**)

History of dyslipidemia (**Appendix 22**)

History of diabetes (defined by any of the following criteria):

Diabetes diagnostic code (**Appendix 23**)

Insulin prescribed prior to index date [BNF chapter 6.1.1]

Oral antidiabetic agent prescribed prior to index date [BNF chapter 6.1.2:]

History of atherosclerotic cardiovascular disease (**Appendix 24**)

History of edema (**Appendix 25**)

History of gout (**Appendix 26**)

History of osteoarthritis (**Appendix 27**)

History of arthritis other than AS, OA, RA or gout (**Appendix 28**)

History of renal failure or impairment (**Appendix 29**)

Historical entries that have a missing date value will be excluded.

The proportion of patients in each nominal level will be determined for all categorical variables. For continuous variables means, standard deviations, medians, minimum and maximum values will be calculated to describe the distribution among the subset of patients who have non-missing data for that variable. Selected continuous variables (age, calendar time, and blood pressure) also will be analyzed as categorical variables using the cut-points

defined above. Measurements of lifestyle factors (current smoking status, BMI) will be determined from the last observation of these variables recorded on or before the date of entry into the cohort. Diagnosis codes in medical records that have a missing date value will be excluded.

Patient baseline characteristics (during the 6 months prior to entry in to the cohort) will be determined and described as above for the entire study population, and in subgroups defined by:

The first course of anti-inflammatory treatment for AS (by COX-2 inhibitor vs. non-selective NSAIDs). The first course of treatment for AS is defined as that prescription which coincides with or follows the AS diagnosis that determined the patient's entry into the cohort.

The first course of anti-inflammatory treatment for AS (by specific drug: as described in **section IV. F. Exposures of Interest and Definition of Exposure**

Use vs. non-use of any anti-inflammatory drug (COX-2 inhibitor or non-selective NSAIDs) during the entire study follow-up

Characteristics of Patients Prescribed Treatment for AS 'Off-label'

Characteristics of patients prescribed the more commonly used NSAIDs or COX-2 inhibitors "off label" will be examined to inform the potential for channelling of patients with certain characteristics to such treatment.

From the date of market approval for etoricoxib in the UK (15 Apr. 2002) and Germany (24 Aug 2004) until 31 Dec. 2006, etoricoxib, celecoxib and etodolac did not have a labeled indication for AS (in January 2007 celecoxib received an AS indication). During this time period patients in the AS cohort were presumably equally likely to have received any of these three drugs 'off-label' (assuming they did not have another indication for a given drug - OA, RA, or gout for etoricoxib, OA or RA for celecoxib and etodolac). On the other hand, the commonly used traditional NSAIDs diclofenac, ibuprofen, naproxen, and indomethacin all had an AS indication during this time period (approved treatment).

To assess patient characteristics related to 'off-label' treatment, the same characteristics that are described in the preceding section [Patient baseline characteristics (at entry into the AS cohort)] will be assessed in patients treated for AS "off label" vs. with approved treatments as described above. This analysis will be performed using UK and Germany patients. The analysis will compare the characteristics of the two groups as determined by data on or during the 183 days prior to the date of initiation of the first course of anti-inflammatory treatment for AS during the time period from the date of market approval for etoricoxib in the UK (15 Apr. 2002) and Germany (24 Aug. 2004) until 31 Dec. 2006. The first course of treatment for AS is defined as that prescription which coincides with or follows the AS diagnosis that determined the patient's entry into the cohort.

If there are insufficient numbers of patients treated off-label for their first course of anti-inflammatory treatment to inform the analysis then alternative ways to compare patients treated "off label" vs. with approved treatments will be explored.

Use of non-selective NSAIDs and COX-2 Inhibitors during follow-up

It is recognized that the use of coxibs will be largely influenced by their availability over the years, with some available for longer periods of time than others. The use of non-selective NSAIDs and COX-2 inhibitors will be described during follow-up as follows:

Counts and proportions of patients receiving any COX-2 inhibitor vs. any non-selective NSAID as the first course of anti-inflammatory treatment for AS, defined as the first prescription for a COX-2 inhibitor or a non-selective NSAID which coincides with or follows the AS diagnosis that determined the patient's entry into the cohort.

Counts and proportions of patients receiving a specific COX-2 inhibitor (etoricoxib, rofecoxib, celecoxib, valdecoxib, lumiracoxib) or non-selective NSAID (meloxicam, etodolac, diclofenac, ibuprofen, naproxen, indomethacin, or "other non-selective NSAIDs" listed in the British National Formulary (BNF) chapter 10.1.1 as a group) as the first course of anti-inflammatory treatment for AS, defined as the first prescription for a COX-2 inhibitor or a non-selective NSAID which coincides with or follows the AS diagnosis that determined the patient's entry into the cohort.

Counts and proportions of patients receiving any COX-2 inhibitor vs. any non-selective NSAID at any time during follow-up (these groups will not be mutually exclusive).

Counts and proportions of patients receiving a specific COX-2 inhibitor (etoricoxib, rofecoxib, celecoxib, valdecoxib, lumiracoxib) or non-selective NSAID (meloxicam, etodolac, diclofenac, ibuprofen, naproxen, indomethacin, or "other non-selective NSAIDs" listed in the British National Formulary (BNF) chapter 10.1.1 as a group) at any time during follow-up (these groups will not be mutually exclusive).

Patients who never receive any anti-inflammatory drug (COX-2 inhibitor or non-selective NSAID) during their entire follow-up will also be enumerated.

Duration of follow-up

Duration of follow-up in patient years will be described overall by means, standard deviations, medians, minimum and maximum values.

Duration of Exposure

Duration of exposure in patient years will be described by means, standard deviations, medians, minimum and maximum values as follows:

For the first course of anti-inflammatory treatment prescribed for AS (by any COX-2 inhibitor vs. any non-selective NSAIDs). The first course of anti-inflammatory treatment prescribed for AS is defined as that prescription which coincides with or follows the AS diagnosis that determined the patient's entry into the cohort.

For the first course of specific anti-inflammatory treatment prescribed for AS (by individual drug: etoricoxib, rofecoxib, celecoxib, valdecoxib, lumiracoxib, meloxicam, etodolac, diclofenac, ibuprofen, naproxen, indomethacin, or "other non-selective NSAIDs" listed in the British National Formulary (BNF) chapter 10.1.1 as a group)

For all courses combined (the sum of all courses) of anti-inflammatory treatment prescribed for AS (any COX-2 inhibitor vs. any non-selective NSAIDs) during the entire study follow-up.

For all courses combined (the sum of all courses) of anti-inflammatory treatment prescribed for AS (by individual drug as described **in section IV. F. Exposures of Interest and Definition of Exposure**

Incidence of Clinical Outcomes

A listing of each clinical outcome will be generated. The listing will include the patient identification number, gender, age at time of event, type of event, the date of the event, a prior medical history of the same event, and if applicable, the specific medication, dose and duration of current exposure to any of the drugs of interest. The total number of patients with events overall, and the subsets of events that occur in patients currently exposed to each drug of interest will be enumerated.

The crude (unadjusted) rates (counts and proportions) and incidence rates (per 1000 person years at risk) of clinical outcomes will be assessed as follows:

Overall in the cohort (regardless of exposure)

During periods of non-use of any COX-2 inhibitor or non-selective NSAID

For each clinical outcome, the incidence rate will be calculated as the total number of first occurrences of each type of medical event in each group, divided by the total aggregate person-time (expressed as patient-years) at risk accrued in that group at the time of analysis. For a given patient the time at risk for a given clinical outcome is defined as the time from entry into the cohort until the earliest of the specific clinical outcome being analyzed, death, transfer out of the medical practice, or the end of the study period (see **IV. E. AS Cohort Entry and Follow-up**)

Patients who have a prior medical history of an AE of interest code in their electronic medical record before the date of their first prescription for a given drug of interest will be identified. For each clinical outcome, incidence rate calculations as described above will be done separately in patients with and without a prior medical history of that event.

It is recognized that for patients with a medical history of some outcomes that are often chronic (e.g., hypertension, CHF, renal impairment) it will be difficult to distinguish a new event during follow-up from a prior event that established the baseline medical history. Therefore the results of these analyses need to be interpreted cautiously.

Case-control (comparative) analysis

Although a retrospective cohort design was considered. a nested-case control approach was chosen for the comparative analyses because:

In this study population is it is expected that patients will have multiple exposures and changes in potential confounders over time; in the cohort approach these would need to be modeled as time dependent covariates which is complex and difficult.

The conditional logistic regression analysis allows for comparison of multiple exposures to a common referent group in the same model.

Thus the case-control design is felt to provide simplicity in the analytic approach and in the interpretation of results compared with that of the retrospective cohort design. Future analyses may permit other analytical approaches if the study power is sufficient.

For each clinical outcome, the primary case-control analyses will be done in patients without a prior history of that event. Secondary analyses will be done in patients with a prior medical history of that event. Interpretation of the secondary analysis results will be hampered by uncertainty as to whether a diagnosis in the medical record of a patient during follow-up is actually a new diagnosis or simply the rerecording of a prior diagnosis addressed during a clinical encounter.

Disease Risk Scores

Because the number of potential confounders is large and the numbers of most clinical outcomes of interest is expected to be small disease risk scores appropriate to each outcome will be created to replace multiple potential confounders in the regression models to facilitate modeling the association of the outcomes with the exposures. These risk scores will be calculated from separate regression models of outcomes occurring at any time during the study period in the unexposed [non-users of COX-2 inhibitors or NSAIDs (if this group is too small or contains too few events for a given model then the entire AS cohort will be used)]. These models will include the designated variables as independent predictors of the disease outcome except the exposure variables. The definitions of the potential confounders are as described in section **IV.H.1.a. Patient baseline characteristics,** except that they will be assessed in the 6 months prior to the outcomes used to develop the models. The variables that will be used for creation of the disease risk scores for each outcome model are shown in the following Table. Some variables that are continuous will be categorized in order to facilitate including missing values into the model, as shown in the column labeled "Variable".

	Disease Risk Score*				
Variable	**GI ulcers / bleeding**	**Vascular (all types) and Sudden / Unexplained Death**	**HTN**	**CHF**	**Acute renal impairment / failure**
Smoking status (current, past, never, missing)	X	X	X	X	
Alcohol use (y/n)	X		X		
BMI (continuous)		X	X	X	
Number of prior health care encounters (continuous)	X	X	X	X	X
Systolic blood pressure (<120, 120-139, ≥140)		X	X	X	X
Diastolic blood pressure (<80, 80-89, ≥90)		X	X	X	X
Use of high dose (≥300 mg) prescription aspirin (y/n)	X				
Use of antiplatelet therapy (y/n)	X	X			
Use of disease-modifying anti-rheumatic drugs (y/n)	X	X			
Use of oral corticosteroids (y/n)	X		X		
Use of gastroprotective agents (y/n)	X				
Use of cardiovascular or lipid-modifying medications (y/n)		X	X	X	
Use of oral contraceptives (y/n)		X			
Use of estrogen replacement therapy (y/n)		X			
Prior GI PUB (y/n)	X				
Prior MI (y/n)		X		X	
Prior CHD other than MI, or angina (y/n)		X		X	
Prior ischemic cerebrovascular disease or TIA (y/n)		X			
Prior hemorrhagic cerebrovascular disease (y/n)		X			
Prior DVT or PE (y/n)		X			
Prior kidney disease (y/n)			X		X
Prior acute renal failure/impairment (y/n)			X		X
Prior hypertension (y/n)		X	X	X	X
Prior CHF (y/n)				X	
Prior RA (y/n)	X	X			
Prior IBD (y/n)	X				
Prior PAD (y/n)		X			
Prior dyslipidemia (y/n)		X			
Prior diabetes (y/n)		X	X		X

* GI = gastrointestinal; vascular (all types) = cardiac, cerebrovascular, peripheral vascular; HTN = hypertension; CHF = congestive heart failure. All variables determined in the 6 month period prior to the index date (see methods)

A risk score (RS) will then be calculated for each person in the cohort at baseline and again for the case-control in the logistic regression analysis (see next section) using data from the 6 months prior to the event date for the case. The RS will be the linear predictor corresponding to the terms:

RS = Ba*Ia + Bb*Ib +Bc*Ic + etc.

where Ba is the coefficient from the logistic regression for the first item in the risk score model and Ia is an indicator variable that indicates whether or not the first item is present for the given person, and so on. This score will then be used to divide the unexposed (or alternatively the entire study population) into approximate quintiles, resulting in a set of cut-points RS1, RS2, RS3, RS4.

Once these cut-points have been derived, the classification will be applied to the entire population (including the exposed) to calculate 5 indicator variables for the quintiles of the risk score (QRS1, QRS2, etc.), as follows:

QRS1: RS <RS1

QRS2: RS1 ≤ RS <RS2

QRS3: RS2 ≤ RS <RS3

QRS4: RS3 ≤ RS <RS4

QRS5: RS ≥ RS4.

These indicator variables will then be used in further modeling, in place of the individual potential confounders that comprise them.

Logistic regression modeling of the association of drugs of interest with clinical outcomes

When the requisite numbers of events are available for comparative analyses, matched case control analyses will be conducted using conditional logistic regression to assess the association of the drugs of interest with each clinical outcome specified in section **IV.G. Clinical Outcomes of Interest**. The resulting measures of association between the drugs of interest and the outcomes will be the odds ratios and associated 95% confidence intervals for each drug of interest relative to no exposure to any anti-inflammatory treatment. No statistical significance testing will be performed.

The case-control analysis will be conducted separately for each country using a separate model for each outcome. Each model will control for potential confounders via matching, the use of the outcome-specific baseline disease risk score, and an indicator for the etoricoxib prescribing habits of the practice. In addition, two-level modeling will be used to fit the data from different countries / databases to get a combined summary odds ratio. The first level will be a logistic regression for each country / database. On a second level, we will combine the estimated effect from each country / database with another linear regression to obtain a pooled odds ratio estimate. This two-level modeling is equivalent to a logistic regression including exposure as a fixed effect and the country and country-by-exposure interaction as random effects. This approach will be implemented using a non-linear mixed model.

A given patient may be selected as a case or a control in more than one analysis. A patient may also be selected as a case in one analysis and a control in another analysis. The date of diagnosis of the outcome will be designated the index date for the case. Up to 5 controls will

be matched to each case on age, gender, calendar year of entry in into the AS cohort, and country. The end of follow-up for each control must occur at a date later than the index date for the case. For UK cases, controls will be selected first from the same database as the case, then from other databases as needed. Controls will be assigned an index date that is the same as the case to which he/she is matched.

For each case and his/her controls, exposure status will be assessed on the index date for each of the study drugs of interest. Exposure status on the 'index' date will be classified as 'current', 'recent', 'prior', or 'unexposed' (mutually exclusive categories), as follows:

'Current' when the most recent exposure (calculated duration of the most recent prescription + 14 days) **overlaps** the 'index' date.

'Recent' when the most recent exposure (calculated duration of the most recent prescription + 14 days) **ended on a date 1 to 60 days prior to** the 'index' date (does not overlap index date).

'Prior' when the most recent exposure (calculated duration of the most recent prescription + 14 days) ended on a date 61 to 180 days prior to the 'index' date (does not overlap index date).

'Non-exposure' when none of the above applies. In other words the most recent exposure (calculated duration of the most recent prescription + 14 days) ended on a date 181 or more days prior to the 'index' date, OR when the patient did not have any prescriptions during his/her follow-up in the study.

For each outcome, the association of exposure to etoricoxib and each of the other drugs of interest with the outcome will be assessed using conditional logistic regression (with matching on age, gender, calendar year of entry in into the AS cohort, and country), and controlling for:

The baseline disease risk score appropriate to the outcome

Quartile of number of etoricoxib prescriptions for the practice attended by the patient. This will be derived from the total number of etoricoxib prescriptions over the entire study period for each practice. This is intended to address potential confounding by different etoricoxib prescribing habits among the GPs.

If any of the above potential confounders do not contribute significantly to the estimates of drug effects in a specific model they will be dropped from that specific model.

In each model, exposure to etoricoxib and each of the other drugs of interest will be characterized (current or recent vs. not currently exposed to any COX-2 or non-selective NSAID) as independent variables in the model. Thus for the GI outcome for example, the model will estimate the odds ratios (OR) and associated 95% confidence intervals (95% CI) for exposure to etoricoxib and each of the other drugs of interest (vs. no exposure to any of the study drugs of interest) as well as the OR and 95% CI for the baseline disease risk score for the outcome, as follows:

OR (95% CI) for Risk Factor Given GI Clinical Outcome	
Risk Factor	OR (95% CI)
Non-exposure (no current or recent COX-2 or NSAID)	1.0 (referent)
Etoricoxib	
Current	
Prior	
Recent	
Rofecoxib	
Current	
Prior	
Recent	
Celecoxib	
Current	
Prior	
Recent	
Valdecoxib	
Current	
Prior	
Recent	
Lumiracoxib	
Current	
Prior	
Recent	
Meloxicam	
Current	
Prior	
Recent	
Etodolac	
Current	
Prior	
Recent	
Diclofenac	
Current	
Prior	
Recent	
Ibuprofen	
Current	
Prior	
Recent	
Naproxen	
Current	
Prior	
Recent	
Indomethacin	
Current	
Prior	
Recent	
“Other Non-Selective NSAIDs”	
Current	
Prior	
Recent	
Multiple COX-2 / NSAIDs	
Prior	
Current	
Recent	
GI Baseline Disease Risk Score	

Using the same model, the measures of associations for the various drugs of interest will be compared with current exposure to naproxen as an active comparator.

Because of the multiple comparisons being made (12 exposures for each of 10 outcomes) in the main analysis, there is an increased risk of false positive signals. Accordingly, the 95% confidence interval for a given OR will be "flagged" as a potential signal if the corresponding p-value (for an implicit test of OR=1) is statistically significant after application of the

Mehrotra and Heyse multiplicity adjustment to control the false discovery rate (FDR) at a desired low level. (Mehrotra 2004) Following the pre-stated double false discovery rate (DFDR) multiplicity adjustment, the "statistical significance" cut-off for any individual p-value depends on the level of desired false discovery rate control (e.g., 5% vs. 10%), the mean number of AEs within each "body system", the observed event rates, etc. The MAH will provide a list of "flagged" AEs without any adjustment, and with a DFDR adjustment with overall FDR control at 5%, 10% or 15%. Future cumulative updates to the analysis will be used to assess the longitudinal characteristics of the flagging mechanism

To examine the potential for immeasurable time bias due to the fact that inpatient exposure to the drugs of interest is not observable (Suissa 2008), the record for each case and his/her selected controls will be examined for hospital admissions within the 6 months prior to the index date. If there are a significant number of such occurrences an indicator variable for hospitalization (yes, no) will be included in the analyses.

Dose-specific analyses will be considered for each drug of interest depending on the number of cases available for analysis at the various dose levels.

Sensitivity analyses will be performed as follows:

By adding 28 days to the duration of each prescription for purposes of defining exposure”

By stratifying the analysis based on whether the index date for the case-control set is before or after the COX-2 urgent safety restriction (i.e., <17Feb05 vs. ≥17Feb05).

By analyzing only the UK data, and again using only the GPRD and THIN databases (to understand the effect of potential differences in the quality and completeness of the data in the different countries / databases)

By excluding data from France from the analysis, since there is no etoricoxib exposure in France during the study period.

REPORTING OF SERIOUS ADVERSE EVENTS

No reporting to regulatory agencies of individual Serious Adverse Events (SAE) is planned as part of this retrospective observational database study. This is consistent with Council for International Organizations of Medical Sciences (CIOMS) V, which states that for epidemiological studies, individual case reporting is generally not appropriate unless there is specific attribution of an individual case (i.e., within the medical record). The study results will be included in a report at the end of study. Interim reports may be provided on an annual basis to the regulatory agencies until completion of the study. Aggregate reports may be provided to regulatory agencies in the Periodic Safety Update Reports (PSUR) as soon as available.

Evaluation of individual cases is not a planned component of this retrospective observational database study. In the event an evaluation is required for a specific health outcome of interest, the protocol would be amended or the evaluation would be conducted under a separate protocol and the results would be summarized in a report aggregating the data.

SAMPLE SIZE CONSIDERATIONS

Preliminary analyses indicate that there are approximately 6439 patients who appear to be eligible for inclusion in the AS cohort (see following Table). Among them, there are approximately 33,160 patient-years of follow-up for these patients (approximately 5.1 patient-years per patient). About 435 of these patients were exposed to etoricoxib (6.8% of all patients), for a total of approximately 432 patient-years of exposure (1.3% of total follow-up time). Thus the anticipated amount of exposure to etoricoxib in the cohort is expected to be small at this time. Exposure to other NSAIDs appears to be greater than that for etoricoxib in this cohort.

Preliminary Numbers of Patients and Exposure to Etoricoxib in the study Population

	GPRD	**THIN**	**UK Disease Analyzer**	**France Disease Analyzer**	**Germany Disease Analyzer**	**Overall**	
No. of Eligible AS Patients							
Overall	3034	475	895	992	1053	**6439**	
Males	2330	347	686	514	592	4469	
Females	704	128	209	468	461	1970	
Total Duration of Follow-up (In Days)							**(Overall, years)**
Overall	6980264	993600	2935826	806844	395269	12111803	33160.3
Males	5455582	731611	2254756	443316	218309	9103574	24924.2
Females	1524682	261989	681070	363528	176960	3008229	8236.1
Number of Patients Exposed In Follow-up Period							
Etoricoxib							
Overall	272	48	66	0	49	435	
Males	192	36	46	0	29	303	
Females	80	12	20	0	20	132	
Total Duration of Exposure (In Days)							**(Overall, years)**
Etoricoxib							
Overall	107496	17312	26879	0	6082	157769	432
Males	82036	12951	20681	0	3191	118859	325.4
Females	25460	4361	6198	0	2891	38910	106.5

To estimate the expected numbers of clinical outcomes that might be available for analysis, rates from prior GPRD studies done by the MAH were examined. In a prior GPRD study of the incidence of cardiovascular events in an AS population in the UK (men and women combined, excluding those with prior non-fatal MIs or strokes) the incidence of MI was 0.42 / 100 patient years and that for stroke was 0.36 / 100 patient-years, regardless of treatment). (Cook 2004) Based on this rate and the anticipated number of patient years of follow-up in the cohort, and assuming the gender and age distributions are similar in this study with the current one, the expected numbers of first time incident MIs and strokes in this study would be about 139 and 119, respectively.

In a different prior GPRD study of the use of etoricoxib among patients with indication for etoricoxib (OA, RA, arthritis not specified, or gout - on average an older population than in the AS study above) the incidence rates of clinical events was estimated among etoricoxib users during the first year follow-up and during the first course of etoricoxib exposure (with the exposure truncated when other NSAIDs prescription written). (Watson 2008) The incidence rates of clinical events relevant to this study, including both patients with and without prior events, are as shown in the following Table (note rates are per 1000 / patient years).

Table

Incidence of Clinical Outcomes during the First Year Follow-Up and During the First Course of Etoricoxib Exposure (Exposure Truncated when Other NSAIDs Prescription Written; Includes Patients with Prior Events

Outcome	Sub-cohort 1[†] Incidence rate[††] (n/N)	Sub-cohort 2[‡] Incidence rate[††] (n/N)	Sub-cohort 3 [§] Incidence rate[††] (n/N)	Sub-cohort 4 [‖] Incidence rate[††] (n/N)
Gastrointestinal Disease (PUBs)	13.07 (23/7525)	14.25 (28/9414)	9.11 (7/3346)	0.00 (0/1035)
Renal Impairment/Failure	4.54 (8/7525)	4.57 (9/9414)	10.40 (8/3346)	4.81 (1/1035)
Heart failure/Left ventricular dysfunction	10.23 (18/7525)	3.05 (6/9414)	10.40 (8/3346)	9.62 (2/1035)
Vascular				
Cardiovascular System Event	25.74 (45/7525)	21.43 (42/9414)	11.70 (9/3346)	24.18 (5/1035)
Coronary Heart Disease	19.41 (34/7525)	14.78 (29/9414)	6.50 (5/3346)	9.63 (2/1035)
Acute Myocardial Infarction	5.11 (9/7525)	5.09 (10/9414)	3.90 (3/3346)	4.81 (1/1035)
Ischemic Heart Disease	14.83 (26/7525)	13.75 (27/9414)	5.20 (4/3346)	4.81 (1/1035)
Cerebrovascular Event	7.40 (13/7525)	7.12 (14/9414)	5.20 (4/3346)	14.48 (3/1035)
Intracerebral Hemorrhage	0.00 (0/7525)	0.51 (1/9414)	0.00 (0/3346)	0.00 (0/1035)
Cerebral Infarction	0.00 (0/7525)	0.51 (1/9414)	1.30 (1/3346)	4.82 (1/1035)
Cerebrovascular Accident NOS‡‡	2.27 (4/7525)	4.07 (8/9414)	1.30 (1/3346)	9.62 (2/1035)
Transient Ischemic Attack	6.82 (12/7525)	2.54 (5/9414)	3.90 (3/3346)	0.00 (0/1035)
Sudden/unexplained death	0.00 (0/7525)	0.00 (0/9414)	0.00 (0/3346)	0.00 (0/1035)
Hypertension	58.99 (102/7525)	61.79 (120/9414)	53.88 (41/3346)	53.73 (11/1035)

[†] First etoricoxib prescription on 1 April 2002 to 30 September 2003

[‡] First etoricoxib prescription on 1 October 2003 to 30 September 2004

[§] First etoricoxib prescription on 1 October 2004 to 17 February 2005

[‖] First etoricoxib prescription on 18 February 2005 to 30 June 2005

[††] Per 1000 person year

[‡‡] Not Otherwise Specified

Source: Watson 2008

Based on the results in this study and the total person years of follow-up in the current study (33,160) one might approximately expect the following types of events to occur as follows in the current study

Type of event	Approximate rate / 100 pt-yrs	Expected no. of cases in current study
GI PUB	1.2	398
Renal Failure	0.4	133
Heart Failure	0.8	265
Any CV system	2.0	663
MI	0.5	166
Stroke	0.4	133
Hypertension	5.5	1823

Sample size calculations were conducted using commercial software (Power Analysis and Sample Size System version 08.0.4.) for matched case-control designs. (Hintz 2008) The following table shows the number of cases needed to detect with 80% power various ORs for the association of etoricoxib in the current study.

Odds Ratio	No. of Cases needed
2.00	1345
2.50	694
3.00	444
3.50	319
4.00	246
* Assumes 1.4% prevalence of exposure to etoricoxib (based on person-time), 5 controls per case, and one-sided alpha of 0.05)	

Thus the power to detect a minimal clinically meaningful increase in the risk of most clinical outcomes with exposure to etoricoxib given the present study size will be very limited and interpretation of the results will be difficult. Therefore a "stepped approach" is planned for the comparative analysis of clinical outcomes, as described in section **IV. H. Analysis.** For each clinical outcome, the case-control analysis and estimates of the association of the drugs of interest will be undertaken when there are at least 700 events (in the entire cohort) for analysis. This minimal number of events will provide 80% power to detect a 2.5-fold increase in the risk of the event with etoricoxib compared with non-exposure given this study design. For those clinical outcomes where the minimum required 700 events are not available at the time of this initial analysis, counts and listings of events will be provided as described in section **IV. H. 1. e. Incidence of Clinical Outcomes.** Future cumulative updates to this analysis are planned by the MAH; thus all outcomes will likely eventually reach the minimum 700 events needed for analysis.

LIMITATIONS

This study has a number of limitations that potentially will affect the validity of findings or the interpretation of the results. This section describes some of these limitations; however there may be additional limitations that are not apparent at the time the protocol was written.

Medical Care Models in the Countries and Databases

In the UK, GPs are the gatekeeper and primary point of contact for patient care. Patients can register with only one GP at a time. Many patients stay with the same GP for long periods of time. In Germany and France, there is no requirement for people to register with a GP. Patients in these countries are able to change their GP as they wish. As a result it is likely that on average patients in Germany and France do not stay with the same GP for as long as patients in the UK do. As a result, the completeness of the data from GP practices in these countries is not likely to be as good as that from the UK. Also as a result of the above, there may be a greater possibility in Germany and France that a patient will appear in the database more than once. The case-control analysis will match controls to cases on country, and preferentially to the same database, as a means to at least partially control for these differences among countries.

The data from this study are from GPs. In the UK, most consultations (e.g. doctor visit, prescription, a specialist referral) occur in primary care. However, the GPs will not typically capture health services provided by direct access to some health care providers including the emergency room. In Germany and France, where patients are free to seek medical care from any doctor, the proportion of consultations occurring in primary care is likely lower. Therefore there may be important outcomes diagnosed in an emergency room setting or elsewhere that are not captured in the GP records. It is likely that most serious outcomes will eventually come to the attention of the GP, although the delay in such information being recorded by the GP is unknown. It is not clear if these issues will bias the results of the analysis.

Etoricoxib received marketing authorization in France in August 2008, near the end of the study period for this protocol. Therefore there will be little or no etoricoxib exposure in French patients with AS in this study. However, the inclusion of France in the study population will increase the numbers of patients who are users of other drugs besides etoricoxib (celecoxib, non-selective NSAIDs) in the study. Thus the data from France will contribute to the precision of the estimates of effect for those products.

AS Diagnosis

It is likely that the true onset of AS is earlier than recorded in medical records for most AS patients. According to a recent review “The most common presenting symptom is low back pain. Usually, pain is centered over the sacrum and may radiate to the groin and buttocks and down the legs. The typical patient is a young man who has repeated episodes of back pain waking him at night and associated with spinal stiffness in the morning. Low back pain persists, even at rest. The pain pattern is characteristic of bilateral sacroiliitis.” (Peh 2005) Given this clinical presentation it is expected that the recorded diagnosis of AS will generally

not represent the true onset of the disease. Patients with more severe or aggressive disease may be diagnosed earlier in their course of disease than those with less severe or aggressive disease. In addition, mild cases of AS may go undetected. (Peh 2005) It is not clear if these issues will bias the results of the analysis.

Exposure to Study Drugs of Interest

In light of the fact that this study will measure GP prescribing and not actual drug use by patients, any inferences about drug use by patients will require that the following set of assumptions all hold true: 1) all prescriptions were dispensed to patients on the same day that they were issued by each practice's computer system; 2) patients consumed the drugs under study as directed on consecutive days after the date that each prescription was issued; and 3) patients consumed the entire quantity of drug supplied in each prescription. The limitations of inferring actual NSAID use from GP prescribing data recorded in electronic databases have been reviewed elsewhere. [Ilkhanoff 2005])

The databases do not capture prescriptions issued by hospital-based specialists (e.g., consultant rheumatologists), nor during hospital admission. This could lead to a problem coined "immeasurable time bias: (Suissa, 2008). The analysis will determine whether hospital admissions occurred in a meaningful number of cases and controls in the six months prior to the index date. If this is the case, then appropriate measures will be taken to assess whether this ha any effect on the results.

In addition, it is expected that some patients will have been treated for back pain with NSAIDs prior to a recorded AS diagnosis. Patients with more severe or aggressive disease may be treated with NSAIDs earlier in their course of disease than those with less severe or aggressive disease. It is not clear if such patients would be preferentially channeled to certain NSAIDs. It is not clear if this issue will bias the results of the analysis.

Clinical Outcomes

The clinical outcomes under study are based on GP recorded diagnoses based on clinical care standards. It is expected that there will be some degree of misclassification of clinical outcomes due to misdiagnoses. There may be a greater proportion of erroneous diagnoses for some outcomes (TIA, hypertension) compared with others (MI, acute renal failure). It is not clear if this issue will bias the results of the analysis. Also, In analyzing the incidence of clinical outcomes, there may be some disadvantage in GI event rates for older NSAIDs that were available before PPIs. Lastly, the study period spans 20 years, during which population risks for various events may have changed, e.g. the number of CV events in the general population has declined due to introduction of statins, and NSAID-associated GI risk has decreased due to increased awareness and greater use of proton pump inhibitors.

Potential Confounding and Analysis

This study has been designed to reduce the potential for confounding through features of the study design and the analytic methods. Nevertheless there is likely some degree of residual confounding in the assessment of the associations between the drugs under study and the clinical outcomes due to inaccurately measured or unmeasured confounders. For example,

data regarding lifestyle factors such as smoking are not completely available in the databases, and data regarding the use of over the counter medicines, such as aspirin, are not captured at all. In addition, there is potential for channeling bias in this study because it is feasible that patients prescribed etoricoxib are those patients at greater risk of some of the clinical outcomes. For example, those with prior GI bleeding or those who use low dose aspirin may be preferentially prescribed etoricoxib over non-selective NSAIDs.

The use of propensity scores (for exposure to etoricoxib) to balance groups at "baseline" was considered. However there were several difficulties anticipated with this approach. The use of propensity scores is optimal with very large datasets and a large proportion of exposed patients, which allows for calculating propensity scores using many dozens of variables. With only about 6500 total patients (and only 450 patients exposed to etoricoxib) the numbers patients that could be used to construct propensity scores in this study is limited, which would subsequently limit the numbers of variables one could use in the propensity score models. In addition, with propensity score matching some cases are typically lost because of the inability to find controls that match on the case propensity score. Given the anticipated small numbers of cases anticipated for some outcomes in this study, the loss of some case would be counterproductive. Lastly, it is anticipated that many patients in this study will have follow-up data for a number of years and for some there will be more than one instance of exposure to etoricoxib; in this situation it is not readily apparent at what point in time one would calculate the propensity score for exposure to etoricoxib.

The presence of channeling will be assessed by examining the presence of risk factors for the outcomes by treatment groups. Control for potential confounding due the above issues will be attempted through matching and the use of the baseline disease risk scores in the analysis as described in section **IV. H. 2. a. Disease Risk Scores**; however confounding is not likely that it will be fully controlled. The net effect of any resulting "residual" confounding is not able to be measured.

Study Power

The power of this study to detect clinically important increases in the risk of outcomes with the drugs of interest is very low. This is because the prevalence of AS is low, the use of etoricoxib in the AS population has been low to date, and the AS population is relatively young and thus lower risk of some of the clinical outcomes of interest. The MAH has previously committed to updating this study as new data accrue for use of etoricoxib in the AS population as a result of the 2008 CHMP approval of this indication. Future updated analyses will be done on a cumulative basis. The MAH also has committed to exploring the possibility of adding data from additional databases to this study in the future in order to increase the study power.

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