THIS PROTOCOL AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK & CO., INC., WHITEHOUSE STATION, NJ, U.S.A.

SPONSOR:

Merck & Co., Inc.
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ, 08889-0100, U.S.A.

TITLE:

Safety Data on Etoricoxib from Swedish Registries of Spondyloarthropathy / Ankylosing Spondylitis Patients

PRINCIPAL INVESTIGATOR:

PPD

CONTACT INFORMATION:

PPD
Sweden
Office Phone: PPD
Office Fax: PPD

SITES:

Not applicable

Version / Date

1.1 / 11 Apr. 2011

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse experience
AS	Ankylosing Spondylitis
ACE	Acetyl cholinesterase
CHMP	Committee Human Medicinal Products
CI	Confidence interval
COX-2	Cyclooxygenase-2
DVT	Deep venous thrombosis
EDGE	Etoricoxib vs. Diclofenac Sodium GI Tolerability and Effectiveness study
EMEA	European Medicines Evaluation Agency
EMA	European Medicines Agency
GI	Gastrointestinal
GP	General Practitioner
GPRD	General Practice Research Database
MEDAL	Multinational Etoricoxib and Diclofenac Arthritis Long-term Program
MI	Myocardial infarction
NSAID	Nonsteroidal anti-inflammatory drugs
nsNSAID	non-selective NSAID
OA	Osteoarthritis
PASS	Post-authorization safety study
PE	Pulmonary embolism
PI	Principal Investigator
PUB	Perforations, ulcers or bleeding
PY	Person-years or patient-years
RA	Rheumatoid arthritis
SPC	Summary of product characteristics
UK	United Kingdom

SPONSOR CONTACT INFORMATION

PPD

Merck Research Laboratories
P.O. Box 1000 (UG2CD-48)
North Wales, PA 19454-2505
PPD
Office: PPD
Fax: PPD

I. CHANGES TO THE PROTOCOL SINCE PRIOR VERSION

For this version of the protocol (V1.1) an additional clinical outcome of "Hypertension, severe" (defined as hospital admission with a primary diagnosis of hypertension) was added. See Section VI. METHODS, I. DATA LINKAGES, *Assessment of clinical outcomes (p. 15).*

II. 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 registry of patients with AS taking etoricoxib.

III. BACKGROUND AND RATIONALE

A. 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 primarily designed to demonstrate efficacy, it provided only limited 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.

In addition to the above clinical trial data, a nested case-control post-authorization safety study of etoricoxib and other anti-inflammatory therapies in a cohort of patients with AS using data from general practice databases in the UK, France and Germany been performed and reported to the CHMP in May 2010. 11,169 patients from the UK, Germany and France with AS met the inclusion criteria for the analysis. The characteristics of the cohort were consistent with the known epidemiology of AS. The baseline comorbid disease burden for the cohort was generally low (perhaps partly due to the use of a 6-month baseline period to assess medical history). Relatively large proportions of the cohort used gastroprotective or cardiovascular medications during the baseline period. Relatively few patients in the cohort received etoricoxib and the amount of exposure to the treatment was limited. The doses of etoricoxib prescribed to patients in the study cohort were consistent with the labeling for the AS indication. The incidences of prespecified clinical outcomes of interest (including upper GI, cardiovascular, cerebrovascular, renal, congestive heart failure and hypertension events) were relatively low. Overall, only 29 clinical events of the above types occurred in 28 patients while currently exposed to etoricoxib. Given the limited exposure to etoricoxib in the study, and the small numbers of patients with clinical outcome events of interest while exposed to etoricoxib it was not possible to draw firm conclusions regarding the safety profile of etoricoxib for the indication of AS from these results from the analysis (the analysis will be updated annually to accrue more exposure / clinical events of interest).

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

B. STUDY RATIONALE

This study is being conducted by Merck & Co. Inc. as a post-licensure commitment to the European Medicines Agency (EMA). The rationale for the study is to provide additional post-marketing safety data regarding the use of etoricoxib for the indication of ankylosing spondylitis.

IV. OBJECTIVES

The specific project objectives are to:

- Describe the characteristics of Swedish patients with inflammatory spondyloarthropathy / ankylosing spondylitis (SpA/AS)
- Describe the use of etoricoxib and other COX-2 inhibitors / nsNSAIDs in Swedish patients with SpA/AS.
- Estimate and compare the rates of clinical outcomes of special interest (gastrointestinal, renovascular, cardiovascular and cerebrovascular) with use of etoricoxib and other COX-2 inhibitors / nsNSAIDs in Swedish patients with SpA/AS.

V. HYPOTHESES

This study is for estimation purposes. The clinical outcomes of interest as stated in the objectives above are known to be associated with anti-inflammatory treatments (nsNSAIDs and COX-2 selective inhibitors) and are described in drug class labeling. Comparisons of clinical outcomes among the drugs of interest will be made by descriptive comparison of the point estimates for the incidence rates and their associated 95% CIs, using both clinical and epidemiological judgment and in light of the limitations of this observational study. No formal statistical significance testing will be performed for purposes of such comparisons.

VI. METHODS

A. STUDY DESIGN

This study is a population- and register-based nationwide matched cohort study using data from 1987-2010, with updated linkage and repeat analysis planned for 2013-14.

B. STUDY PERIOD

The study period will begin on 1 Jan 2001 and end on 31 Dec. 2010 (or the latest date for which data are available from the various registers). For the updated linkage the end of the study period will be determined at a later date.

C. BASELINE PERIOD

Data prior to 2001 (as far back as 1987) will used as available to characterize baseline characteristics of the study population.

D. ELIGIBILITY CRITERIA

A patient will be eligible for inclusion on the first date all of the following criteria are met:

- Attended an out-patient clinic 2001-2010
- Age >=16 years on the date attended the out-patient clinic
- Registered with an ICD-code corresponding to SPA/AS (i.e. ICD10: M46.1, M46.8, M46.9, and ICD9: 720B, 720C or 720X for the appropriate periods) and AS (i.e. ICD10: M459 and ICD9: 720A for the appropriate periods)

E. COHORT ENTRY DATE

The date that a given patient meets all eligibility criteria will be designated as the cohort entry date.

F. STUDY ACCRUAL

This study is designed as a retrospective analysis of patient level data using a series of Swedish national health care-related registers. There will be no active enrollment or follow-up of patients, and no data will be collected directly from patients.

G. PATIENT FOLLOW-UP

Patients will be followed until the earliest of emigration, death, or the end of the study period. Patients will be assigned to groups based on coded prescriptions that were dispensed to the patients 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**)

H. DATA SOURCES

Swedish health-care is public, tax-funded, and population-based. Referral to hospital is based on geography rather than insurance-status. Health- and demographic information is registered in a series of national registers with an extreme degree of completeness. Linkage of data from

different registers is possible through the use of unique personal identifiers, issued to all Swedish residents alive in 1947 or born thereafter.

For this study, data from the following registers will be utilized:

- *The Swedish Patient Register (of Hospital Discharges and Outpatients Visits)*

  In this register, close to 100% of all hospital discharges 1987 and onwards are registered, including date of discharge, discharging hospital and department, and medical discharge diagnoses (assigned by physicians) according to ICD-10. Since 2001, this register also contains information on outpatient visits (dates, diagnoses, and department) for non-GP care (e.g., paediatric outpatient departments).This register will be used to identify the study population of patients with SpA/AS, determine baseline characteristics, and to identify clinical outcomes. Validations against medical files suggest that for many diagnoses (including Rheumatoid Arthritis), the validity is around 90%.

- *Swedish Register of Total Population and Population Changes*

  This is the Swedish census register, updated weekly, covering information on all residents in Sweden, including certain basic demographic information. This register will be used to determine baseline characteristics and to ascertain end of follow-up.

- *The Swedish Cancer Register*

  This nationwide register, with an internationally exceptionally high coverage, has been in operation since 1958 and includes information on all diagnosed malignancies (registration is mandatory by law for clinicians and pathologists), including type (ICD 7-10, ICD-O et cetera), date, and department. This register will be used to assess baseline history of gastrointestinal cancer.

- *The Swedish Cause of Death Register*

  This register includes data on date and cause (ICD-7-10) of death for all deaths among Swedish residents 1952 and onwards. This register will be used to identify clinical outcomes and to ascertain end of follow-up.

- *The Swedish Biologics Register*

  This is a profession-based rheumatology register of patients with rheumatic diseases (RA initially) >16 years of age starting treatment with a biologic drug. For patients with RA, the register includes an estimated 90% of all RA patients receiving biological therapy in Sweden. Currently, some 2500 patients with SpA/AS starting a biologic are also registered because of the biologic start (whether the 90% coverage that pertains to RA patients applies also to SpA/AS is currently not clear). This register will be used to identify treatment with biologicals.

- *The Swedish Prescribed Drug Register*

  In operation since Q3 2005, this nationwide register covers information on dispensed drugs in the out-patient setting including treatments given by "consultant rheumatologists" in out-patient care. This register will be used to determine baseline medication use and to exposure to etoricoxib, other COX-2 inhibitors, and nsNSAIDs prescribed in the out-patient setting. It does not capture drugs given while in hospital and includes only a proportion of non-dispensed drugs such as infusion biologics for SpA/AS. The latter treatments are captured in the *Swedish Biologics Register* for those patients included in that register.

I. DATA LINKAGES

For this study, the following data linkages will be performed at Statistics Sweden and at the National Board of Health and Welfare; the data will be delivered to the PI as a de-identified dataset for analysis:

- *Assembly of a national cohort of individuals with Spondyloarthropathy including those given a diagnoses of AS:*

  Through ICD-codes for SpA and AS all individuals who meet entry criteria will be identified.. The out-patient and any available hospitalisation data for a given patient will be assembled.

- *Assessment of vital status throughout follow-up:*

  Through linkage of all unique individuals in (i) to the Swedish Cause of Death Register and to the Swedish Register of Total Population and Population Changes, a last date of potential follow-up (and all deaths including underlying and contributory causes of death) will be identified. These registers will include data on vital status through 2010, and causes of death through 2009.

- *Assessment of baseline prior medications:*

  Through linkage to the Swedish Prescribed Drug Register, all dispensing of drugs during the baseline period will be identified, including substance (ATC-coding), amount dispensed, and date of dispensing, for purposes of baseline characteristics or for adjustment of potential confounders during analyses of clinical outcomes will also be identified, including:

  - Treatments for rheumatic conditions: non-biologic and biologic disease modifying anti-rheumatic drugs (DMARDs),oral corticosteroids

  - Gastro-protective medications: proton pump inhibitors (PPI), histamine 2 receptor blockers (H2s), misoprostol

  - Cardiovascular / lipid medications: diuretics, anti-hypertensives, treatments for heart failure, lipid-lowering drugs

- Diabetes medications: insulin, oral anti-diabetic
- Anticoagulants / antiplatelet therapy: warfarin, low molecular weight heparin (LMWH), tranexamic acid, other anti-coagulants or anti-platelet drugs
- Prescription aspirin (any dose)
- Narcotic and non-narcotic analgesics: codeine, morphine / morphine derivatives, tramadol hydrochloride, prescription acetaminophen, etc.

- *Assessment of baseline comorbid conditions*

Through linkage of all unique individuals with SpA/AS to the Swedish Patient Register, all out-patient records and all hospitalisations during the baseline period will be identified (date, ICD-code, duration of hospital stay, hospital and department type (medical specialty). These records will be used for purposes of baseline characteristics or for adjustment of potential confounders during analyses of clinical outcomes. Baseline comorbid conditions will be identified based on ICD-codes for the following diagnoses (by body system):

- Cardiovascular: cardiac valvular disease, arrhythmia
- Peripheral vascular: deep venous thrombosis (DVT), pulmonary embolism (PE)
- Endocrine / metabolism: diabetes mellitus (DM), hyperlipidemia
- Renal: hypertension, nephritis (any type)
- Gastrointestinal: colorectal cancer, dyspeptic and other abdominal pain
- Hepatic: alcoholism, liver failure
- SpA / AS-related: Prior recorded diagnosis of SpA, AS, and Low Back Pain

In addition, recorded diagnoses of any of the clinical outcomes (see below) will also be tabulated during the baseline period.

- *Assessment of exposure to etoricoxib and other NSAIDs:*

  Through linkage of all above-mentioned individuals to the Swedish Prescribed Drug Register, all dispensing of etoricoxib, other COX-2 selective inhibitors, and nsNSAID treatments Q3 2005-2010 will be identified, including substance (ATC-coding), amount dispensed, and date of dispensing.

- *Assessment of clinical outcomes*

  Through linkage of all unique individuals with SpA/AS to the Swedish Patient Register, all hospitalisations and all outpatients visits for each study subject following cohort entry date through study end date will be identified (date, ICD-code, duration of hospital stay, hospital and department type (medical specialty). Using these data the first occurrence of each clinical outcome in a given patient will be identified based on ICD-codes for the following diagnoses of interest (by body system):

  - Atherosclerotic / thrombotic cardiovascular: angina pectoris, acute myocardial infarction (MI), percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass grafting, death from acute MI, sudden death presumed to be of cardiac origin

  - Congestive heart failure

  - Atherosclerotic / thrombotic cerebrovascular: stroke (not classified as to type), ischemic stroke, hemorrhagic stroke.

  - Hypertension, severe (defined as hospital admission with a primary diagnosis of hypertension)

  - Renovascular: renal insufficiency (chronic & acute), dialysis

  - Gastrointestinal: varix bleeding,, esophageal, gastric and duodenal ulcer (with and without complications of bleeding or perforation), intestinal bleeding

J. APPROACHES TO SPECIFIC PROJECT OBJECTIVES

The following approaches will be taken to address the specific objectives:

1. Description of Swedish patients with SpA/AS

To describe characteristics of Swedish patients with SpA/AS, the study population will be defined as those meeting all of the eligibility criteria as defined in section **V.C. ELIGIBILITY CRITERIA**:

Data on number (%) of patients, proportions or univariate statistics for the below characteristics will be provided:

- Demographics (age in ten-year bands, sex, educational level using a three-level scale, county of residence)

- SpA/AS disease phenotype (ever recorded occurrence of diagnosis code indicating: an AS-diagnosis, uveitis, inflammatory bowel disease, psoriasis, urethritis, hip-joint replacement surgery, aortic valve surgery)

- Duration since first recorded SpA/AS diagnosis code

- Duration since first recorded diagnosis of Low Back Pain

- Baseline Prior Medications (ever recorded dispensing of any medication listed in section **V. METHODS, H. DATA LINKAGES**)

- Baseline Prior co-morbidities (ever recorded (hospitalisation / outpatient visit for any condition) listed in section V. METHODS, H. DATA LINKAGES)

2. Description of the use of etoricoxib and other NSAIDs in Swedish patients with SpA/AS.

The use of etoricoxib, other COX-2 selective inhibitors, and nsNSAIDs in the study population will be identified from Q32005 until the end of the study period. Data will be presented as follows:

- Ever recorded use of etoricoxib, other COX-2 selective inhibitors, and nsNSAIDs, including time between first and last prescription, cumulative amount (dose in mg) prescribed, interval (in days) between prescriptions, and proportion of patients prescribed both etoricoxib and other selective or nsNSAIDs during the study period, including the major treatment sequences (e.g., etoricoxib followed by other coxib or other NSAID and the reverse).

- Cumulative proportion of patients with SpA/AS exposed also to DMARDs or biologics during the study period.

- Predictors of use of etoricoxib, other COX-2 selective inhibitors, (compared with nsNSAIDs as the referent).t Investigated predictors will include: demography (age, sex, and educational level), phenotype (AS manifestations), and baseline co-morbidities, baseline prior medications.

3. Estimation of crude rates of clinical outcomes with use of etoricoxib, other COX-2 selective inhibitors, and other NSAIDs

Crude incidence rates of clinical outcomes with use of etoricoxib, other COX-2 selective inhibitors, and other NSAIDs during follow-up will be estimated. A clinical outcome event will be attributed to exposure to one of the study drugs of interest if the date of the diagnosis falls within the exposure time

window, as defined in the following section, for the specific analysis. Events that occur in patients who are not exposed will be tabulated and reported.

For a given clinical outcome, patients will be censored from further follow-up on the diagnosis date of the specific outcome or the end of follow-up for the patient, as defined in section V. METHODS, G. PATIENT FOLLOW-UP. However, a patient may be included in more than one clinical outcome analysis, with different follow-up times for each, if he/she has more than one type of outcome during the study period.

The number of events of a given type attributed to the exposure category will be divided by the total person time of exposure to that category across the entire cohort.

Event rates for the clinical outcomes will be assessed overall, and in patients with a without a history of the specific event type of interest during the baseline period, in the following groups according to diagnosis:

- Prevalent SpA/AS overall, prevalent SpA alone, and prevalent AS alone where prevalent is defined as patients with a prior diagnosis of SpA or AS during the baseline period. or after cohort entry but before 1 Jan 2007.

- Incident SpA/AS overall, incident SpA alone, and incident AS alone where incident is defined as SpA/AS individuals with no SpA/AS diagnosis codes in the patient register before 1 Jan 2007, and less than 6 months of accumulated exposure to any of the drugs of interest between July 2005 and January 2007.

Adjusted comparisons of incidence rates according to exposure will be performed as described V. METHODS, M. COMPARATIVE ANALYSIS

K. EXPOSURES OF INTEREST AND DEFINITION OF EXPOSURE

Below follows an outline of the intended exposure-definitions to be used. Based on the results of analyses for objective 2, these definitions may be subject to revision. In that event, a revised protocol will be produced.

The drug exposures of interest for this study are etoricoxib, other COX-2 selective inhibitors (as a group), and nsNSAIDs (as a group). For assessments of exposure to the drugs of interest the dates of a dispensing of each during the study period will be identified. No delay in exposure following the date of dispensing will be assumed.

The duration of a given prescription will be calculated based on the prescribed daily dose and the number of tablets supplied. The patient will be assumed to be exposed to the drug for a period equal to the duration of the prescription starting on the date of dispensing. The last date covered by the duration of the prescription as calculated above will be the prescription "end" date. If a patient receives another prescription for the same drug prior the prescription end date it will be assumed that the patient will start that prescription on the day following the end date of the of the prior prescription.

The data will be examined for the frequency with which patients receive prescriptions for another drug of interest (etoricoxib, other COX-2 selective inhibitor or nsNSAID) prior to the prescription end date for the prior medication(s). Depending on the findings one of several methods will be used to classify this exposure (e.g., censor the exposure to the first prescription when the new one is dispensed, count the patient as exposed to both drugs during the overlap of the two dispensings, count the patient as being exposed to "multiple drugs" [as a separate exposure category], etc.) After this examination specific methods to analyze exposure to multiple drugs will be decided and the protocol amended. This will be done prior to the ascertainment of clinical outcomes in relation to exposures.

Since the drugs of interest may be prescribed for regular as well as for intermittent use, and since the data will allow one to identify the prescribed amount but not the actual used amount, different exposure time definitions are planned, as follows.

- “On drug” exposure, from first date of dispensing and until the prescription “end” date. Time at risk will accumulate as long as there are consecutive overlapping dispensings (another dispensing <= 1 day following the prescription end date for the previous prescription). Time at risk will end on the prescription “end” date for the last prescription and there are no further consecutive overlapping dispensings for that drug.

- On drug + 14 days exposure: as for "on drug" except the prescription “end” date will be defined as 14 days after the last date covered by the duration of the prescription.

- On drug + 30 days exposure: as for "on drug" except the prescription “end” date will be defined as 30 days after the last date covered by the duration of the prescription.

- On drug + 90 days exposure: as for "on drug" except the prescription “end” date will be defined as 90 days after the last date covered by the duration of the prescription.

Prior to implanting these exposure definitions, the patterns of dispensings of the drugs of interest will be examined to assess the feasibility of the definitions. Depending on the findings other exposure classifications could be employed instead of or in addition to these. After this examination the final specific exposure definitions will be determined and the protocol amended. This will be done prior to the ascertainment of clinical outcomes in relation to exposures.

L. COMPARATIVE ANALYSIS

This section describes the analytic approaches that will be used for purposes of comparisons of incidence rates according to exposure. Given the potential for some analyses to be limited by sparse data, some analyses described here may in the end not be done.

As mentioned above, rates will be calculated in the following groups / subgroups, using the 3 different approaches to exposure (on drug, on drug + 14 days, on drug + 30 days):

- Overall
    - By history of specific event (yes / no)
    - By SpA / AS diagnosis (SpA only, AS only, combined)
    - By prevalent / incident SpA/AS as defined
    - By combinations of both of the above

A clinical outcome event will be attributed to one of the study drugs of interest if the date of the diagnosis falls within the exposure time window for the specific analysis as defined in the previous section. Events that occur in patients who are not exposed will also be tabulated and reported.

Crude rates of outcomes attributed to exposure to etoricoxib will be compared with the corresponding crude rates attributed to exposure to the other drugs of interest, as follows:

- First, rates of the specified outcomes of interest will be compared between SpA/AS patients who are exposed to etoricoxib, and SpA/AS patients who are exposed to other COX-2 selective inhibitors. Definitions of risk-time for these "comparator exposures" will be identical to that for etoricoxib.

- Second, rates for the specified outcomes of interest will be compared between SpA/AS patients who are exposed to etoricoxib and SpA/AS-patients who are exposed to nsNSAIDs. Definitions of risk-time for these "comparator exposures" will be identical to that for etoricoxib.

Rates will also be compared using Poisson-regression. The following covariates will be evaluated for purposes of adjustment for confounding:, age, sex, county of residence, marital status, time since first recorded SpA/AS diagnosis code, SpA/AS phenotypes, time since first recorded low back pain diagnosis, baseline co-morbidity registrations, baseline prior medications, and previous use of etoricoxib, other COX-2 selective inhibitors and nsNSAIDs. The feasibility of using propensity scores to adjust for baseline factors predictive of receipt of etoricoxib will be explored as another means to adjust for baseline differences across exposure groups will be explored as well. Based on the availability of the above covariates and model fitting, factors which are shown to importantly affect the relative risks will be included in the final regression models.

Models based on Cox-regression will also be performed. The same covariates will be evaluated for adjustment as with the Poisson-regression, except that time-varying co-morbidity / medication codes will be used. The models will be stratified by time since start of follow-up. Cumulative time on treatment will be assessed as </>= 1 year based on the dispensed amounts and number of iterations. Time since treatment start will assess time overall and separately also the first 30 days since first dispensing. Some patients will have an exposure time of <1 yr and some of >=1 yr. and the intention is to do a stratified analysis to see if the event rates differ by exposure time.

The following sensitivity analyses will be performed:

- According to whether a patient has a recorded AS diagnosis during follow-up, because subjects may switch from the SpA group to the AS and possibly back again
- For thrombotic/embolic cardiovascular (MIs and sudden deaths) and cerebrovascular (ischemic stroke) clinical outcomes - the nsNSAIDs group will exclude exposure to naproxen, since it has demonstrated potent anti-platelet inhibitory properties
- With censoring of patients at biologics exposure
- Because some diagnoses recorded long before cohort entry may no longer be active, with baseline medications and co-morbidities limited to those recorded within two years prior to cohort entry

M. SAMPLE SIZE CONSIDERATIONS

The design of this study is such that virtually 100% of patients with AS / SpA in the Swedish health care system will be identified and included in the analysis. It is common practice in Sweden to refer these patients from primary care to a specialist at least once for evaluation.

The 2008 census of Sweden indicated that there were about 3.84 million women and 3.75 million men in Sweden aged 16 years and older. The best available estimates of the prevalence of undifferentiated SpA and AS together (that is axial SpA) are 0.19% in women and 0.25% in men. Therefore, it is expected that about 16,671 persons (7296 women and 9375 men) with a diagnosis of AS / SpA will be identified in this study. Assuming that all identified patients in the study have a minimum of 5 years of treatment data in the Swedish Prescribed Drug Register, it is estimated that there will be a total of about 83,355 PY of follow-up with treatment data.

Pharmaceutical sales data for Sweden indicate that from 4Q2005 through 2010 among patients with a diagnosis of AS or SpA approximately 2175 patient years of Etoricoxib therapy were sold. Given the study design it is expected that the 2175 person years of therapy hold in this analysis. This represents about 2.6% of the expected total PY of follow-up time in the study with treatment data. For simplicity it will be also assumed that 2.6% of the study population, or 433 patients (with 2165 PY), will be exposed to etoricoxib, leaving 16,237 patients (with 81,185 PY) unexposed to etoricoxib.

To estimate the expected numbers of incident clinical outcomes that might be available for analysis (overall and with use of etoricoxib) in the unexposed to etoricoxib group, rates from a prior population-based cohort study done by Merck of patients of all ages (mean age 46, median age 45) with AS from general medical practices in the UK, Germany and France were used (see table below). The rates (note rates are per 1000 / PY) shown include events regardless of treatment and are restricted to persons without a prior history of a given event.

Table

Number (%) Of Patients and Incidence Of Clinical Outcomes Overall
During Follow-Up*
Patients Without A Medical History Of The Respective Outcome
UK (GPRD, THIN & IMS), Germany (IMS) and France (IMS)

Clinical Outcome	n/N (%)	Incidence /1000 py‡
Gastrointestinal Ulcer, Perforation or Bleeding	401 /11071 (3.62)	5.59
All Vascular Events	941 /11169 (8.43)	13.33
Ischemic / Thrombotic Cardiac Events:	340 / 11166 (3.04)	4.65
Acute Myocardial Infarction	196 / 11091 (1.77)	2.67
Unstable Angina Pectoris	162 / 11136 (1.45)	2.20
Ischemic / Thrombotic Cerebrovascular Events:	343 / 11168 (3.07)	4.68
Ischemic Stroke	97 / 11143 (0.87)	1.30
Stroke NOS†	218 / 11110 (1.96)	2.97
Transient Ischemic Attack	112 / 11147 (1.00)	1.51
Hemorrhagic Cerebrovascular Events:	19 / 11167 (0.17)	0.25
Hemorrhagic Stroke	19 / 11167 (0.17)	0.25
Thromboembolic Peripheral Vascular Events	316 / 11169 (2.83)	4.31
Deep Venous Thrombosis	271 / 11121 (2.44)	3.70
Pulmonary Embolism	47 / 11159 (0.42)	0.63
Arterial Embolism / Thrombosis	17 / 11166 (0.15)	0.23
Sudden / Unexplained Death	63 / 11169 (0.56)	0.84
Acute Renal Failure	146 / 11127 (1.31)	1.98
Congestive Heart Failure / Left Ventricular Dysfunction	310 / 11044 (2.81)	4.26
Hypertension	1332 / 10093 (13.20)	21.38

* Each row is not mutually exclusive; an individual patient may be counted in more then one row, but is counted only once in a given row.

† NOS=not otherwise specified as ischemic or hemorrhagic.

‡ py=person years

Thus, assuming that the gender and age distributions are similar in the above prior study and the current one, using the above rates and the estimated 83,355 PY of follow-up with treatment data, and it is expected that the following numbers of clinical outcomes

(disregarding treatment) will be available for analysis among AS patients, with accompanying treatment data, in the current study.

	Approximate rate / 1000 pt-yrs	Expected no. of cases in the current study	
Type of event		Overall	In those not exposed to etoricoxib
Cardiovascular			
Acute MI	2.67	223	217
Sudden death (presumed cardiac)	0.84	70	68
Heart Failure	4.26	355	346
Cerebrovascular			
Stroke NUD	0.30	25	24
Ischemic stroke	0.13	11	11
Hemorrhagic stroke	0.03	3	2
Gastrointestinal			
Upper GI PUB	5.59	466	454

Based in the above information the estimated power (based on the normal approximation with continuity correction) to detect various relative increases in the rates of the outcomes expected to occur most often [MI, heart failure (HF), and PUBs] with etoricoxib exposure relative to nsNSAIDs in the current study are as shown in the following table.

	Power (%)		
RR	MI	HF	PUB
1.5	10	3	4
2.0	16	14	21
2.5	22	35	48
3.0	28	60	76
3.5	32	82	93
4.0	39	94	98
4.5	42	99	100
5.0	46	100	100
* Assumes 2.6% prevalence of exposure to etoricoxib and a 2-sided alpha of 0.05			
source: http://www.openepi.com/OE2.3/Power/PowerCohort.htm			

Thus, if the assumptions of the study power analysis hold, this study will have low power to detect an increased RR of <3.0 for HF and PUBs, and very low power to detect any increased RR of MI (or the other less frequent outcomes), with etoricoxib relative to the comparison groups. The statistical power will be further reduced in the various stratified / subgroup analyses that are planned. However, the assumptions used in these estimations, which came from other EU countries, may not hold in Sweden. For example, the mean age of the AS population is Sweden is approximately 10 years older than that in the prior population-based observational study that generated the rates above. Therefore, the clinical outcomes rates for some of the outcomes in this study may in fact be higher than in the previous study.

Nevertheless, given the above information is based on outcome event rate data from other studies in different countries and assumptions regarding exposure to etoricoxib the information should be viewed as rough estimates only.

VII. STUDY PROCEDURES

A. INFORMED CONSENT AND INSTITUTIONAL REVIEW BOARD

Prior to being finalized this protocol will be reviewed by the CHMP of the EMA, and will undergo review and approval by the IRB at the Karolinska Institutet.

B. DATA PRIVACY

All information from registers provided to the PI by the Swedish National Board of Health and Welfare will be without personal identification numbers. The data will furthermore be securely stored following the rules from the Swedish data inspection authorities.

C. SAFETY REVIEW COMMITTEE

This study will not have an external Safety Review Committee.

D. STUDY RESULTS REPORTING

Interim reports on study progress will be submitted to the EMA on an annual basis. Aggregate results reports for the first and second data linkage will be reported to the EMA when these reports are final.

E. ADVERSE EXPERIENCE REPORTING

1. Definition of Serious Adverse Experiences

"Serious Adverse Experience" (SAE) means an adverse experience which is fatal or life threatening, results in persistent or significant disability, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, or is a congenital anomaly, cancer, the result of an overdose or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered a Serious Adverse Experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

2. Reporting of Adverse Experiences

No reporting of individual cases to regulatory agencies is planned as part of this retrospective observational database study. This is consistent with the pharmacovigilance guidelines drawn up by the European Commission in accordance with Article 106 of Directive 2001/83/EC of the European Parliament and the Council are published as Volume 9A of The Rules Governing Medicinal Products in the EU section 7.4.2 Reporting of Adverse Reactions: "In certain study designs, such as case-control or retrospective cohort studies…in which it is not feasible or appropriate to make an assessment of causality between medical events recorded and the medicinal products at individual case level, expedited reporting of Individual Case Safety Reports is not required." Because there is no access to individual patient charts for this study, no specific attribution of cases is possible. Interim reports on study progress will be submitted to the EMA on an annual basis. Aggregate results reports for the first and second data linkage will be reported to the EMA when these reports are final.

VIII. DATA MANAGEMENT, DATA ACCESS, QUALITY CONTROL

The following process / methods for data management, access, and quality control will be employed:

All analyses will be performed using SAS or SPSS. De-identified data will be stored on secure server. Access will be limited to the co-workers of this project.

Data quality will be assessed using three approaches: The quality of the AS-diagnosis will be assessed based on a currently performed AS-validation survey in southern Sweden. The quality of specific events of interest will rely on previous validations surveys performed for the outcome of interest (e.g., MI validation studies). The correctness of program scripts et cetera will be assessed by having at least two persons perform the overall analysis per project.

IX. STUDY MANAGEMENT AND COLLABORATORS

Regular meetings at an agreed upon schedule will be conducted for purposes of discussing study progress and oversight of study conduct. Initially, this will consist of telephone conferences every 4 weeks. The project group consists of:

- PI and expert consultant: (responsible for oversight of the project, including developing the protocol / analysis plan, obtaining IRB approval and other required permissions, acquiring data, cleaning and analyzing the data, performing quality control checks on the data and analysis programs, reviewing results of the analysis, drafting and finalizing reports):
  - PI: PPD
  - Expert consultant: PPD
- Lead analyst (responsible for data cleaning, programming, and statistical analysis): Research staff at PPD
- Merck Epidemiology Project Leader: PPD

X. LIMITATIONS

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

A. DIAGNOSIS OF AS / SPA

It is likely that the true onset of AS / SpA is earlier than recorded in medical records for most AS patients. Given the typical clinical presentation it is expected that the recorded diagnosis of AS / SpA 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. It is not clear if these issues will bias the results of the analysis.

B. EXPOSURE TO STUDY DRUGS OF INTEREST

In light of the fact that this study will use data on prescribing and not actual drug use by patients to assess exposure to the drugs of interest, 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 as recorded by the computer system; 2) patients consumed the drugs exactly as directed; 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 treatments administered during hospital admission. This could lead to a problem coined “immeasurable time bias"; immeasurable time refers to a period of time during follow-up, in a cohort study during which a subject cannot be recognized as being exposed.[Suissa 2008]. However, hospital admissions are likely to be for short periods, and hospitalized patients are likely to receive their prescribed medication from home (unless there are contra-indications).

In addition, it is expected that some patients will have been treated for back pain with anti-inflammatory therapy prior to a recorded AS diagnosis. Patients with more severe or aggressive disease may be treated with anti-inflammatory therapy 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 COX-2 selective inhibitors or nsNSAIDs. Also, it is expected that some patients will have been treated for back pain with anti-inflammatory therapy prior to the availability of the prescription drug database that will be used to define exposure in this study; therefore this exposure history will not be available. It is also not clear if this issue will bias the results of the analysis.

C. CLINICAL OUTCOMES

The clinical outcomes under study are based on recorded diagnoses based on clinical care standards. There may be some degree of misclassification of clinical outcomes due to misdiagnoses. There may be a greater proportion of erroneous diagnoses for some outcomes compared with others. Clinical records will not be reviewed to ascertain the accuracy of the recorded diagnoses. It is not clear if this issue will bias the results of the analysis.

D. POTENTIAL CONFOUNDING AND BIAS

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. Control for potential confounding will be attempted in the analysis, however it not likely that confounding will be fully controlled and the net effect of any resulting "residual" confounding is not able to be measured.

In addition, there is potential for channeling bias in this study because it is feasible that patients prescribed etoricoxib or another of the drugs of interest 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. Potential confounding due to channeling may be mitigated by calculating propensity scores for receipt of etoricoxib and adjusting for this propensity in the comparative analyses.

E. STUDY POWER

The power of this study to detect minimal clinically important increases in the risk of the clinical outcomes with etoricoxib relative to the other study drugs is 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 at lower risk of some of the clinical outcomes of interest. Power will be further reduced in the various stratified / subgroup analyses that are planned.

The MAH has previously committed to updating this study as new data accrue for use of etoricoxib in the AS population. It is anticipated that the study update will include greater exposure to etoricoxib, and thus provide greater study power, although the degree to which it will do so is not known.

XI. REFERENCES

Gran JT, Husby G. The epidemiology of ankylosing spondylitis. Seminars Arth Rheum 1993;22(5):319-34.

Ilkhanoff L, Lewis JD, Hennessy S, Berlin JA, Kimmel SE. Potential limitations of electronic database studies of prescription non-aspirin non-steroidal anti-inflammatory drugs (NANSAIDs) and risk of myocardial infarction (MI). Pharmacoepidemiol Drug Safety 2005;14:513-22.

Suissa S. Immeasurable Time Bias in Observational Studies of Drug Effects on Mortality. Am J Epidemiol 2008;168:329–335.