PASS INFORMATION

Title	Final Report 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
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Marketing authorisation holder(s)	**Merck Sharp & Dohme Limited** Hertford Road, Hoddesdon Hertfordshire EN11 9BU United Kingdom
Joint PASS	No
Research question and objectives Pr Proprietary	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. The objectives of this study are to: 1. Describe the use of etoricoxib in European patients with AS 2. Describe the characteristics of those who use etoricoxib 3. 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: a. Relative to non-use of these medications b. Relative to each other

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1. Abstract

Title

Final Report: 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

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Keywords

Etoricoxib (MK-0663; ARCOXIA), ankylosing spondylitis, retrospective analysis, clinical outcomes, safety

Rationale and background

The rationale for the study is to describe the use of etoricoxib, and to further characterize the safety profile of etoricoxib with respect to specific clinical outcomes of interest, in European patients with AS.

Research question and objectives

The objectives of this study are to:

1. Describe the use of etoricoxib in European patients with AS
2. Describe the characteristics of those who use etoricoxib
3. 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):
   a. Relative to non-use of these medications
   b. Relative to each other

Study design

This study is a population-based cohort of patients with AS from general medical practices in the UK, France, and Germany with a nested case control component to assess associations between drug exposures of interest and clinical outcomes relevant to patients using COX-2 inhibitors / NSAIDS.

Setting

UK: Clinical Practice Research Datalink, The Health Improvement Network database, IMS Disease Analyser
Germany: IMS Disease Analyser
France: IMS Disease Analyser

The study period starts within each database with data from the earliest eligible patient according to the inclusion / exclusion criteria. For this update, the end of the exposure period is 30Jun2013 and the end of the study period is 30Jun2014.

Subjects and study size, including dropouts

27,381 subjects were eligible for the study.

Variables and data sources

AS diagnoses, baseline demographics, medications and comorbidities, exposure, and outcomes were all obtained from the databases listed above. Outcomes included gastrointestinal events, ischemic/thrombotic cardiac, cerebrovascular, and peripheral vascular events, haemorrhagic cerebrovascular events, congestive heart failure, hypertension, acute renal impairment or failure, and sudden / unexplained death.

Results

27,381 patients from the UK, Germany and France with AS met the inclusion criteria. The characteristics of the cohort were consistent with the known epidemiology of AS. The baseline comorbid disease burden was generally low (perhaps partly due to the average age of the cohort and the use of a relatively short baseline period of 6 months to assess medical history). Relatively few patients in the cohort received etoricoxib and exposure was limited in this analysis. Out of 27,381 patients, 1,080 patients were exposed to etoricoxib (3.9% of all patients) as their first non-steroidal. The doses of etoricoxib prescribed to patients in this cohort were consistent with the EU labelling for the AS indication. The incidences of most prespecified clinical outcomes of interest were uncommon among patients without a prior history of a given event.

A total of 177 clinical outcome events of interest occurred in 152 patients (104 events in 92 men and 73 events in 60 women) while 'currently' exposed to etoricoxib. Case-control analyses of the association of etoricoxib and other NSAID exposure to hypertension and to the composite outcome of all vascular events plus sudden death showed that current, recent, or prior exposure generally did not increase the risk of these events relative to no exposure. None of the results demonstrated a significant association for etoricoxib, and the results for the other NSAIDs were generally similar.

Discussion

Overall, the results of this analysis suggest, given the characteristics of the patient population, the safety profile of etoricoxib in the treatment of AS is consistent with the safety profile of the product as labelled and as previously demonstrated during clinical development and through post-marketing pharmacovigilance. The results of this study do not change the previously established favourable benefit-risk profile for etoricoxib.

Marketing Authorisation Holder

Merck Sharp & Dohme Corp.

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2. List of abbreviations

AE	Adverse Experience
AS	Ankylosing Spondylitis
ACE	Acetyl cholinesterase
BNF	British National Formulary
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CHMP	Committee Human Medicinal Products
CI	Confidence interval
COX-2	Cyclooxygenase-2
CPRD	Clinical Practice Research Datalink
CVD	Cerebrovascular disease
DBP	Diastolic blood pressure
DFDR	Double False Discovery Rate
DM	Diabetes Mellitus
DVT	Deep venous thrombosis
DRS	Disease Risk Score
EDGE	Etoricoxib vs. Diclofenac Sodium GI Tolerability and Effectiveness study
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EPIC	Epidemiology and Pharmacology Information Core (company)
FDR	False Discovery Rate
GI	Gastrointestinal
GP	General Practitioner
GPRD	General Practice Research Database, currently known as CPRD
H2-receptor	Histamine 2-receptor
HTN	Hypertension
IBD	Inflammatory Bowel Disease
ISEAC	Independent Scientific and Ethics Advisory Committee
MAH	Marketing Authorization Holder
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
NA	Not applicable
NHS	National Health Service
NOS	Not otherwise specified
NSAIDs	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
OR	Odds Ratio
OTC	Over the Counter

PAD	Peripheral Artery Disease
PAS	Post-authorization safety
PASS	Post-authorization safety study
PE	Pulmonary embolism
PUBs	Perforations, ulcers or bleedings
Py / P-Y	Person year(s)
RA	Rheumatoid arthritis
RS	Risk Score
SBP	Systolic blood pressure
SD	Standard Deviation
SPC	Summary of product characteristics
TBD	To be determined
THIN	The Health Improvement Network
TIA	Transient Ischemic Attack
UAP	Unstable Angina Pectoris
UK	United Kingdom

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4. Other responsible parties

Not applicable

5. Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	TBD	1986	Data collection started at the date that the earliest eligible patient met the inclusion / exclusion criteria within one of the databases
End of data collection	31Dec2013	30Jun2014	Included all data available from data vendors when analyses were started
Registration in the EU PAS register	NA	NA	Not registered
2009 Preliminary Report	15Dec09	15Dec09	
2010 Interim Report	24May10	24May10	
2011 Interim Report	24Jun11	24Jun11	
2012 Interim Report	05Jul12	05Jul12	
2013 Interim Report	22Jul13	22Jul13	
2014 Interim Report	30Jul14	30Aug14	
2015 Final Report	30-Jul15	30Nov15	Delayed to allow resolution of data issues and to permit submission as part of Type II variation

6. Rationale and background

Note: highlighted text is taken from the original protocol so in some cases, it refers to things that would be done in future years.

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).

Etoricoxib was also approved for the treatment of moderate pain associated with dental surgery in 2012.

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.

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 etoricoxib 90 mg or 120 mg and naproxen based on 95% CIs for treatment differences excluding 0.

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 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 analysed, including patient categories across a range of baseline cardiovascular risk.

As with other drugs in the same class, the SmPC for etoricoxib which was agreed during the referral procedures in June 2008 (**Protocol 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

This study is being conducted by Merck & Co. Inc. as a post-licensure commitment to the European Medicines Agency (EMA). 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.

7. Research question and objectives

The objectives of this study are to:

1. Describe the use of etoricoxib in European patients with AS
2. Describe the characteristics of those who use etoricoxib
3. 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):
    a. Relative to non-use of these medications
    b. Relative to each other

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 labelling. 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.

8. Amendments and updates

Number	Date	Section of study protocol	Amendment or update (Note: each update to the protocol has been submitted with the corresponding report)	Reason
1	27May2010	All	Update: Extended the study period for follow-up of patients to 31Dec2008; extended the period for including exposure to 31Dec2007	Accumulate additional patients, exposure, clinical outcomes

Number	Date	Section of study protocol	Amendment or update (Note: each update to the protocol has been submitted with the corresponding report)	Reason
2	27Jun2011	All	Update: Extended the study period for follow-up of patients to 31Dec2009; extended the period for including exposure to 31Dec2008	Accumulate additional patients, exposure, clinical outcomes
3	05Jul2012	All	Update: Extended the study period for follow-up of patients to 31Dec2010; extended the period for including exposure to 31Dec2009	Accumulate additional patients, exposure, clinical outcomes
4	06Jul2012	Protocol Appendix 2	Update: Revised description of the procedures to identify practices common to CPRD and THIN databases	Improve identification of overlapping practices / patients

Number	Date	Section of study protocol	Amendment or update (Note: each update to the protocol has been submitted with the corresponding report)	Reason
5	08Jul2013	All	Update: Extended the study period for follow-up of patients to 31Dec2011; extended the period for including exposure to 31Dec2010	Accumulate additional patients, exposure, clinical outcomes
6	28Jul2014	All	Update: Extended the study period for follow-up of patients to 31Dec2012; extended the period for including exposure to 31Dec2011	Accumulate additional patients, exposure, clinical outcomes
7	28Jul2014	N/A	Update: Revised drug code lists based on changes to British National Formulary and Anatomical Therapeutic Chemical classification	Keep drug code lists up to date

Number	Date	Section of study protocol	Amendment or update (Note: each update to the protocol has been submitted with the corresponding report)	Reason
8	28Jul2015	All	Update: Extended the study period for follow-up of patients to 30Jun2014; extended the period for including exposure to 30Jun2013	Accumulate additional patients, exposure, clinical outcomes

9. Research methods

9.1. Study design

The study design is a population based cohort of patients with AS from general medical practices, with a nested case-control component to assess associations between drug exposures of interest and clinical outcomes relevant to patients using COX-2 inhibitors / NSAIDs.

To maximize the study size and person-time of follow-up during exposure to the study drugs of interest, data sources for this analysis includes the Clinical Practice Research Datalink (CPRD) in the UK (formerly known as General Practice Research Database (GPRD), The Health Improvement Network (THIN) database in the UK, and the IMS Disease Analyser Databases (Disease Analyser) in the UK, France and Germany. In addition, the start of the study period is prior to the introduction of COX-2 selective inhibitors to provide ample person-time of follow-up in patients with and without exposure to traditional non-selective NSAIDs. The end of the study period for this update is 30Jun2014

9.2. Setting

UK:

- Clinical Practice Research Datalink (CPRD)
- The Health Improvement Network (THIN) database in the UK
- IMS Disease Analyser Database

Germany:

- IMS Disease Analyser Database

France:

- IMS Disease Analyser Database

The study period starts within each database with data from the earliest eligible patient according to the inclusion / exclusion criteria. The end of the exposure period for this update is 30Jun2013. The end of the study period for this update is 30Jun2014.

9.3. Subjects

To be eligible for inclusion in the AS cohort the patient record must have satisfied all of the following:

1. *A recorded AS diagnosis in the database, as documented by one or more of the following Read codes. Corresponding OXMIS and ICD-10 codes were 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

2. *A recorded AS diagnosis following applicable "acceptable data quality" indicators as follows:*
   - For GPRD, the Up-to-Standard date for the practice and the presence of an acceptable patient-level data quality flag
   - For THIN, the Acceptable Mortality Reporting date for the practice
   - For UK, Germany and France IMS, the For Disease Analyser, the earliest of the above dates for GPRD or THIN were applied to all practices in the databases.

3. *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.*

4. *Complete information on gender and birth year. No lower age limit was specified, although in the future patients <10 years of age will be excluded from the study as it is likely that the diagnosis of AS is inaccurate in such patients.*

The date of the first recorded AS diagnosis in an eligible patient defined the patient's entry into the cohort (cohort entry date). Each patient was 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 General Practitioner (GP); the date of last medical event (clinical or therapy) was 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 (31 Dec. 2014).
- Date of death

For the 2015 report, we 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. This was particularly an issue with the Germany IMS data where the number of patients more than doubled.

9.4. Variables

9.4.1 Exposure

Oral formulations of the following drugs were examined during the exposure period through 30Jun2013 (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) 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).

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 was assessed during follow-up. Exposure is classified as follows:

- 'Current' when the most recent exposure (calculated duration of the most recent prescription + 14 days) overlaps the 'index' date (date of the event of interest).
- '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).
- 'Non-exposure' when the most recent exposure (calculated duration of the most recent prescription + 14 days) ended on a date 60 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.

Note that by these exposure definitions a patient with an outcome diagnosis on a given index date could have several different exposures relevant to that outcome. For example the patient could be classified as having a current exposure to one drug and a recent or prior exposure to another drug. A patient who received more than one prescription for a non-steroidal anti-inflammatory drug on the same day was counted as having 'Multiple COX-2/NSAID' exposures.

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.

Note: Because of 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. All drug code lists were manually updated after thorough review to maximize completeness and accuracy. A few drug products were included based on substance/brand names in addition to BNF and ATC chapters.

9.4.2 Outcomes

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):

1. Gastrointestinal clinical event (ulcer, perforation or bleeding) **(Protocol Appendix 3)**
2. Ischemic / thrombotic cardiac events: fatal and non-fatal acute myocardial infarction **(Protocol Appendix 4)**, unstable angina pectoris **(Protocol Appendix 5)**
3. Ischemic / thrombotic cerebrovascular events: fatal and non-fatal ischemic (or not otherwise specified as haemorrhagic) stroke **(Protocol Appendix 7 & 8)**, or transient ischemic attack **(Protocol Appendix 9)**.
4. Haemorrhagic cerebrovascular events: fatal and non-fatal haemorrhagic stroke **(Protocol Appendix 10),**
5. Thromboembolic peripheral vascular events: deep venous thrombosis (DVT) **(Protocol Appendix 11)**, pulmonary embolism (PE) **(Protocol Appendix 12)**, or peripheral arterial embolism / thrombosis **(Protocol Appendix 19)**
6. Acute Renal impairment or failure **(Protocol Appendix 29)**,
7. Hypertension (based on the combination of a code that qualifies as a hypertension outcome diagnosis in **(Protocol 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]).
8. Congestive heart failure / left ventricular dysfunction **(Protocol Appendix 15)**,
9. Sudden / unexplained death **(Protocol Appendix 16)**
10. 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.

9.5. Data sources and measurement

Note: GPRD is now known as CPRD. Text taken from the protocol still refers to the original name of the database.

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 Analyser Database (Disease Analyser) 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 **(Protocol** (**Appendix 2**). For those practices that are identified as contributing to both databases, the data from the GPRD database will be used.

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 Analyser 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 Analyser is subject to internal validation and quality checks at IMS

9.6. 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. In addition, there is potential for channelling 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 presence of channelling 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 the Disease Risk Score section of **Section 9.8**; however it is not likely that confounding will be fully controlled. The net effect of any resulting "residual" confounding and any resulting bias is not able to be measured.

There are a number of additional limitations of this study (See **Section 11.2**.) including:

- Data are derived from GP's and some outcomes may not be captured
- True onset of AS is not known
- Exposure to drugs in this study measures prescribing and not actual drug use by patients
- Some clinical outcomes may be misclassified
- Data on lifestyle factors are limited and data on OTC NSAID use are not available

It is not clear whether any of these limitations could bias the results of this analysis.

9.7. Study size

Estimates provided are based on the original protocol. The number of patients and patient years is incremented for each year's report, but the study size (number of patients, exposure, etc.) and power have not been recalculated for each year's interim report.

Preliminary analyses indicate that there are approximately 6439 patients who appear to be eligible for inclusion in the AS cohort (see **Methods Table 1**). 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.

Methods Table 1 Preliminary Numbers of Patients and Exposure to Etoricoxib in the study Population

	CPRD	THIN	UK Disease Analyser	France Disease Analyser	Germany Disease Analyser	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	432.0
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 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 of 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 **Methods Table 2** (note rates are per 1000 / patient years).

Methods Table 2 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 Haemorrhage	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.

Methods Table 3

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.

Methods Table 4

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 9.9.2.** 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 9.9.1.** 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.

9.8. Data transformation

See **Section 9.4** for description of some calculated variables.

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 modelling 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 9.9.1** Main Summary Measures - 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 **Methods Table 5**. Some variables that are continuous will be categorized in order to facilitate including missing values into the model, as shown in the column labelled "Variable".

Methods Table 5

	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 haemorrhagic 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 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 modelling, in place of the individual potential confounders that comprise them.

9.8.1 Data management

We conducted all statistical analyses using SAS version 9.3.1.

This observational cohort study will be conducted using the CPRD, THIN, and IMS databases. The data are collected electronically as a routine clinical practice in the UK, Germany, and France. Data collection and management will follow the existing protocols established by CPRD, THIN, and IMS. Validation and quality control of data collected within CPRD, THIN, and IMS are documented in the published literature.

9.9. Statistical methods

9.9.1. Main summary measures

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]. (See note in **Section 9.4.1** regarding changes to drug code lists)
- 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) (**Protocol Appendix 3**)
- History of MI (**Protocol Appendix 4**)
- History of unstable angina pectoris (**Protocol Appendix 5**)
- History of acute or subacute coronary heart disease other than MI or unstable angina pectoris (**Protocol Appendix 6**)
- History of ischemic cerebral infarction (**Protocol Appendix 7**)
- History of Cerebrovascular Accident – Not Otherwise Specified (**Protocol Appendix 8**)
- History of TIA (**Protocol Appendix 9**)
- History of haemorrhagic cerebrovascular disease (**Protocol Appendix 10**)
- History of DVT or PE (**Protocol Appendix 11 or 12**)
- History of kidney disease (**Protocol Appendix 13**)
- History of hypertension (**Protocol Appendix 14**)
- History of heart failure or left ventricular dysfunction (**Protocol Appendix 15**)
- History of rheumatoid arthritis (**Protocol Appendix 17**)
- History of inflammatory bowel disease (Crohn's disease or ulcerative colitis) (**Protocol Appendix 18**)
- History of peripheral arterial disease (arterial embolism / thrombosis, intermittent claudication, or peripheral vascular disease) (**Protocol Appendices 19, 20, and 21**)
- History of dyslipidemia (**Protocol Appendix 22**)
- History of diabetes (defined by any of the following criteria)
- Diabetes diagnostic code (**Protocol 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 (**Protocol Appendix 24**)
- History of edema (**Protocol Appendix 25**)
- History of gout (**Protocol Appendix 26**)
- History of osteoarthritis (**Protocol Appendix 27**)
- History of arthritis other than AS, OA, RA or gout (**Protocol Appendix 28**)

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 analysed 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 9.4** .Variables - 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. Note: the "off-label" analysis will include AS patients who received the relevant NSAIDs and Coxibs before approval of the AS indication.

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 labelled 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 9.4** Variables - 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:

1. Overall in the cohort (regardless of exposure)
2. 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 analysed, death, transfer out of the medical practice, or the end of the study period.

The incidence (rate/1000 person-years [py]) of the outcomes in patients with no exposure to any of the study drugs of interest, and in patients with current exposure to each of the study drugs of interest will be calculated. These incidence rates will be calculated using the entire cohort. The same individual can contribute person-time to the denominators for the different incidence rate calculations (for the rate in the non-exposed and the rate in one or more of the treatment categories) as his/her exposure varies during follow-up.

The rate for the non-exposed will be calculated as follows: patients who do not have a prescription for an NSAID or COX-2 inhibitor written on the day they entered the cohort contribute non-exposed person-time for the incidence rate denominator until the earliest of the following censoring dates:

- The date of the first NSAID / COX 2 prescription (i.e., if a patient was taking an NSAID / COX 2 on the day they entered the cohort then he would be censored immediately and would not contribute any person-time).
- The date of the first recorded outcome diagnosis
- The date transferred out of the practice
- The end of follow-up for the patient / end of study period
- The date of death

An outcome diagnosis recorded after entry into the cohort and during non-exposed person time will be included in the numerator of the incidence rate in the non-exposed. The resulting incidence rate during non-exposed person time may be viewed as the "background" rate of a given outcome in the AS cohort without non-steroidal anti-inflammatory exposure. However, note that patients contributing person-time in this manner may have been previously exposed to NSAIDs or COX-2 inhibitors before entering the AS cohort, so the cohort will not be truly naïve to non-steroidal anti-inflammatory therapies.

For the incidence rates with current exposure to the study drugs of interest, the numerator will be the number of patients with a given outcome diagnosis recorded in patients during a period of 'current' exposure for a given study drug, and the denominator will be the sum of all person-years of current exposure among all patients who received that drug at any time during 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.

9.9.2. Main statistical methods

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 modelled 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.

Logistic regression modelling 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 9.4.** 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 modelling 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 modelling 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:

Methods Table 6

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.

9.9.3. Missing values

All missing values will be summarized in a “missing” category. In the case control analysis, variables with missing values of 60% or more will be excluded from the regression models.

9.9.4. Sensitivity analyses

- 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 analysing 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.

9.9.5. Amendments to the statistical analysis plan

Each year the exposure period and study period for follow-up of patients has been extended by an additional year. In 2015, we extended the exposure period and study period by 1.5 years.

9.10. Quality control

CPRD, THIN, and IMS have extensive quality control procedures to ensure that research data are of high quality. These include numerous edit checks for plausibility and consistency of dates and other data fields.

10. Results

10.1. Participants

A total of 27,381 patients with AS were included in the study population. Of these, 10,341 were from UK CPRD/THIN, 1,993 were from UK IMS, 11,952 were from Germany IMS, and 3,095 were from France IMS. The large increase in patients since the 2014 report is due to the observation 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. This was particularly an issue with the Germany IMS data where the number of patients more than doubled. This resulted in an increase in the absolute numbers of patients in many tables, but did not have a substantial effect on rates of various outcomes.

10.2. Descriptive data

10.2.1 Numbers of Patients According To First Non-steroidal Anti-inflammatory Treatment

The numbers (%) of patients in the cohort according to their first prescription for non-steroidal anti-inflammatory treatment for AS after entry into the cohort are shown in **Table 1**. Of the 27,381 patients in the cohort, 3,218 (11.8%) had a COX-2 inhibitor as their first course of non-steroidal anti-inflammatory therapy. Of these, 849 (3.1%) received celecoxib, 1080 (3.9%) etoricoxib, 12 (0.04%) lumiracoxib, 808 (3.0%) meloxicam, 437 (1.6%) rofecoxib, and 32 (0.1%) valdecoxib. Of the 14,500 (53.0%) patients who received a non-selective NSAID as their first course of non-steroidal anti-inflammatory therapy after entry into the cohort, 6,505 (23.8%) received diclofenac, 192 (0.7%) etodolac, 3,498 (12. 8%) ibuprofen, 1,225 (4.5%) indomethacin, 1,603 (5.9%) naproxen, and 1,477 (5.4%) other non-selective NSAIDs. One hundred seven (0.4%) members of the cohort received multiple non-steroidal anti-inflammatory prescriptions as their first treatment for AS, and 9,556 patients (34.9%) did not receive any non-steroidal anti-inflammatory after entry into the cohort.

Based on the updates to the drug code lists due to formulary changes, in some cases, the number/percentage of patients exposed to specific NSAIDs has changed. In particular, a number of additional codes for diclofenac were added. This resulted in an increase in the number / percentage of patients exposed to diclofenac and a corresponding decrease in the number of patients in the "other non-selective NSAIDs" and "multiple non-steroidal anti-inflammatory" groups. This applies to many of the tables throughout the report, but did not change any of the conclusions from prior years.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 1a** for UK CPRD + THIN, **Table 1b** for UK IMS, **Table 1c** for Germany IMS, and **Table 1d** for France IMS). Note: the annexes by country / database are labelled with letters rather than numbers for consistency with the 5 prior interim reports. All of the tables generated by the statistical programs are identified with a number corresponding to the table for the overall cohort and a letter corresponding to the country/database.

Table 1
Number (%) of Patients
By First Course of Anti-Inflammatory Treatment for AS
After Entry into the AS Cohort†
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

First Course of Anti-Inflammatory Treatment for AS During Follow-up: n (%) COX-2 Selective Inhibitors	N=27,381
COX-2 Selective Inhibitors	**3,218 (11.75)**
Celecoxib	849 (3.10)
Etoricoxib	1,080 (3.94)
Lumiracoxib	12 (0.04)
Meloxicam	808 (2.95)
Rofecoxib	437 (1.60)
Valdecoxib	32 (0.12)
Non-Selective NSAIDS	**14,500 (52.96)**
Diclofenac	6,505 (23.76)
Etodolac	192 (0.70)
Ibuprofen	3,498 (12.78)
Indometacin	1,225 (4.47)
Naproxen	1,603 (5.85)
Other non-selective NSAIDs‡	1,477 (5.39)
Multiple Drugs	**107 (0.39)**
None	**9,556 (34.90)**

† The First Course of Anti-Inflammatory Treatment is defined as the first prescription for a COX-2 inhibitor of a non-selective NSAID which coincides with or follows the AS diagnosis that determined the patient's entry into the cohort.
‡ Aceclofenac, Acemetacin, Azapropazone, Dexketoprofen, Fenbufen, Fenoprofen, Feprazone, flurbiprofen, Ketoprofen, Lornoxicam, Mefenamic acid, Nabumetone, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac, Tenoxicam, Tiaprofenic acid, Tolfenamic Acid, Tolmetin.

10.2.2 Numbers of Patients According To Any Non-steroidal Anti-inflammatory Treatment

The numbers (%) of patients in the cohort according to prescription for a given non-steroidal anti-inflammatory treatment at any time during the follow-up period are shown in **Table 2**. Because patients may have received more than one non-steroidal anti-inflammatory drug prescription during the study period, and may have received prescriptions for different specific non-steroidal anti-inflammatory drugs during the follow-up, a given patient may be counted in multiple rows in this Table. Patients who received multiple prescriptions for non-steroidal anti-inflammatory drugs on one or more dates during the study period are not included in this analysis. Overall during the follow-up period, 6,135 (22.4%) of patients received a COX-2 inhibitor (2,640 or 9.6% received etoricoxib). Fifteen thousand, nine hundred forty four (58.2%) received a non-selective NSAID at some time during follow-up. About 34.9% did not receive any prescriptions for non-steroidal anti-inflammatory treatment during the follow-up period.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 2a** for UK CPRD + THIN, **Table 2b** for UK IMS, **Table 2c** for Germany IMS, and **Table 2d** for France IMS).

Table 2
Number (%) of Patients Receiving Anti-Inflammatory Treatment for AS
At Any Time During Follow-up[†]
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Anti-Inflammatory Treatment for AS During Follow-up: n (%) COx-2 Selective Inhibitors	N=27,381
COX-2 Selective Inhibitors	**6,135 (22.41)**
Celecoxib	2,124 (7.76)
Etoricoxib	2,640 (9.64)
Lumiracoxib	32 (0.12)
Meloxicam	1,992 (7.28)
Rofecoxib	1,161 (4.24)
Valdecoxib	137 (0.50)
Non-Selective NSAIDS	**15,944 (58.23)**
Diclofenac	9,552 (34.89)
Etodolac	573 (2.09)
Ibuprofen	6,306 (23.03)
Indometacin	1,996 (7.29)
Naproxen	3,865 (14.12)
Other non-selective NSAIDs[‡]	2,885 (10.54)
None	**9,556 (34.90)**

[†] Any prescription for Anti-Inflammatory Treatment at any time during follow-up Each row is not mutually exclusive ; an individual patient may be counted in more than one row, but is counted only once in a given row

[‡] Aceclofenac, Acemetacin, Azapropazone, Dexketoprofen, Fenbufen, Fenoprofen, Feprazone, flurbiprofen, Ketoprofen, Lornoxicam, Mefenamic acid, Nabumetone, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac, Tenoxicam, Tiaprofenic acid, Tolfenamic Acid, Tolmetin.

10.2.3 Baseline Characteristics

Baseline characteristics (**Table 3**) were assessed in the 6 months prior to cohort entry, except for smoking status, alcohol use and body mass index (BMI) which were assessed using all available records for each patient. The majority of patients are missing data for smoking status, use of alcohol, information about referral to a rheumatologist, information about x-ray of the spine, and blood pressure measurements. This is because these data are not available in the IMS databases, and are missing for some patients in the CPRD and THIN databases. Thus the percentages of patients with missing data are higher in the UK, Germany and France IMS databases **Note that percentages are calculated based on the total numbers of subjects in each group, including those with missing data.**

The mean (SD) age at baseline was about 48.2 (16.0) years, with a median age of 47.0 years. The cohort is about 62.3% male, consistent with the predominance of AS in males. Among those with data on smoking status (note that 63.0% had missing information regarding smoking status) about 32.6% were current smokers, while about 18.9% and 48.6% were ex- and non-smokers, respectively. Among those with data on alcohol use (note that 71.8% had missing information regarding alcohol use) about 80.7% of the cohort is classified as currently using alcohol at baseline. Mean (SD) and median baseline BMI are 26.5 (5.1) and 25.8, respectively; among those with BMI data, 21.1% had a BMI ≥ 30. About 41.5% of the patients entered the cohort prior to the COX-2 inhibitor Urgent Safety Restriction of 17 Feb. 2005. The baseline mean (SD) and median number of health care encounters for the cohort was 4.8 (4.8) and 3.0, respectively. Among those with referral and x-ray data (note 62.2% had missing information regarding these parameters) about 9.0% had been referred to a rheumatologist and about 2.3% had received a radiograph of the sacrum or spine during the 6 month prior to entry baseline period. Baseline mean (SD) and median systolic blood pressure (SBP) were 130.3 (18.3) and 130.0 mmHg, respectively. The range of baseline SBP was 80.0 to 235.0 mmHg. About 67.8% of patients had missing data for blood pressure due to the lack of this information in the IMS databases. Among those with blood pressure data, about 24.1%, 44.4% and 31.6% of patients had baseline SBP values of <120, 120-139, and ≥140 mmHg, respectively. Baseline mean (SD) and median diastolic blood pressure (DBP) were 77.9 (10.1) and 80.0 mmHg, respectively. The range of baseline SBP was 40.0 to 135.0 mmHg. Among those with blood pressure data, about 46.4%, 39.7% and 13.9% of patients had baseline SBP values of <80, 80-89, and ≥90 mmHg, respectively. Note that the baseline blood pressure (most recent value in the 6 months prior to cohort entry) is not necessarily the blood pressure at the time a given patient is started on treatment; in fact it may represent the blood pressure while being treated with non-steroidal anti-inflammatory drugs (prior to the AS diagnosis that qualifies the patient for entry in to the cohort). Thus one should not assume based on these results alone that large proportions of the cohort have blood pressures that are poorly controlled.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 3a** for UK CPRD + THIN, **Table 3b** for UK IMS, **Table 3c** for Germany IMS, and **Table 3d** for France IMS).

Table 3
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Characteristic	N=27,381
Age (years)	
Mean	48.16
Std. Dev.	16.01
Minimum	10.00
Median	47.00
Maximum	110.00
Age<65 Years n (%)	22,629 (82.64)
Age≥65 Years n (%)	4,752 (17.36)
Gender: n (%)	
Male	17,049 (62.27)
Female	10,332 (37.73)
Smoking status (most recent): n (%) **	
Non-Smoker	4,924 (48.55)
Current Smoker	3,305 (32.58)
Ex-Smoker	1,914 (18.87)
Missing	17,238 ()
Alcohol status (most recent): n (%) **	
Non-Alcohol Use	1,370 (17.74)
Current Alcohol Use	6,232 (80.70)
Ex-Alcohol Use	120 (1.55)
Missing	19,659 ()
Body mass index (kg/m2) (most recent) **	
Mean	26.51
Std. Dev.	5.08
Minimum	11.40
Median	25.80
Maximum	54.80
<25	5,319 (41.94)
25-29.9	4,690 (36.98)
≥30	2,674 (21.08)
Missing	14,698 ()
Year of entry into cohort: n (%)	
1986	1 (0.00)
1987	4 (0.01)
1988	19 (0.07)
1989	71 (0.26)

Table 3
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Characteristic	N=27,381
1990	256 (0.93)
1991	354 (1.29)
1992	527 (1.92)
1993	541 (1.98)
1994	547 (2.00)
1995	547 (2.00)
1996	610 (2.23)
1997	615 (2.25)
1998	668 (2.44)
1999	683 (2.49)
2000	811 (2.96)
2001	910 (3.32)
2002	1,081 (3.95)
2003	1,258 (4.59)
2004	1,623 (5.93)
2005	1,751 (6.39)
2006	1,812 (6.62)
2007	1,845 (6.74)
2008	2,235 (8.16)
2009	2,098 (7.66)
2010	1,921 (7.02)
2011	1,997 (7.29)
2012	1,331 (4.86)
2013	1,265 (4.62)
Cohort entry before cox-2 Urgent Safety Restriction (17Feb05): n (%)	
Yes	11,370 (41.53)
No	16,011 (58.47)
Total number of prior health care encounters*	
Mean	4.76
Std. Dev.	4.84
Minimum	1.00
Median	3.00
Maximum	104.00
Referral to Rheumatologist: n (%) **	
Yes	931 (9.00)
No	9,410 (91.00)

Table 3
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Characteristic	N=27,381
Missing	17,040 ()
X-ray of the sacrum or spine: n (%) **	
Yes	242 (2.34)
No	10,099 (97.66)
Missing	17,040 ()
Both Referral to Rheumatologist and X-ray of the sacrum or spine: n (%) **	
Yes	37 (0.36)
No	10,304 (99.64)
Missing	17,040 ()
Mean SBP (mmHg) (most recent) **	
Mean	130.29
Std. Dev.	18.31
Minimum	80.00
Median	130.00
Maximum	235.00
<120	2,121 (24.07)
120-139	3,908 (44.36)
≥140	2,781 (31.57)
Missing	18,571 ()
Mean DBP (mmHg) (most recent) **	
Mean	77.92
Std. Dev.	10.08
Minimum	40.00
Median	80.00
Maximum	135.00
<80	4,090 (46.42)
80-89	3,496 (39.68)
≥90	1,224 (13.89)
Missing	18,571 ()

* Total number of visits to GP and referrals to specialists in the 6 months prior to cohort entry
** Percentage shown are based on patients who are not missing data

Table 4 shows baseline characteristics according to the first type of treatment for AS (COX-2, NSAID, multiple non-steroidal anti-inflammatory agents, or no NSAIDs) after entry into the cohort. For a given patient this may not have been their first ever treatment with a non-steroidal anti-inflammatory agent.

Compared with those whose first non-steroidal anti-inflammatory prescription was a non-selective NSAID (n=14,500), those prescribed a COX-2 selective agent (n=3,218) were older, more often female, slightly less likely to be a current smoker or to currently use alcohol, and less likely to have entered the cohort prior to the COX-2 Urgent Safety Restriction during the baseline period.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 4a** for UK CPRD + THIN, **Table 4b** for UK IMS, **Table 4c** for Germany IMS, and **Table 4d** for France IMS.

Table 4
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Type of First Anti-Inflammatory Prescription for Treatment of AS
After Entry into the Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Characteristics	Type of First Anti-Inflammatory Prescription			
	COX-2 Inhibitor N=3,218	NSAID N=14,500	Multiple N=107	None N=9,556
Age (years)				
Mean	47.81	46.91	46.04	50.19
Std. Dev.	15.35	15.40	14.28	16.93
Minimum	15.00	10.00	15.00	10.00
Median	47.00	46.00	44.00	49.00
Maximum	99.00	110.00	85.00	98.00
Age<65 Years n (%)	2,695 (83.75)	12,437 (85.77)	93 (86.92)	7,404 (77.48)
Age≥65 Years n (%)	523 (16.25)	2,063 (14.23)	14 (13.08)	2,152 (22.52)
Gender: n (%)				
Male	1,967 (61.12)	9,434 (65.06)	79 (73.83)	5,569 (58.28)
Female	1,251 (38.88)	5,066 (34.94)	28 (26.17)	3,987 (41.72)
Smoking status (most recent): n (%) **				
Non-Smoker	764 (47.99)	3,093 (48.54)	24 (54.55)	1,043 (48.85)
Current Smoker	514 (32.29)	2,177 (34.17)	17 (38.64)	597 (27.96)
Ex-Smoker	314 (19.72)	1,102 (17.29)	3 (6.82)	495 (23.19)
Missing	1,626 ()	8,128 ()	63 ()	7,421 ()
Alcohol status (most recent): n (%) **				
Non-Alcohol Use	248 (19.25)	816 (16.84)	7 (20.59)	299 (19.25)
Current Alcohol Use	1,019 (79.11)	3,973 (81.97)	27 (79.41)	1,213 (78.11)
Ex-Alcohol Use	21 (1.63)	58 (1.20)	0 (0.00)	41 (2.64)
Missing	1,930 ()	9,653 ()	73 ()	8,003 ()
Body mass index (kg/m2) (most recent) **				
Mean	26.58	26.52	25.38	26.44
Std. Dev.	5.04	5.05	4.05	5.19
Minimum	13.60	11.40	14.49	13.12
Median	25.99	25.80	25.60	25.71
Maximum	53.60	54.68	33.60	54.80
<25	759 (39.84)	3,349 (42.12)	21 (42.86)	1,190 (42.85)
25-29.9	730 (38.32)	2,928 (36.82)	21 (42.86)	1,011 (36.41)
≥30	416 (21.84)	1,675 (21.06)	7 (14.29)	576 (20.74)
Missing	1,313 ()	6,548 ()	58 ()	6,779 ()

Table 4
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Type of First Anti-Inflammatory Prescription for Treatment of AS
After Entry into the Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Characteristics	Type of First Anti-Inflammatory Prescription			
	COX-2 Inhibitor N=3,218	NSAID N=14,500	Multiple N=107	None N=9,556
Year of entry into cohort: n (%)				
1986	0 (0.00)	1 (0.01)	0 (0.00)	0 (0.00)
1987	0 (0.00)	4 (0.03)	0 (0.00)	0 (0.00)
1988	1 (0.03)	16 (0.11)	0 (0.00)	2 (0.02)
1989	2 (0.06)	59 (0.41)	0 (0.00)	10 (0.10)
1990	4 (0.12)	214 (1.48)	2 (1.87)	36 (0.38)
1991	5 (0.16)	310 (2.14)	4 (3.74)	35 (0.37)
1992	9 (0.28)	440 (3.03)	9 (8.41)	69 (0.72)
1993	6 (0.19)	456 (3.14)	3 (2.80)	76 (0.80)
1994	11 (0.34)	464 (3.20)	5 (4.67)	67 (0.70)
1995	25 (0.78)	430 (2.97)	2 (1.87)	90 (0.94)
1996	36 (1.12)	459 (3.17)	4 (3.74)	111 (1.16)
1997	50 (1.55)	457 (3.15)	1 (0.93)	107 (1.12)
1998	48 (1.49)	471 (3.25)	2 (1.87)	147 (1.54)
1999	74 (2.30)	463 (3.19)	3 (2.80)	143 (1.50)
2000	127 (3.95)	503 (3.47)	4 (3.74)	177 (1.85)
2001	162 (5.03)	536 (3.70)	7 (6.54)	205 (2.15)
2002	211 (6.56)	615 (4.24)	4 (3.74)	251 (2.63)
2003	282 (8.76)	635 (4.38)	7 (6.54)	334 (3.50)
2004	278 (8.64)	844 (5.82)	10 (9.35)	491 (5.14)
2005	181 (5.62)	992 (6.84)	8 (7.48)	570 (5.96)
2006	225 (6.99)	937 (6.46)	0 (0.00)	650 (6.80)
2007	192 (5.97)	918 (6.33)	9 (8.41)	726 (7.60)
2008	296 (9.20)	982 (6.77)	5 (4.67)	952 (9.96)
2009	285 (8.86)	902 (6.22)	3 (2.80)	908 (9.50)
2010	248 (7.71)	786 (5.42)	3 (2.80)	884 (9.25)
2011	187 (5.81)	716 (4.94)	3 (2.80)	1,091 (11.42)
2012	149 (4.63)	479 (3.30)	5 (4.67)	698 (7.30)
2013	124 (3.85)	411 (2.83)	4 (3.74)	726 (7.60)
Cohort entry before cox-2 Urgent Safety Restriction (17Feb05): n (%)				
Yes	1,354 (42.08)	7,523 (51.88)	69 (64.49)	2,424 (25.37)

Table 4
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Type of First Anti-Inflammatory Prescription for Treatment of AS
After Entry into the Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Characteristics	Type of First Anti-Inflammatory Prescription			
	COX-2 Inhibitor N=3,218	NSAID N=14,500	Multiple N=107	None N=9,556
No	1,864 (57.92)	6,977 (48.12)	38 (35.51)	7,132 (74.63)
Total number of prior health care encounters*				
Mean	5.81	4.94	3.61	4.15
Std. Dev.	5.65	4.73	3.01	4.64
Minimum	1.00	1.00	1.00	1.00
Median	4.00	3.00	3.00	3.00
Maximum	86.00	104.00	19.00	59.00
Referral to Rheumatologist: n (%) **				
Yes	159 (9.71)	611 (9.22)	4 (7.41)	157 (7.76)
No	1,478 (90.29)	6,017 (90.78)	50 (92.59)	1,865 (92.24)
Missing	1,581 ()	7,872 ()	53 ()	7,534 ()
X-ray of the sacrum or spine: n (%) **				
Yes	16 (0.98)	186 (2.81)	0 (0.00)	40 (1.98)
No	1,621 (99.02)	6,442 (97.19)	54 (100.00)	1,982 (98.02)
Missing	1,581 ()	7,872 ()	53 ()	7,534 ()
Both Referral to Rheumatologist and X-ray of the sacrum or spine: n (%) **				
Yes	3 (0.18)	28 (0.42)	0 (0.00)	6 (0.30)
No	1,634 (99.82)	6,600 (99.58)	54 (100.00)	2,016 (99.70)
Missing	1,581 ()	7,872 ()	53 ()	7,534 ()
Mean SBP (mmHg) (most recent) **				
Mean	129.98	130.05	125.72	131.40
Std. Dev.	17.20	18.22	19.56	19.35
Minimum	85.00	80.00	100.00	80.00
Median	130.00	130.00	120.00	130.00
Maximum	230.00	235.00	200.00	232.00
<120	339 (23.17)	1,355 (24.46)	12 (30.77)	415 (23.47)
120-139	673 (46.00)	2,459 (44.39)	19 (48.72)	757 (42.82)
≥140	451 (30.83)	1,726 (31.16)	8 (20.51)	596 (33.71)
Missing	1,755 ()	8,960 ()	68 ()	7,788 ()
Mean DBP (mmHg) (most recent) **				
Mean	78.00	78.05	77.15	77.43

Table 4
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Type of First Anti-Inflammatory Prescription for Treatment of AS
After Entry into the Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Type of First Anti-Inflammatory Prescription			
Characteristics	COX-2 Inhibitor N=3,218	NSAID N=14,500	Multiple N=107	None N=9,556
Std. Dev.	9.23	10.18	8.52	10.46
Minimum	50.00	40.00	60.00	42.00
Median	80.00	80.00	80.00	80.00
Maximum	125.00	135.00	95.00	120.00
<80	681 (46.55)	2,516 (45.42)	17 (43.59)	876 (49.55)
80-89	608 (41.56)	2,213 (39.95)	18 (46.15)	657 (37.16)
≥90	174 (11.89)	811 (14.64)	4 (10.26)	235 (13.29)
Missing	1,755 ()	8,960 ()	68 ()	7,788 ()

* Total number of visits to GP and referrals to specialists in the 6 months prior to cohort entry
** Percentage shown are based on patients who are not missing data

Baseline characteristics according to the specific first non-steroidal anti-inflammatory therapy in the patients' records following entry into the cohort are shown in **Table 5.** For a given patient this may not have been their first ever treatment with a non-steroidal anti-inflammatory agent.

Among the 3,410 patients receiving COX-2 selective agents, 1,080 received etoricoxib, 849 celecoxib, 12 lumiracoxib, 437 rofecoxib, 32 valdecoxib, and 808 the semi-selective agent meloxicam.

The mean (SD) and median ages of those receiving etoricoxib as their first non-steroidal anti-inflammatory treatment following entry into the cohort are 45.9 (15.7), and 45.0 years, respectively. This group was 60.4% men, and about 12.7% entered the cohort before the COX-2 Urgent Safety Restriction. They have a mean (SD) and median of 6.4 (5.8) and 5.0 prior health encounters during the baseline period, respectively. About 8.3% had seen a rheumatologist during the baseline period (note 562 patients were missing this information). Their mean (SD) and median baseline SBP was about 127.3 (15.7) and 128.0 mmHg, respectively. Their mean (SD) and median baseline DBP was about 77.1 (8.9) and 80.0 mmHg, respectively. About 56.1% of those receiving etoricoxib had missing data for blood pressure. When excluding patients with missing data, about 27.6%, 47.9% and 24.5% of patients had baseline SBP values of <120, 120-139, and ≥140 mmHg, respectively. When excluding patients with missing data, about 49.8%, 42.2% and 8.0% of patients had baseline DBP values of <80, 80-89, and ≥90 mmHg, respectively. **Note that the baseline blood pressure (most recent value in the 6 months prior to cohort entry) is not necessarily the blood pressure at the time a given patient is started on etoricoxib treatment.**

Compared with celecoxib, those receiving etoricoxib as their first non-steroidal anti-inflammatory therapy are younger, more likely to be female, more likely to smoke, much less likely to have entered the cohort following the Urgent Safety Restriction and had lower mean and median baseline SBP. The proportion of patients with baseline SBP and DBP ≥140 or ≥90 mmHg, respectively, were also lower in patients receiving etoricoxib compared with celecoxib.

The numbers and baseline characteristics of patients receiving specific non-selective NSAIDs, "other NSAIDs", and multiple agents as their first non-steroidal anti-inflammatory therapy are also shown in **Table 5;** 6,505 patients received diclofenac, 3,498 ibuprofen, 1,225 indomethacin, 1,603 naproxen, and 1,477 "other NSAIDs". One hundred seven patients received multiple NSAIDs as their first non-steroidal anti-inflammatory therapy following entry into the cohort, and 9,556 did not receive any non-steroidal anti-inflammatory treatment.

Note: Based on the updates to the drug code lists due to formulary changes, in some cases, the number/percentage of patients exposed to specific NSAIDs has changed. In particular, a number of additional codes for diclofenac were added. This resulted in an increase in the number / percentage of patients exposed to diclofenac and a corresponding decrease in the number of patients in the "other non-selective NSAIDs" and "multiple non-steroidal anti-inflammatory" groups.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 5a** for UK CPRD + THIN, **Table 5b** for UK IMS, **Table 5c** for Germany IMS, and **Table 5d** for France IMS).

Table 5
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
Age (years)							
Mean	45.93	49.11	59.92	47.46	50.27	47.94	47.57
Std. Dev.	15.69	14.70	17.36	14.92	16.09	10.95	14.71
Minimum	15.00	15.00	33.00	15.00	15.00	26.00	15.00
Median	45.00	48.00	55.50	46.00	49.00	50.00	46.00
Maximum	88.00	99.00	81.00	88.00	92.00	69.00	89.00
Age<65 Years n (%)	919 (85.09)	706 (83.16)	7 (58.33)	688 (85.15)	345 (78.95)	30 (93.75)	164 (85.42)
Age≥65 Years n (%)	161 (14.91)	143 (16.84)	5 (41.67)	120 (14.85)	92 (21.05)	2 (6.25)	28 (14.58)
Gender: n (%)							
Male	652 (60.37)	530 (62.43)	8 (66.67)	477 (59.03)	280 (64.07)	20 (62.50)	130 (67.71)
Female	428 (39.63)	319 (37.57)	4 (33.33)	331 (40.97)	157 (35.93)	12 (37.50)	62 (32.29)
Smoking status (most recent): n (%) **							
Non-Smoker	255 (48.66)	190 (48.10)	2 (50.00)	195 (46.54)	118 (50.21)	4 (26.67)	83 (56.46)
Current Smoker	176 (33.59)	121 (30.63)	0 (0.00)	143 (34.13)	69 (29.36)	5 (33.33)	40 (27.21)
Ex-Smoker	93 (17.75)	84 (21.27)	2 (50.00)	81 (19.33)	48 (20.43)	6 (40.00)	24 (16.33)
Missing	556 ()	454 ()	8 ()	389 ()	202 ()	17 ()	45 ()
Alcohol status (most recent): n (%) **							
Non-Alcohol Use	81 (19.61)	70 (21.60)	1 (50.00)	68 (19.60)	28 (14.36)	0 (0.00)	24 (18.90)
Current Alcohol Use	325 (78.69)	247 (76.23)	1 (50.00)	276 (79.54)	163 (83.59)	7 (100.00)	102 (80.31)
Ex-Alcohol Use	7 (1.69)	7 (2.16)	0 (0.00)	3 (0.86)	4 (2.05)	0 (0.00)	1 (0.79)
Missing	667 ()	525 ()	10 ()	461 ()	242 ()	25 ()	65 ()

Table 5
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
Body mass index (kg/m2) (most recent) **							
Mean	26.52	26.71	26.46	26.51	26.61	26.96	26.18
Std. Dev.	5.26	4.93	3.57	5.12	4.76	3.74	5.60
Minimum	15.12	16.10	21.00	13.60	15.57	19.70	16.10
Median	25.88	26.20	27.11	25.80	26.00	26.00	25.10
Maximum	52.05	45.30	31.12	53.60	42.29	34.53	49.00
<25	255 (41.40)	188 (38.76)	2 (33.33)	197 (39.80)	110 (39.01)	7 (33.33)	68 (48.57)
25-29.9	225 (36.53)	184 (37.94)	3 (50.00)	194 (39.19)	113 (40.07)	11 (52.38)	47 (33.57)
≥30	136 (22.08)	113 (23.30)	1 (16.67)	104 (21.01)	59 (20.92)	3 (14.29)	25 (17.86)
Missing	464 ()	364 ()	6 ()	313 ()	155 ()	11 ()	52 ()
Year of entry into cohort: n (%)							
1986	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
1987	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
1988	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.23)	0 (0.00)	0 (0.00)
1989	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.12)	1 (0.23)	0 (0.00)	1 (0.52)
1990	0 (0.00)	2 (0.24)	0 (0.00)	0 (0.00)	2 (0.46)	0 (0.00)	5 (2.60)
1991	0 (0.00)	2 (0.24)	0 (0.00)	2 (0.25)	1 (0.23)	0 (0.00)	4 (2.08)
1992	0 (0.00)	2 (0.24)	0 (0.00)	5 (0.62)	2 (0.46)	0 (0.00)	3 (1.56)
1993	0 (0.00)	3 (0.35)	0 (0.00)	1 (0.12)	2 (0.46)	0 (0.00)	2 (1.04)
1994	2 (0.19)	2 (0.24)	0 (0.00)	5 (0.62)	2 (0.46)	0 (0.00)	4 (2.08)
1995	1 (0.09)	5 (0.59)	0 (0.00)	13 (1.61)	4 (0.92)	2 (6.25)	3 (1.56)

Table 5
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
1996	0 (0.00)	7 (0.82)	0 (0.00)	23 (2.85)	6 (1.37)	0 (0.00)	1 (0.52)
1997	2 (0.19)	4 (0.47)	0 (0.00)	40 (4.95)	4 (0.92)	0 (0.00)	5 (2.60)
1998	1 (0.09)	4 (0.47)	0 (0.00)	30 (3.71)	13 (2.97)	0 (0.00)	5 (2.60)
1999	3 (0.28)	9 (1.06)	0 (0.00)	44 (5.45)	18 (4.12)	0 (0.00)	10 (5.21)
2000	1 (0.09)	22 (2.59)	0 (0.00)	44 (5.45)	59 (13.50)	1 (3.13)	9 (4.69)
2001	10 (0.93)	50 (5.89)	0 (0.00)	25 (3.09)	77 (17.62)	0 (0.00)	8 (4.17)
2002	14 (1.30)	63 (7.42)	0 (0.00)	45 (5.57)	89 (20.37)	0 (0.00)	16 (8.33)
2003	36 (3.33)	85 (10.01)	0 (0.00)	63 (7.80)	90 (20.59)	8 (25.00)	13 (6.77)
2004	61 (5.65)	84 (9.89)	0 (0.00)	48 (5.94)	66 (15.10)	19 (59.38)	12 (6.25)
2005	61 (5.65)	46 (5.42)	4 (33.33)	68 (8.42)	0 (0.00)	2 (6.25)	16 (8.33)
2006	99 (9.17)	60 (7.07)	5 (41.67)	61 (7.55)	0 (0.00)	0 (0.00)	20 (10.42)
2007	86 (7.96)	51 (6.01)	3 (25.00)	52 (6.44)	0 (0.00)	0 (0.00)	11 (5.73)
2008	131 (12.13)	106 (12.49)	0 (0.00)	59 (7.30)	0 (0.00)	0 (0.00)	13 (6.77)
2009	159 (14.72)	75 (8.83)	0 (0.00)	51 (6.31)	0 (0.00)	0 (0.00)	10 (5.21)
2010	136 (12.59)	56 (6.60)	0 (0.00)	56 (6.93)	0 (0.00)	0 (0.00)	7 (3.65)
2011	119 (11.02)	44 (5.18)	0 (0.00)	24 (2.97)	0 (0.00)	0 (0.00)	6 (3.13)
2012	84 (7.78)	37 (4.36)	0 (0.00)	28 (3.47)	0 (0.00)	0 (0.00)	4 (2.08)
2013	74 (6.85)	30 (3.53)	0 (0.00)	20 (2.48)	0 (0.00)	0 (0.00)	4 (2.08)
Cohort entry before cox-2 Urgent Safety Restriction (17Feb05): n (%)							
Yes	137 (12.69)	350 (41.22)	0 (0.00)	400 (49.50)	437 (100.00)	30 (93.75)	103 (53.65)
No	943 (87.31)	499 (58.78)	12 (100.00)	408 (50.50)	0 (0.00)	2 (6.25)	89 (46.35)

Table 5
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
Total number of prior health care encounters*							
Mean	6.37	5.58	5.75	5.62	5.30	4.53	7.31
Std. Dev.	5.75	5.73	4.61	5.31	5.92	3.41	6.01
Minimum	1.00	1.00	2.00	1.00	1.00	1.00	1.00
Median	5.00	4.00	4.00	4.00	4.00	4.00	6.00
Maximum	61.00	46.00	16.00	42.00	86.00	15.00	38.00
Referral to Rheumatologist: n (%) **							
Yes	43 (8.30)	40 (9.76)	1 (50.00)	37 (8.51)	38 (14.50)	0 (0.00)	19 (11.59)
No	475 (91.70)	370 (90.24)	1 (50.00)	398 (91.49)	224 (85.50)	10 (100.00)	145 (88.41)
Missing	562 ()	439 ()	10 ()	373 ()	175 ()	22 ()	28 ()
X-ray of the sacrum or spine: n (%) **							
Yes	2 (0.39)	6 (1.46)	0 (0.00)	6 (1.38)	2 (0.76)	0 (0.00)	4 (2.44)
No	516 (99.61)	404 (98.54)	2 (100.00)	429 (98.62)	260 (99.24)	10 (100.00)	160 (97.56)
Missing	562 ()	439 ()	10 ()	373 ()	175 ()	22 ()	28 ()
Both Referral to Rheumatologist and X-ray of the sacrum or spine: n (%) **							
Yes	1 (0.19)	1 (0.24)	0 (0.00)	0 (0.00)	1 (0.38)	0 (0.00)	1 (0.61)
No	517 (99.81)	409 (99.76)	2 (100.00)	435 (100.00)	261 (99.62)	10 (100.00)	163 (99.39)
Missing	562 ()	439 ()	10 ()	373 ()	175 ()	22 ()	28 ()
Mean SBP (mmHg) (most recent) **							
Mean	127.33	131.65	134.00	131.12	131.04	122.29	131.03
Std. Dev.	15.68	17.03	19.80	18.94	17.02	12.28	18.40

Table 5
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
Minimum	85.00	85.00	120.00	90.00	96.00	100.00	90.00
Median	128.00	130.00	134.00	130.00	130.00	126.00	130.00
Maximum	200.00	207.00	148.00	230.00	200.00	137.00	180.00
<120	131 (27.64)	73 (19.47)	0 (0.00)	86 (22.45)	47 (21.17)	2 (28.57)	36 (24.83)
120-139	227 (47.89)	179 (47.73)	1 (50.00)	170 (44.39)	91 (40.99)	5 (71.43)	60 (41.38)
≥140	116 (24.47)	123 (32.80)	1 (50.00)	127 (33.16)	84 (37.84)	0 (0.00)	49 (33.79)
Missing	606 ()	474 ()	10 ()	425 ()	215 ()	25 ()	47 ()
Mean DBP (mmHg) (most recent) **							
Mean	77.13	78.86	79.00	78.37	77.76	77.14	77.49
Std. Dev.	8.92	9.42	1.41	9.42	9.15	10.75	10.63
Minimum	50.00	55.00	78.00	50.00	50.00	60.00	50.00
Median	80.00	80.00	79.00	80.00	80.00	78.00	80.00
Maximum	110.00	122.00	80.00	125.00	104.00	95.00	104.00
<80	236 (49.79)	161 (42.93)	1 (50.00)	178 (46.48)	100 (45.05)	5 (71.43)	69 (47.59)
80-89	200 (42.19)	159 (42.40)	1 (50.00)	152 (39.69)	95 (42.79)	1 (14.29)	53 (36.55)
≥90	38 (8.02)	55 (14.67)	0 (0.00)	53 (13.84)	27 (12.16)	1 (14.29)	23 (15.86)
Missing	606 ()	474 ()	10 ()	425 ()	215 ()	25 ()	47 ()

* Total number of visits to GP and referrals to specialists in the 6 months prior to cohort entry
** Percentage shown are based on patients who are not missing data

Table 5
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
Age (years)							
Mean	46.75	48.10	45.81	44.60	48.08	46.04	50.19
Std. Dev.	15.19	16.62	13.73	14.89	14.88	14.28	16.93
Minimum	10.00	10.00	12.00	10.00	12.00	15.00	10.00
Median	46.00	48.00	44.00	44.00	46.00	44.00	49.00
Maximum	110.00	96.00	89.00	87.00	104.00	85.00	98.00
Age<65 Years n (%)	5,610 (86.24)	2,875 (82.19)	1,088 (88.82)	1,438 (89.71)	1,262 (85.44)	93 (86.92)	7,404 (77.48)
Age≥65 Years n (%)	895 (13.76)	623 (17.81)	137 (11.18)	165 (10.29)	215 (14.56)	14 (13.08)	2,152 (22.52)
Gender: n (%)							
Male	4,346 (66.81)	1,973 (56.40)	962 (78.53)	1,098 (68.50)	925 (62.63)	79 (73.83)	5,569 (58.28)
Female	2,159 (33.19)	1,525 (43.60)	263 (21.47)	505 (31.50)	552 (37.37)	28 (26.17)	3,987 (41.72)
Smoking status (most recent): n (%) **							
Non-Smoker	1,374 (49.18)	569 (46.60)	238 (46.94)	524 (48.38)	305 (49.19)	24 (54.55)	1,043 (48.85)
Current Smoker	968 (34.65)	417 (34.15)	198 (39.05)	353 (32.59)	201 (32.42)	17 (38.64)	597 (27.96)
Ex-Smoker	452 (16.18)	235 (19.25)	71 (14.00)	206 (19.02)	114 (18.39)	3 (6.82)	495 (23.19)
Missing	3,711 ()	2,277 ()	718 ()	520 ()	857 ()	63 ()	7,421 ()
Alcohol status (most recent): n (%) **							
Non-Alcohol Use	335 (16.29)	165 (19.21)	48 (12.31)	140 (15.07)	104 (21.40)	7 (20.59)	299 (19.25)
Current Alcohol Use	1,696 (82.49)	687 (79.98)	339 (86.92)	771 (82.99)	378 (77.78)	27 (79.41)	1,213 (78.11)
Ex-Alcohol Use	25 (1.22)	7 (0.81)	3 (0.77)	18 (1.94)	4 (0.82)	0 (0.00)	41 (2.64)
Missing	4,449 ()	2,639 ()	835 ()	674 ()	991 ()	73 ()	8,003 ()

Table 5
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
Body mass index (kg/m2) (most recent) **							
Mean	26.54	26.98	26.06	26.20	26.32	25.38	26.44
Std. Dev.	5.07	5.11	4.79	5.06	4.84	4.05	5.19
Minimum	11.40	12.90	15.80	15.50	16.30	14.49	13.12
Median	25.80	26.30	25.30	25.59	25.68	25.60	25.71
Maximum	54.68	53.10	47.30	49.60	44.80	33.60	54.80
<25	1,462 (41.65)	653 (38.21)	304 (47.28)	520 (44.56)	342 (43.68)	21 (42.86)	1,190 (42.85)
25-29.9	1,306 (37.21)	633 (37.04)	241 (37.48)	419 (35.90)	282 (36.02)	21 (42.86)	1,011 (36.41)
≥30	742 (21.14)	423 (24.75)	98 (15.24)	228 (19.54)	159 (20.31)	7 (14.29)	576 (20.74)
Missing	2,995 ()	1,789 ()	582 ()	436 ()	694 ()	58 ()	6,779 ()
Year of entry into cohort: n (%)							
1986	1 (0.02)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
1987	0 (0.00)	0 (0.00)	2 (0.16)	0 (0.00)	2 (0.14)	0 (0.00)	0 (0.00)
1988	1 (0.02)	2 (0.06)	5 (0.41)	4 (0.25)	4 (0.27)	0 (0.00)	2 (0.02)
1989	10 (0.15)	12 (0.34)	15 (1.22)	13 (0.81)	8 (0.54)	0 (0.00)	10 (0.10)
1990	54 (0.83)	34 (0.97)	34 (2.78)	34 (2.12)	53 (3.59)	2 (1.87)	36 (0.38)
1991	76 (1.17)	56 (1.60)	51 (4.16)	45 (2.81)	78 (5.28)	4 (3.74)	35 (0.37)
1992	157 (2.41)	86 (2.46)	60 (4.90)	42 (2.62)	92 (6.23)	9 (8.41)	69 (0.72)
1993	176 (2.71)	91 (2.60)	58 (4.73)	43 (2.68)	86 (5.82)	3 (2.80)	76 (0.80)
1994	174 (2.67)	101 (2.89)	61 (4.98)	46 (2.87)	78 (5.28)	5 (4.67)	67 (0.70)
1995	199 (3.06)	91 (2.60)	45 (3.67)	38 (2.37)	54 (3.66)	2 (1.87)	90 (0.94)

Table 5
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
1996	200 (3.07)	100 (2.86)	56 (4.57)	39 (2.43)	63 (4.27)	4 (3.74)	111 (1.16)
1997	226 (3.47)	89 (2.54)	51 (4.16)	37 (2.31)	49 (3.32)	1 (0.93)	107 (1.12)
1998	208 (3.20)	85 (2.43)	61 (4.98)	43 (2.68)	69 (4.67)	2 (1.87)	147 (1.54)
1999	195 (3.00)	102 (2.92)	49 (4.00)	51 (3.18)	56 (3.79)	3 (2.80)	143 (1.50)
2000	261 (4.01)	102 (2.92)	47 (3.84)	37 (2.31)	47 (3.18)	4 (3.74)	177 (1.85)
2001	297 (4.57)	88 (2.52)	38 (3.10)	45 (2.81)	60 (4.06)	7 (6.54)	205 (2.15)
2002	300 (4.61)	106 (3.03)	70 (5.71)	58 (3.62)	65 (4.40)	4 (3.74)	251 (2.63)
2003	324 (4.98)	132 (3.77)	59 (4.82)	51 (3.18)	56 (3.79)	7 (6.54)	334 (3.50)
2004	457 (7.03)	190 (5.43)	52 (4.24)	59 (3.68)	74 (5.01)	10 (9.35)	491 (5.14)
2005	509 (7.82)	258 (7.38)	54 (4.41)	63 (3.93)	92 (6.23)	8 (7.48)	570 (5.96)
2006	493 (7.58)	201 (5.75)	59 (4.82)	77 (4.80)	87 (5.89)	0 (0.00)	650 (6.80)
2007	470 (7.23)	258 (7.38)	58 (4.73)	65 (4.05)	56 (3.79)	9 (8.41)	726 (7.60)
2008	448 (6.89)	257 (7.35)	72 (5.88)	115 (7.17)	77 (5.21)	5 (4.67)	952 (9.96)
2009	391 (6.01)	288 (8.23)	55 (4.49)	108 (6.74)	50 (3.39)	3 (2.80)	908 (9.50)
2010	350 (5.38)	242 (6.92)	38 (3.10)	115 (7.17)	34 (2.30)	3 (2.80)	884 (9.25)
2011	256 (3.94)	252 (7.20)	42 (3.43)	131 (8.17)	29 (1.96)	3 (2.80)	1,091 (11.42)
2012	159 (2.44)	153 (4.37)	14 (1.14)	118 (7.36)	31 (2.10)	5 (4.67)	698 (7.30)
2013	113 (1.74)	122 (3.49)	19 (1.55)	126 (7.86)	27 (1.83)	4 (3.74)	726 (7.60)
Cohort entry before cox-2 Urgent Safety Restriction (17Feb05): n (%)							
Yes	3,391 (52.13)	1,509 (43.14)	821 (67.02)	690 (43.04)	1,009 (68.31)	69 (64.49)	2,424 (25.37)
No	3,114 (47.87)	1,989 (56.86)	404 (32.98)	913 (56.96)	468 (31.69)	38 (35.51)	7,132 (74.63)

Table 5
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
Total number of prior health care encounters*							
Mean	4.79	4.78	4.10	6.47	4.66	3.61	4.15
Std. Dev.	4.67	4.46	3.90	5.69	4.49	3.01	4.64
Minimum	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Median	3.00	3.00	3.00	5.00	3.00	3.00	3.00
Maximum	104.00	52.00	30.00	43.00	35.00	19.00	59.00
Referral to Rheumatologist: n (%) **							
Yes	227 (8.22)	113 (9.60)	40 (6.80)	121 (9.93)	91 (12.64)	4 (7.41)	157 (7.76)
No	2,534 (91.78)	1,064 (90.40)	548 (93.20)	1,097 (90.07)	629 (87.36)	50 (92.59)	1,865 (92.24)
Missing	3,744 ()	2,321 ()	637 ()	385 ()	757 ()	53 ()	7,534 ()
X-ray of the sacrum or spine: n (%) **							
Yes	89 (3.22)	40 (3.40)	10 (1.70)	16 (1.31)	27 (3.75)	0 (0.00)	40 (1.98)
No	2,672 (96.78)	1,137 (96.60)	578 (98.30)	1,202 (98.69)	693 (96.25)	54 (100.00)	1,982 (98.02)
Missing	3,744 ()	2,321 ()	637 ()	385 ()	757 ()	53 ()	7,534 ()
Both Referral to Rheumatologist and X-ray of the sacrum or spine: n (%) **							
Yes	14 (0.51)	6 (0.51)	1 (0.17)	3 (0.25)	3 (0.42)	0 (0.00)	6 (0.30)
No	2,747 (99.49)	1,171 (99.49)	587 (99.83)	1,215 (99.75)	717 (99.58)	54 (100.00)	2,016 (99.70)
Missing	3,744 ()	2,321 ()	637 ()	385 ()	757 ()	53 ()	7,534 ()
Mean SBP (mmHg) (most recent) **							
Mean	129.24	132.12	131.52	128.70	130.72	125.72	131.40
Std. Dev.	18.08	19.16	19.26	16.34	19.03	19.56	19.35

Table 5
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
Minimum	82.00	90.00	85.00	80.00	80.00	100.00	80.00
Median	130.00	130.00	130.00	130.00	130.00	120.00	130.00
Maximum	235.00	215.00	200.00	190.00	190.00	200.00	232.00
<120	589 (25.13)	227 (22.52)	106 (23.66)	252 (24.85)	145 (24.96)	12 (30.77)	415 (23.47)
120-139	1,070 (45.65)	419 (41.57)	182 (40.63)	493 (48.62)	235 (40.45)	19 (48.72)	757 (42.82)
≥140	685 (29.22)	362 (35.91)	160 (35.71)	269 (26.53)	201 (34.60)	8 (20.51)	596 (33.71)
Missing	4,161 ()	2,490 ()	777 ()	589 ()	896 ()	68 ()	7,788 ()
Mean DBP (mmHg) (most recent) **							
Mean	78.08	78.53	78.96	77.28	77.93	77.15	77.43
Std. Dev.	10.13	10.13	10.30	9.98	10.53	8.52	10.46
Minimum	45.00	40.00	50.00	47.00	40.00	60.00	42.00
Median	80.00	80.00	80.00	79.00	80.00	80.00	80.00
Maximum	135.00	130.00	118.00	120.00	110.00	95.00	120.00
<80	1,053 (44.92)	437 (43.35)	182 (40.63)	520 (51.28)	255 (43.89)	17 (43.59)	876 (49.55)
80-89	966 (41.21)	408 (40.48)	184 (41.07)	370 (36.49)	232 (39.93)	18 (46.15)	657 (37.16)
≥90	325 (13.87)	163 (16.17)	82 (18.30)	124 (12.23)	94 (16.18)	4 (10.26)	235 (13.29)
Missing	4,161 ()	2,490 ()	777 ()	589 ()	896 ()	68 ()	7,788 ()

* Total number of visits to GP and referrals to specialists in the 6 months prior to cohort entry

10.2.4 Baseline Medical History

Recent baseline medical history (in the 6 months prior to cohort entry) for the AS cohort as a whole is shown in **Table 6**. The comorbid disease burden for the population was generally low. This may be partly due to the mean age of the cohort (48 years), and partly due to the length of the baseline period during which the medical history was assessed (6 months prior to cohort entry). It may also be due to the fact that the patients included in these analyses are primarily seen by GP's and most are not using systemic medications. About 3.1 to 7.5% of the cohort have chronic arthritis (OA, RA, non-specific). Medical history of gastrointestinal PUB was low, as was that for myocardial infarction, cerebrovascular events, and peripheral vascular diagnoses. History of acute or subacute coronary heart disease (other than MI or unstable angina) was present in 2.4% of the cohort, while medical history of renal disease and CHF were both present in about 1.0%. About 10.1% of the cohort had a baseline history of hypertension diagnosis, 1.8% IBD, 4.4% dyslipidemia, and 5.2 % diabetes (diagnosis or anti-diabetic medication).

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 6a** for UK CPRD + THIN, **Table 6b** for UK IMS, **Table 6c** for Germany IMS, and **Table 6d** for France IMS).

Table 6
AS Cohort Baseline Medical History
(Assessed During the 6 Months Prior to Entry into the Cohort)
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	N=27,381
Medical History[†]: n (%)	
Osteoarthritis	1,054 (3.85)
Rheumatoid Arthritis	847 (3.09)
Gout	175 (0.64)
Arthritis NOS	2,061 (7.53)
GI PUB	207 (0.76)
MI	180 (0.66)
UAP	69 (0.25)
Acute or Subacute CHD (excluding MI or UAP)	665 (2.43)
Atherosclerotic Cardiovascular Disease	74 (0.27)
Ischemic CVD or TIA	123 (0.45)
Hemorrhagic CVD	6 (0.02)
DVT or PE	164 (0.60)
Edema	99 (0.36)
Renal Disease	285 (1.04)
Acute Renal Failure	98 (0.36)
Hypertension (diagnosis only)	2,757 (10.07)
CHF	273 (1.00)
IBD	500 (1.83)
PAD	132 (0.48)
Dyslipidemia	1,194 (4.36)
DM (diagnosis or medication)	1,411 (5.15)

[†] NOS = Not Otherwise Specified; PUB = Perforation, Ulcer, Bleeding; MI = Myocardial Infarction; UAP = Unstable Angina Pectoris; CHD = Coronary Heart Disease; CVD = Cerebrovascular Disease; TIA = Transient Ischemic Attack; DVT = Deep Venous Thrombosis; PE = Pulmonary Embolism; CHF = Congestive Heart Failure or Left Ventricular Dysfunction; IBD = Inflammatory Bowel Disease; PAD = Peripheral Arterial Disease; DM = Diabetes Mellitus;

Table 7 shows other baseline medical history (during the period 6 months to 12 months prior to entry into the cohort) for those patients in the cohort with at least one year of medical history data prior to entry (n=22,488; 82.1% of the total cohort). About 1.4 to 4.0% of this subset have chronic arthritis (OA, RA, non-specific). The pattern of results is similar in this analysis to that in **Table 6** however the absolute numbers are slightly smaller.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 7a** for UK CPRD + THIN, **Table 7b** for UK IMS, **Table 7c** for Germany IMS, and **Table 7d** for France IMS).

Table 7
AS Cohort Baseline Medical History
(Assessed During the Period 6 to 12 Months Prior to Entry into the Cohort)
(Patients with at Least One Year Registration)
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	N=22,488
Medical History[†]: n (%)	
Osteoarthritis	484 (2.15)
Rheumatoid Arthritis	314 (1.40)
Gout	108 (0.48)
Arthritis NOS	904 (4.02)
GI PUB	108 (0.48)
MI	93 (0.41)
UAP	42 (0.19)
Acute or Subacute CHD (excluding MI or UAP)	373 (1.66)
Atherosclerotic Cardiovascular Disease	27 (0.12)
Ischemic CVD or TIA	64 (0.28)
Hemorrhagic CVD	5 (0.02)
DVT or PE	109 (0.48)
Edema	86 (0.38)
Renal Disease	133 (0.59)
Acute Renal Failure	35 (0.16)
Hypertension (diagnosis only)	1,693 (7.53)
CHF	161 (0.72)
IBD	239 (1.06)
PAD	83 (0.37)
Dyslipidemia	652 (2.90)
DM (diagnosis or medication)	957 (4.26)

[†] NOS = Not Otherwise Specified; PUB = Perforation, Ulcer, Bleeding; MI = Myocardial Infarction; UAP = Unstable Angina Pectoris; CHD = Coronary Heart Disease; CVD = Cerebrovascular Disease; TIA = Transient Ischemic Attack; DVT = Deep Venous Thrombosis; PE = Pulmonary Embolism; CHF = Congestive Heart Failure or Left Ventricular Dysfunction; IBD = Inflammatory Bowel Disease; PAD = Peripheral Arterial Disease; DM = Diabetes Mellitus;

Analyses of baseline medical history by type of first non-steroidal anti-inflammatory prescription (COX-2 inhibitor, non-selective NSAID, multiple, or none) for treatment of AS after entry into the cohort are shown in **Table 8.** For a given patient this may not have been their first ever treatment with a non-steroidal anti-inflammatory agent.

Patients prescribed COX-2 inhibitors generally had similar frequencies of baseline medical conditions as did those prescribed a non-selective NSAID.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 8a** for UK CPRD + THIN, **Table 8b** for UK IMS, **Table 8c** for Germany IMS, and **Table 8d** for France IMS).

Table 8
AS Cohort Baseline Medical History
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Type of First Anti-Inflammatory Prescription for Treatment of AS
After Entry into the Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Type of First Anti-Inflammatory Prescription			
	COX-2 Inhibitor N=3,218	NSAID N=14,500	Multiple N=107	None N=9,556
Medical History[†]: n (%)				
Osteoarthritis	131 (4.07)	634 (4.37)	4 (3.74)	285 (2.98)
Rheumatoid Arthritis	118 (3.67)	373 (2.57)	1 (0.93)	355 (3.71)
Gout	19 (0.59)	101 (0.70)	0 (0.00)	55 (0.58)
Arthritis NOS	263 (8.17)	1,035 (7.14)	8 (7.48)	755 (7.90)
GI PUB	32 (0.99)	100 (0.69)	0 (0.00)	75 (0.78)
MI	8 (0.25)	94 (0.65)	1 (0.93)	77 (0.81)
UAP	7 (0.22)	31 (0.21)	2 (1.87)	29 (0.30)
Acute or Subacute CHD (excluding MI or UAP)	66 (2.05)	342 (2.36)	6 (5.61)	251 (2.63)
Atherosclerotic Cardiovascular Disease	11 (0.34)	29 (0.20)	0 (0.00)	34 (0.36)
Ischemic CVD or TIA	12 (0.37)	42 (0.29)	1 (0.93)	68 (0.71)
Hemorrhagic CVD	0 (0.00)	2 (0.01)	0 (0.00)	4 (0.04)
DVT or PE	25 (0.78)	73 (0.50)	0 (0.00)	66 (0.69)
Edema	14 (0.44)	44 (0.30)	0 (0.00)	41 (0.43)
Renal Disease	27 (0.84)	147 (1.01)	3 (2.80)	108 (1.13)
Acute Renal Failure	8 (0.25)	50 (0.34)	0 (0.00)	40 (0.42)
Hypertension (diagnosis only)	273 (8.48)	1,376 (9.49)	11 (10.28)	1,097 (11.48)
CHF	29 (0.90)	122 (0.84)	1 (0.93)	121 (1.27)
IBD	65 (2.02)	225 (1.55)	2 (1.87)	208 (2.18)
PAD	7 (0.22)	70 (0.48)	1 (0.93)	54 (0.57)
Dyslipidemia	124 (3.85)	607 (4.19)	4 (3.74)	459 (4.80)
DM (diagnosis or medication)	141 (4.38)	710 (4.90)	5 (4.67)	555 (5.81)

[†] NOS = Not Otherwise Specified; PUB = Perforation, Ulcer, Bleeding; MI = Myocardial Infarction; UAP = Unstable Angina Pectoris; CHD = Coronary Heart Disease; CVD = Cerebrovascular Disease; TIA = Transient Ischemic Attack; DVT = Deep Venous Thrombosis; PE = Pulmonary Embolism; CHF = Congestive Heart Failure or Left Ventricular Dysfunction; IBD = Inflammatory Bowel Disease; PAD = Peripheral Arterial Disease; DM = Diabetes Mellitus;

Table 9 shows other baseline medical history (assessed during the period 6 months to 12 months prior to entry into the cohort) for those patients in the cohort with at least one year of medical history data prior to entry (n=22,488; 82.1% of the total cohort) by type of first non-steroidal anti-inflammatory prescription for treatment of AS after entry into the cohort. For a given patient this may not have been their first ever treatment with a non-steroidal anti-inflammatory agent.

Patients prescribed COX-2 inhibitors were generally similar to those prescribed a non-selective NSAID in this analysis, except for a slightly lower prevalence of history of hypertension and a slightly higher prevalence of other arthritis.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 9a** for UK CPRD + THIN, **Table 9b** for UK IMS, **Table 9c** for Germany IMS, and **Table 9d** for France IMS).

Table 9
AS Cohort Baseline Medical History
(Assessed During the Period 6 To 12 Months Prior to Entry into the Cohort)
(Patients with at Least One Year Registration)
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Type of First Anti-Inflammatory Prescription			
	COX-2 Inhibitor N=2,605	NSAID N=11,983	Multiple N=85	None N=7,815
Medical History[†]: n (%)				
Osteoarthritis	50 (1.92)	300 (2.50)	0 (0.00)	134 (1.71)
Rheumatoid Arthritis	41 (1.57)	139 (1.16)	1 (1.18)	133 (1.70)
Gout	12 (0.46)	61 (0.51)	0 (0.00)	35 (0.45)
Arthritis NOS	128 (4.91)	466 (3.89)	3 (3.53)	307 (3.93)
GI PUB	15 (0.58)	57 (0.48)	0 (0.00)	36 (0.46)
MI	7 (0.27)	48 (0.40)	0 (0.00)	38 (0.49)
UAP	5 (0.19)	23 (0.19)	1 (1.18)	13 (0.17)
Acute or Subacute CHD (excluding MI or UAP)	37 (1.42)	216 (1.80)	1 (1.18)	119 (1.52)
Atherosclerotic Cardiovascular Disease	5 (0.19)	12 (0.10)	0 (0.00)	10 (0.13)
Ischemic CVD or TIA	15 (0.58)	27 (0.23)	0 (0.00)	22 (0.28)
Hemorrhagic CVD	0 (0.00)	0 (0.00)	0 (0.00)	5 (0.06)
DVT or PE	16 (0.61)	50 (0.42)	0 (0.00)	43 (0.55)
Edema	13 (0.50)	43 (0.36)	0 (0.00)	30 (0.38)
Renal Disease	11 (0.42)	71 (0.59)	1 (1.18)	50 (0.64)
Acute Renal Failure	2 (0.08)	22 (0.18)	0 (0.00)	11 (0.14)
Hypertension (diagnosis only)	162 (6.22)	896 (7.48)	4 (4.71)	631 (8.07)
CHF	21 (0.81)	78 (0.65)	0 (0.00)	62 (0.79)
IBD	35 (1.34)	119 (0.99)	0 (0.00)	85 (1.09)
PAD	7 (0.27)	49 (0.41)	0 (0.00)	27 (0.35)
Dyslipidemia	65 (2.50)	347 (2.90)	1 (1.18)	239 (3.06)
DM (diagnosis or medication)	91 (3.49)	505 (4.21)	3 (3.53)	358 (4.58)

[†] NOS = Not Otherwise Specified; PUB = Perforation, Ulcer, Bleeding; MI = Myocardial Infarction; UAP = Unstable Angina Pectoris; CHD = Coronary Heart Disease; CVD = Cerebrovascular Disease; TIA = Transient Ischemic Attack; DVT = Deep Venous Thrombosis; PE = Pulmonary Embolism; CHF = Congestive Heart Failure or Left Ventricular Dysfunction; IBD = Inflammatory Bowel Disease; PAD = Peripheral Arterial Disease; DM = Diabetes Mellitus;

Recent baseline medical history (during the 6 months prior to entry in to the AS cohort) by specific first non-steroidal anti-inflammatory prescription for treatment of AS after entry into the cohort are shown in **Table 10**. For a given patient, this may not have been their first ever prescription for a non-steroidal anti-inflammatory agent. One thousand eighty patients were prescribed etoricoxib as their first non-steroidal anti-inflammatory treatment after entry into the cohort. Among these patients, the prevalence of baseline comorbidity, including GI and vascular diseases, was generally low during this time period except 8.8%, 1.8%, 3.6% and 4.4% had a baseline medical history of hypertension diagnosis, IBD, dyslipidemia, and diabetes, respectively.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 10a** for UK CPRD + THIN, **Table 10b** for UK IMS, **Table 10c** for Germany IMS, and **Table 10d** for France IMS).

Table 10
AS Cohort Baseline Medical History
(Assessed During the 6 Months Prior to Entry)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
Medical History[†]: n (%)							
Osteoarthritis	39 (3.61)	33 (3.89)	1 (8.33)	28 (3.47)	29 (6.64)	1 (3.13)	8 (4.17)
Rheumatoid Arthritis	55 (5.09)	30 (3.53)	1 (8.33)	19 (2.35)	11 (2.52)	2 (6.25)	2 (1.04)
Gout	12 (1.11)	3 (0.35)	0 (0.00)	2 (0.25)	2 (0.46)	0 (0.00)	0 (0.00)
Arthritis NOS	98 (9.07)	67 (7.89)	1 (8.33)	65 (8.04)	29 (6.64)	3 (9.38)	11 (5.73)
GI PUB	4 (0.37)	10 (1.18)	2 (16.67)	7 (0.87)	9 (2.06)	0 (0.00)	0 (0.00)
MI	3 (0.28)	3 (0.35)	0 (0.00)	1 (0.12)	1 (0.23)	0 (0.00)	0 (0.00)
UAP	2 (0.19)	2 (0.24)	1 (8.33)	1 (0.12)	1 (0.23)	0 (0.00)	0 (0.00)
Acute or Subacute CHD (excluding MI or UAP)	17 (1.57)	15 (1.77)	2 (16.67)	15 (1.86)	14 (3.20)	3 (9.38)	2 (1.04)
Atherosclerotic Cardiovascular Disease	5 (0.46)	3 (0.35)	0 (0.00)	1 (0.12)	2 (0.46)	0 (0.00)	0 (0.00)
Ischemic CVD or TIA	1 (0.09)	1 (0.12)	1 (8.33)	3 (0.37)	6 (1.37)	0 (0.00)	0 (0.00)
Hemorrhagic CVD	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
DVT or PE	11 (1.02)	6 (0.71)	0 (0.00)	4 (0.50)	4 (0.92)	0 (0.00)	0 (0.00)
Edema	6 (0.56)	3 (0.35)	0 (0.00)	4 (0.50)	1 (0.23)	0 (0.00)	0 (0.00)
Renal Disease	12 (1.11)	5 (0.59)	0 (0.00)	7 (0.87)	3 (0.69)	0 (0.00)	0 (0.00)
Acute Renal Failure	5 (0.46)	1 (0.12)	0 (0.00)	1 (0.12)	1 (0.23)	0 (0.00)	0 (0.00)
Hypertension (diagnosis only)	95 (8.80)	69 (8.13)	2 (16.67)	58 (7.18)	45 (10.30)	4 (12.50)	10 (5.21)
CHF	7 (0.65)	7 (0.82)	0 (0.00)	4 (0.50)	11 (2.52)	0 (0.00)	0 (0.00)
IBD	19 (1.76)	19 (2.24)	0 (0.00)	16 (1.98)	11 (2.52)	0 (0.00)	3 (1.56)
PAD	2 (0.19)	3 (0.35)	0 (0.00)	0 (0.00)	1 (0.23)	1 (3.13)	0 (0.00)

Table 10
AS Cohort Baseline Medical History
(Assessed During the 6 Months Prior to Entry)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
Dyslipidemia	39 (3.61)	37 (4.36)	2 (16.67)	24 (2.97)	20 (4.58)	2 (6.25)	0 (0.00)
DM (diagnosis or medication)	48 (4.44)	36 (4.24)	1 (8.33)	31 (3.84)	22 (5.03)	3 (9.38)	8 (4.17)

[†] NOS = Not Otherwise Specified; PUB = Perforation, Ulcer, Bleeding; MI = Myocardial Infarction; UAP = Unstable Angina Pectoris; CHD = Coronary Heart Disease; CVD = Cerebrovascular Disease; TIA = Transient Ischemic Attack; DVT = Deep Venous Thrombosis; PE = Pulmonary Embolism; CHF = Congestive Heart Failure or Left Ventricular Dysfunction; IBD = Inflammatory Bowel Disease; PAD = Peripheral Arterial Disease; DM = Diabetes Mellitus;

Table 10
AS Cohort Baseline Medical History (Assessed During the 6 Months Prior to Entry)
(By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort)
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
Medical History[†]: n (%)							
Osteoarthritis	268 (4.12)	192 (5.49)	26 (2.12)	67 (4.18)	73 (4.94)	4 (3.74)	285 (2.98)
Rheumatoid Arthritis	175 (2.69)	118 (3.37)	28 (2.29)	24 (1.50)	26 (1.76)	1 (0.93)	355 (3.71)
Gout	44 (0.68)	29 (0.83)	12 (0.98)	6 (0.37)	10 (0.68)	0 (0.00)	55 (0.58)
Arthritis NOS	499 (7.67)	283 (8.09)	74 (6.04)	69 (4.30)	99 (6.70)	8 (7.48)	755 (7.90)
GI PUB	38 (0.58)	27 (0.77)	12 (0.98)	11 (0.69)	12 (0.81)	0 (0.00)	75 (0.78)
MI	40 (0.61)	31 (0.89)	9 (0.73)	8 (0.50)	6 (0.41)	1 (0.93)	77 (0.81)
UAP	13 (0.20)	10 (0.29)	1 (0.08)	2 (0.12)	5 (0.34)	2 (1.87)	29 (0.30)
Acute or Subacute CHD (excluding MI or UAP)	180 (2.77)	91 (2.60)	28 (2.29)	12 (0.75)	29 (1.96)	6 (5.61)	251 (2.63)
Atherosclerotic Cardiovascular Disease	14 (0.22)	10 (0.29)	2 (0.16)	0 (0.00)	3 (0.20)	0 (0.00)	34 (0.36)
Ischemic CVD or TIA	20 (0.31)	17 (0.49)	4 (0.33)	0 (0.00)	1 (0.07)	1 (0.93)	68 (0.71)
Hemorrhagic CVD	1 (0.02)	0 (0.00)	0 (0.00)	1 (0.06)	0 (0.00)	0 (0.00)	4 (0.04)
DVT or PE	37 (0.57)	23 (0.66)	4 (0.33)	5 (0.31)	4 (0.27)	0 (0.00)	66 (0.69)
Edema	23 (0.35)	15 (0.43)	4 (0.33)	0 (0.00)	2 (0.14)	0 (0.00)	41 (0.43)
Renal Disease	75 (1.15)	49 (1.40)	7 (0.57)	1 (0.06)	15 (1.02)	3 (2.80)	108 (1.13)
Acute Renal Failure	28 (0.43)	16 (0.46)	2 (0.16)	0 (0.00)	4 (0.27)	0 (0.00)	40 (0.42)
Hypertension (diagnosis only)	671 (10.32)	444 (12.69)	101 (8.24)	44 (2.74)	106 (7.18)	11 (10.28)	1,097 (11.48)
CHF	60 (0.92)	40 (1.14)	10 (0.82)	1 (0.06)	11 (0.74)	1 (0.93)	121 (1.27)
IBD	105 (1.61)	71 (2.03)	10 (0.82)	14 (0.87)	22 (1.49)	2 (1.87)	208 (2.18)

Table 10
AS Cohort Baseline Medical History (Assessed During the 6 Months Prior to Entry)
(By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort)
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
PAD	39 (0.60)	15 (0.43)	8 (0.65)	3 (0.19)	5 (0.34)	1 (0.93)	54 (0.57)
Dyslipidemia	302 (4.64)	195 (5.57)	43 (3.51)	15 (0.94)	52 (3.52)	4 (3.74)	459 (4.80)
DM (diagnosis or medication)	313 (4.81)	228 (6.52)	50 (4.08)	50 (3.12)	61 (4.13)	5 (4.67)	555 (5.81)

NOS = Not Otherwise Specified; PUB = Perforation, Ulcer, Bleeding; MI = Myocardial Infarction; UAP = Unstable Angina Pectoris; CHD = Coronary Heart Disease; CVD = Cerebrovascular Disease; TIA = Transient Ischemic Attack; DVT = Deep Venous Thrombosis; PE = Pulmonary Embolism; CHF = Congestive Heart Failure or Left Ventricular Dysfunction; IBD = Inflammatory Bowel Disease; PAD = Peripheral Arterial Disease; DM = Diabetes Mellitus;

Table 11 shows other baseline medical history assessed during the period 6 months to 12 months prior to entry into the cohort for those patients in the cohort with at least one year of medical history data prior to entry by specific first non-steroidal anti-inflammatory prescription for treatment of AS after entry into the cohort. For a given patient this may not have been their first ever treatment with a non-steroidal anti-inflammatory agent.

In this subset 900 patients were prescribed etoricoxib as their first non-steroidal anti-inflammatory treatment after entry into the cohort. Among these patients, the prevalence of baseline comorbidity, including GI and vascular diseases, was generally low during this time period except 7.3%, 1.3%, 3.4% and 3.7% had a baseline medical history of hypertension diagnosis, IBD, dyslipidemia, and diabetes, respectively.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 11a** for UK CPRD + THIN, **Table 11b** for UK IMS, **Table 11c** for Germany IMS, and **Table 11d** for France IMS).

Table 11
AS Cohort Baseline Medical History
(Assessed During the Period 6 To 12 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
(Patients with at Least One Year Registration)
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=900	Celecoxib N=674	Lumiracoxib N=7	Meloxicam N=656	Rofecoxib N=345	Valdecoxib N=23	Etodolac N=168
Medical History[†]: n (%)							
Osteoarthritis	18 (2.00)	13 (1.93)	0 (0.00)	12 (1.83)	7 (2.03)	0 (0.00)	3 (1.79)
Rheumatoid Arthritis	19 (2.11)	6 (0.89)	0 (0.00)	13 (1.98)	2 (0.58)	1 (4.35)	0 (0.00)
Gout	9 (1.00)	3 (0.45)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Arthritis NOS	50 (5.56)	31 (4.60)	0 (0.00)	29 (4.42)	18 (5.22)	0 (0.00)	4 (2.38)
GI PUB	3 (0.33)	6 (0.89)	1 (14.29)	3 (0.46)	2 (0.58)	0 (0.00)	0 (0.00)
MI	3 (0.33)	0 (0.00)	1 (14.29)	0 (0.00)	3 (0.87)	0 (0.00)	0 (0.00)
UAP	2 (0.22)	2 (0.30)	0 (0.00)	0 (0.00)	1 (0.29)	0 (0.00)	0 (0.00)
Acute or Subacute CHD (excluding MI or UAP)	11 (1.22)	12 (1.78)	1 (14.29)	7 (1.07)	6 (1.74)	0 (0.00)	1 (0.60)
Atherosclerotic Cardiovascular Disease	1 (0.11)	0 (0.00)	0 (0.00)	1 (0.15)	3 (0.87)	0 (0.00)	0 (0.00)
Ischemic CVD or TIA	5 (0.56)	3 (0.45)	0 (0.00)	7 (1.07)	0 (0.00)	0 (0.00)	0 (0.00)
Hemorrhagic CVD	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
DVT or PE	7 (0.78)	6 (0.89)	0 (0.00)	2 (0.30)	1 (0.29)	0 (0.00)	0 (0.00)
Edema	5 (0.56)	5 (0.74)	0 (0.00)	2 (0.30)	1 (0.29)	0 (0.00)	0 (0.00)
Renal Disease	4 (0.44)	2 (0.30)	0 (0.00)	4 (0.61)	1 (0.29)	0 (0.00)	0 (0.00)
Acute Renal Failure	0 (0.00)	1 (0.15)	0 (0.00)	1 (0.15)	0 (0.00)	0 (0.00)	0 (0.00)
Hypertension (diagnosis only)	66 (7.33)	40 (5.93)	0 (0.00)	34 (5.18)	19 (5.51)	3 (13.04)	7 (4.17)
CHF	2 (0.22)	6 (0.89)	0 (0.00)	5 (0.76)	8 (2.32)	0 (0.00)	0 (0.00)
IBD	12 (1.33)	8 (1.19)	0 (0.00)	7 (1.07)	8 (2.32)	0 (0.00)	1 (0.60)

Table 11
AS Cohort Baseline Medical History
(Assessed During the Period 6 To 12 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
(Patients with at Least One Year Registration)
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=900	Celecoxib N=674	Lumiracoxib N=7	Meloxicam N=656	Rofecoxib N=345	Valdecoxib N=23	Etodolac N=168
PAD	0 (0.00)	3 (0.45)	0 (0.00)	1 (0.15)	2 (0.58)	1 (4.35)	0 (0.00)
Dyslipidemia	31 (3.44)	15 (2.23)	0 (0.00)	11 (1.68)	8 (2.32)	0 (0.00)	1 (0.60)
DM (diagnosis or medication)	33 (3.67)	24 (3.56)	1 (14.29)	20 (3.05)	12 (3.48)	1 (4.35)	8 (4.76)

† NOS = Not Otherwise Specified; PUB = Perforation, Ulcer, Bleeding; MI = Myocardial Infarction; UAP = Unstable Angina Pectoris; CHD = Coronary Heart Disease; CVD = Cerebrovascular Disease; TIA = Transient Ischemic Attack; DVT = Deep Venous Thrombosis; PE = Pulmonary Embolism; CHF = Congestive Heart Failure or Left Ventricular Dysfunction; IBD = Inflammatory Bowel Disease; PAD = Peripheral Arterial Disease; DM = Diabetes Mellitus;

Table 11
AS Cohort Baseline Medical History
(Assessed During the Period 6 To 12 Months Prior to Entry into the Cohort)
(Patients with at Least One Year Registration)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Diclofenac N=5,376	Ibuprofen N=2,990	Indomethacin N=904	Naproxen N=1,396	Other Non-Selective NSAIDs N=1,149	Multiple N=85	None N=7,815
Medical History[†]: n (%)							
Osteoarthritis	139 (2.59)	80 (2.68)	16 (1.77)	24 (1.72)	38 (3.31)	0 (0.00)	134 (1.71)
Rheumatoid Arthritis	63 (1.17)	50 (1.67)	10 (1.11)	9 (0.64)	7 (0.61)	1 (1.18)	133 (1.70)
Gout	30 (0.56)	20 (0.67)	5 (0.55)	1 (0.07)	5 (0.44)	0 (0.00)	35 (0.45)
Arthritis NOS	219 (4.07)	150 (5.02)	25 (2.77)	31 (2.22)	37 (3.22)	3 (3.53)	307 (3.93)
GI PUB	18 (0.33)	22 (0.74)	8 (0.88)	3 (0.21)	6 (0.52)	0 (0.00)	36 (0.46)
MI	28 (0.52)	12 (0.40)	4 (0.44)	0 (0.00)	4 (0.35)	0 (0.00)	38 (0.49)
UAP	4 (0.07)	12 (0.40)	1 (0.11)	0 (0.00)	6 (0.52)	1 (1.18)	13 (0.17)
Acute or Subacute CHD (excluding MI or UAP)	106 (1.97)	66 (2.21)	14 (1.55)	9 (0.64)	20 (1.74)	1 (1.18)	119 (1.52)
Atherosclerotic Cardiovascular Disease	5 (0.09)	4 (0.13)	0 (0.00)	0 (0.00)	3 (0.26)	0 (0.00)	10 (0.13)
Ischemic CVD or TIA	10 (0.19)	12 (0.40)	1 (0.11)	1 (0.07)	3 (0.26)	0 (0.00)	22 (0.28)
Hemorrhagic CVD	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	5 (0.06)
DVT or PE	26 (0.48)	20 (0.67)	0 (0.00)	1 (0.07)	3 (0.26)	0 (0.00)	43 (0.55)
Edema	19 (0.35)	16 (0.54)	2 (0.22)	0 (0.00)	6 (0.52)	0 (0.00)	30 (0.38)
Renal Disease	37 (0.69)	27 (0.90)	4 (0.44)	0 (0.00)	3 (0.26)	1 (1.18)	50 (0.64)
Acute Renal Failure	13 (0.24)	6 (0.20)	0 (0.00)	1 (0.07)	2 (0.17)	0 (0.00)	11 (0.14)
Hypertension (diagnosis only)	440 (8.18)	316 (10.57)	41 (4.54)	33 (2.36)	59 (5.13)	4 (4.71)	631 (8.07)

Table 11
AS Cohort Baseline Medical History
(Assessed During the Period 6 To 12 Months Prior to Entry into the Cohort)
(Patients with at Least One Year Registration)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Diclofenac N=5,376	Ibuprofen N=2,990	Indomethacin N=904	Naproxen N=1,396	Other Non-Selective NSAIDs N=1,149	Multiple N=85	None N=7,815
CHF	38 (0.71)	24 (0.80)	3 (0.33)	3 (0.21)	10 (0.87)	0 (0.00)	62 (0.79)
IBD	59 (1.10)	40 (1.34)	4 (0.44)	7 (0.50)	8 (0.70)	0 (0.00)	85 (1.09)
PAD	23 (0.43)	11 (0.37)	5 (0.55)	4 (0.29)	6 (0.52)	0 (0.00)	27 (0.35)
Dyslipidemia	174 (3.24)	116 (3.88)	14 (1.55)	14 (1.00)	28 (2.44)	1 (1.18)	239 (3.06)
DM (diagnosis or medication)	226 (4.20)	165 (5.52)	27 (2.99)	40 (2.87)	39 (3.39)	3 (3.53)	358 (4.58)

NOS = Not Otherwise Specified; PUB = Perforation, Ulcer, Bleeding; MI = Myocardial Infarction; UAP = Unstable Angina Pectoris; CHD = Coronary Heart Disease; CVD = Cerebrovascular Disease; TIA = Transient Ischemic Attack; DVT = Deep Venous Thrombosis; PE = Pulmonary Embolism; CHF = Congestive Heart Failure or Left Ventricular Dysfunction; IBD = Inflammatory Bowel Disease; PAD = Peripheral Arterial Disease; DM = Diabetes Mellitus;

10.2.5 Baseline Non-steroidal Anti-inflammatory Therapy

Univariate statistics for the total daily dose (TDD) of baseline non-steroidal anti-inflammatory treatment (defined as the most recent drug prescribed during the 6 months prior to entry) are given in **Table 12**. Any recorded prescription for non-steroidal anti-inflammatory therapy regardless of frequency of occurrence during the 6 month baseline period prior to entry into the cohort is counted towards baseline non-steroidal anti-inflammatory use. For a given patient, this may not have been their first ever treatment with a non-steroidal anti-inflammatory agent. Patients with multiple non-steroidal anti-inflammatory drugs as the most recent prescription prior to entry into the cohort are not included.

For patients with a history of etoricoxib prescription during the 6-month baseline period (n=554), the mean (SD) and median baseline TDD was 87.0 mg (21.0 mg) and 90.0 mg, respectively. The proportion of patients with baseline etoricoxib TDD >90 mg was 8.3%, and the range was 30.0-180.0 mg. Note that for 47.3% of the patients with a history of etoricoxib prescription during the 6-month baseline period, dose information was not available.

TDD statistics for other baseline non-steroidal anti-inflammatory agents are also shown in **Table 12**.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 12a** for UK CPRD + THIN, **Table 12b** for UK IMS, **Table 12c** for Germany IMS, and **Table 12d** for France IMS).

Table 12
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the AS Cohort)
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	N=27,381
COX-2 Selective Inhibitors	
Celecoxib	
n	438
Mean	255.34
Std. Dev.	94.04
Minimum	28.58
Median	200.00
Maximum	400.00
≤100mg [(n (%)]	5 (1.14)
>100-200mg [(n (%)]	155 (35.39)
>200-400mg [(n (%)]	70 (15.98)
>400mg* [(n (%)]	0 (0.00)
Missing [(n (%)]	208 (47.49)
Etoricoxib	
n	554
Mean	87.02
Std. Dev.	20.97
Minimum	30.00
Median	90.00
Maximum	180.00
≤30mg [(n (%)]	7 (1.26)
>30-60mg [(n (%)]	63 (11.37)
>60-90mg [(n (%)]	176 (31.77)
>90-120mg [(n (%)]	45 (8.12)
>120mg* [(n (%)]	1 (0.18)
Missing [(n (%)]	262 (47.29)
Lumiracoxib	
n	3
Mean	.
Std. Dev.	.
Minimum	.
Median	.
Maximum	.
≤100mg [(n (%)]	0 (0.00)
>100-200mg [(n (%)]	0 (0.00)
>200mg* [(n (%)]	0 (0.00)
Missing [(n (%)]	3 (100.00)
Meloxicam	
n	422

Table 12
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the AS Cohort)
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	N=27,381
Mean	12.53
Std. Dev.	4.12
Minimum	7.00
Median	15.00
Maximum	30.00
≤7.5mg [(n (%)]	100 (23.70)
>7.5-15mg [(n (%)]	191 (45.26)
>15mg* [(n (%)]	5 (1.18)
Missing [(n (%)]	126 (29.86)
Rofecoxib	
n	226
Mean	21.54
Std. Dev.	8.29
Minimum	12.00
Median	25.00
Maximum	50.00
≤12.5mg [(n (%)]	47 (20.80)
>12.5-25mg [(n (%)]	85 (37.61)
>25-50mg [(n (%)]	7 (3.10)
>50mg* [(n (%)]	0 (0.00)
Missing [(n (%)]	87 (38.50)
Valdecoxib	
n	18
Mean	20.00
Std. Dev.	6.32
Minimum	10.00
Median	20.00
Maximum	30.00
≤10mg [(n (%)]	1 (5.56)
>10-20mg [(n (%)]	4 (22.22)
>20mg* [(n (%)]	1 (5.56)
Missing [(n (%)]	12 (66.67)
Non-Selective NSAIDS	
Aceclofenac	
n	43
Mean	187.10
Std. Dev.	34.08
Minimum	100.00
Median	200.00

Table 12
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the AS Cohort)
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	N=27,381
Maximum	200.00
≤200mg [(n (%)]	31 (72.09)
>200mg* [(n (%)]	0 (0.00)
Missing [(n (%)]	12 (27.91)
Acemetacin	
n	16
Mean	152.00
Std. Dev.	38.40
Minimum	120.00
Median	120.00
Maximum	240.00
≤180mg [(n (%)]	14 (87.50)
>180mg* [(n (%)]	1 (6.25)
Missing [(n (%)]	1 (6.25)
Azapropazone	
n	7
Mean	900.00
Std. Dev.	346.41
Minimum	600.00
Median	900.00
Maximum	1200.00
≤1200mg [(n (%)]	4 (57.14)
>1200mg* [(n (%)]	0 (0.00)
Missing [(n (%)]	3 (42.86)
Dexketoprofen	
n	4
Mean	75.00
Std. Dev.	0.00
Minimum	75.00
Median	75.00
Maximum	75.00
≤50mg [(n (%)]	0 (0.00)
>50-75mg [(n (%)]	3 (75.00)
>75mg* [(n (%)]	0 (0.00)
Missing [(n (%)]	1 (25.00)
Diclofenac	
n	4043
Mean	131.52
Std. Dev.	32.43

Table 12
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the AS Cohort)
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	N=27,381
Minimum	1.35
Median	150.00
Maximum	450.00
≤50mg [(n (%)]	63 (1.56)
>50-75mg [(n (%)]	184 (4.55)
>75-100mg [(n (%)]	549 (13.58)
>100-150mg [(n (%)]	1,651 (40.84)
>150mg* [(n (%)]	53 (1.31)
Missing [(n (%)]	1,543 (38.16)
Etodolac	
n	88
Mean	598.80
Std. Dev.	110.98
Minimum	300.00
Median	600.00
Maximum	1200.00
≤300mg [(n (%)]	1 (1.14)
>300-600mg [(n (%)]	80 (90.91)
>600mg* [(n (%)]	2 (2.27)
Missing [(n (%)]	5 (5.68)
Fenbufen	
n	28
Mean	843.75
Std. Dev.	158.33
Minimum	300.00
Median	900.00
Maximum	900.00
≤900mg [(n (%)]	24 (85.71)
>900mg* [(n (%)]	0 (0.00)
Missing [(n (%)]	4 (14.29)
Fenoprofen	
n	2
Mean	2100.00
Std. Dev.	424.26
Minimum	1800.00
Median	2100.00
Maximum	2400.00
≤200mg [(n (%)]	0 (0.00)
>200-400mg [(n (%)]	0 (0.00)

Table 12
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the AS Cohort)
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	N=27,381
>400-600mg [(n (%)]	0 (0.00)
>600-800mg [(n (%)]	0 (0.00)
>800-1200mg [(n (%)]	0 (0.00)
>1200-1600mg [(n (%)]	0 (0.00)
>1600-2000mg [(n (%)]	1 (50.00)
>2000-2400mg [(n (%)]	1 (50.00)
>2400-3200mg [(n (%)]	0 (0.00)
>3200mg* [(n (%)]	0 (0.00)
Missing [(n (%)]	0 (0.00)
Flurbiprofen	
n	53
Mean	193.62
Std. Dev.	68.85
Minimum	50.00
Median	200.00
Maximum	450.00
≤50mg [(n (%)]	1 (1.89)
>50-100mg [(n (%)]	5 (9.43)
>100-150mg [(n (%)]	10 (18.87)
>150-200mg [(n (%)]	24 (45.28)
>200-250mg [(n (%)]	0 (0.00)
>250-300mg [(n (%)]	6 (11.32)
>300mg* [(n (%)]	1 (1.89)
Missing [(n (%)]	6 (11.32)
Ibuprofen	
n	2031
Mean	1272.07
Std. Dev.	382.02
Minimum	300.00
Median	1200.00
Maximum	2400.00
≤400mg [(n (%)]	12 (0.59)
>400-600mg [(n (%)]	68 (3.35)
>600-800mg [(n (%)]	87 (4.28)
>800-1200mg [(n (%)]	630 (31.02)
>1200-1600mg [(n (%)]	114 (5.61)
>1600-2000mg [(n (%)]	136 (6.70)
>2000mg* [(n (%)]	34 (1.67)
Missing [(n (%)]	950 (46.77)

Table 12
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the AS Cohort)
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	N=27,381
Indomethacin	
n	815
Mean	110.03
Std. Dev.	52.33
Minimum	25.00
Median	100.00
Maximum	800.00
≤25mg [(n (%)]	11 (1.35)
>25-50mg [(n (%)]	27 (3.31)
>50-75mg [(n (%)]	193 (23.68)
>150mg* [(n (%)]	19 (2.33)
>75-150mg [(n (%)]	268 (32.88)
Missing [(n (%)]	297 (36.44)
Ketoprofen	
n	103
Mean	187.50
Std. Dev.	73.05
Minimum	50.00
Median	200.00
Maximum	400.00
≤150mg [(n (%)]	23 (22.33)
>150-200mg [(n (%)]	61 (59.22)
>200mg* [(n (%)]	8 (7.77)
Missing [(n (%)]	11 (10.68)
Lornoxicam	
n	10
Mean	12.13
Std. Dev.	4.48
Minimum	8.00
Median	12.26
Maximum	16.00
≤12mg [(n (%)]	2 (20.00)
>12-16mg [(n (%)]	2 (20.00)
>16mg* [(n (%)]	0 (0.00)
Missing [(n (%)]	6 (60.00)
Mefenamic Acid	
n	32
Mean	1258.62
Std. Dev.	340.58

Table 12
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the AS Cohort)
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	N=27,381
Minimum	750.00
Median	1500.00
Maximum	2000.00
≤1000mg [(n (%)]	9 (28.13)
>1000-1500mg [(n (%)]	19 (59.38)
>1500mg* [(n (%)]	1 (3.13)
Missing [(n (%)]	3 (9.38)
Nabumetone	
n	77
Mean	1171.64
Std. Dev.	394.59
Minimum	1000.00
Median	1000.00
Maximum	3000.00
≤500mg [(n (%)]	0 (0.00)
>500-1000mg [(n (%)]	54 (70.13)
>1000mg* [(n (%)]	13 (16.88)
Missing [(n (%)]	10 (12.99)
Naproxen	
n	920
Mean	898.58
Std. Dev.	215.84
Minimum	125.00
Median	1000.00
Maximum	3000.00
≤250mg [(n (%)]	5 (0.54)
>250-500mg [(n (%)]	101 (10.98)
>500-1000mg [(n (%)]	625 (67.93)
>1000mg* [(n (%)]	11 (1.20)
Missing [(n (%)]	178 (19.35)
Phenylbutazone	
n	24
Mean	392.31
Std. Dev.	184.67
Minimum	200.00
Median	400.00
Maximum	900.00
≤300mg [(n (%)]	6 (25.00)
>300-400mg [(n (%)]	5 (20.83)

Table 12
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the AS Cohort)
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	N=27,381
>400mg* [(n (%)]	2 (8.33)
Missing [(n (%)]	11 (45.83)
Piroxicam	
n	365
Mean	20.85
Std. Dev.	6.27
Minimum	8.57
Median	20.00
Maximum	60.00
≤10mg [(n (%)]	14 (3.84)
>10-20mg [(n (%)]	187 (51.23)
>20-30mg [(n (%)]	10 (2.74)
>30mg* [(n (%)]	13 (3.56)
Missing [(n (%)]	141 (38.63)
Sulindac	
n	9
Mean	350.00
Std. Dev.	141.42
Minimum	200.00
Median	400.00
Maximum	600.00
≤300mg [(n (%)]	3 (33.33)
>300-400mg [(n (%)]	4 (44.44)
>400mg* [(n (%)]	1 (11.11)
Missing [(n (%)]	1 (11.11)
Tenoxicam	
n	15
Mean	20.00
Std. Dev.	0.00
Minimum	20.00
Median	20.00
Maximum	20.00
≤20mg [(n (%)]	12 (80.00)
>20mg* [(n (%)]	0 (0.00)
Missing [(n (%)]	3 (20.00)
Tiaprofenic Acid	
n	31
Mean	563.64
Std. Dev.	132.90

Table 12
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the AS Cohort)
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	N=27,381
Minimum	300.00
Median	600.00
Maximum	900.00
≤600mg [(n (%)]	21 (67.74)
>600mg* [(n (%)]	1 (3.23)
Missing [(n (%)]	9 (29.03)
Tolmetin	
n	1
Mean	.
Std. Dev.	.
Minimum	.
Median	.
Maximum	.
≤200mg [(n (%)]	0 (0.00)
>400-600mg [(n (%)]	0 (0.00)
>600-800mg [(n (%)]	0 (0.00)
>800-1200mg [(n (%)]	0 (0.00)
>1200-1600mg [(n (%)]	0 (0.00)
>1600-1800mg [(n (%)]	0 (0.00)
>1800mg* [(n (%)]	0 (0.00)
Missing [(n (%)]	1 (100.00)

* Indicates doses above the maximum recommended dose for AS, or for other indications if AS indication is not labeled

Similar analyses of the total daily dose (TDD) of baseline non-steroidal anti-inflammatory treatment (defined as the most recent drug prescribed during the 6 months prior to entry), according to first type of non-steroidal anti-inflammatory treatment (COX-2 selective agent, non-selective NSAID, multiple agents, or none) following entry in the AS cohort are shown in **Table 13**. Any recorded prescription for non-steroidal anti-inflammatory therapy regardless of frequency of occurrence during the 6 month baseline period prior to entry into the cohort is counted towards baseline non-steroidal anti-inflammatory use. For a given patient, this may not have been their first ever treatment with a non-steroidal anti-inflammatory agent. Patients with multiple non-steroidal anti-inflammatory drugs as the most recent prescription prior to entry into the cohort are not included.

Among patients whose first non-steroidal anti-inflammatory treatment following entry in the AS cohort was a COX-2 inhibitor (n=3,218), 470 have a baseline history of etoricoxib use; among these, the mean (SD) baseline TDD of etoricoxib was 86.9 mg (21.2 mg), the median baseline TDD was 90.0 mg, and the range was 30.0-180.0 mg. The proportion with baseline etoricoxib TDD >90 mg was 8.3%. Forty three patients whose first non-steroidal anti-inflammatory treatment following entry into the cohort was a NSAID had prior history of etoricoxib use, 1 patient whose first non-steroidal anti-inflammatory treatment following entry into the cohort was multiple NSAIDs had prior history of etoricoxib use, and 40 patients with no non-steroidal anti-inflammatory treatment following entry in the AS cohort had a baseline history of etoricoxib use (**Table 13**).

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 13a** for UK CPRD + THIN, **Table 13b** for UK IMS, **Table 13c** for Germany IMS, and **Table 13d** for France IMS).

Table 13
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Type of First Anti-Inflammatory Prescription for Treatment of AS
After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Type of First Anti-Inflammatory Prescription			
	COX-2 Inhibitor N=3,218	NSAID N=14,500	Multiple N=107	None N=9,556
COX-2 Selective Inhibitors				
Celecoxib				
n	383	27	1	27
Mean	258.35	222.22	200.00	260.00
Std. Dev.	96.05	64.68	.	96.61
Minimum	28.58	200.00	200.00	200.00
Median	200.00	200.00	200.00	200.00
Maximum	400.00	400.00	200.00	400.00
≤100mg [(n (%)]	5 (1.31)	0 (0.00)	0 (0.00)	0 (0.00)
>100-200mg [(n (%)]	131 (34.20)	16 (59.26)	1 (100.00)	7 (25.93)
>200-400mg [(n (%)]	65 (16.97)	2 (7.41)	0 (0.00)	3 (11.11)
>400mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	182 (47.52)	9 (33.33)	0 (0.00)	17 (62.96)
Etoricoxib				
n	470	43	1	40
Mean	86.89	85.00	90.00	91.88
Std. Dev.	21.24	21.06	.	17.21
Minimum	30.00	60.00	90.00	60.00
Median	90.00	90.00	90.00	90.00
Maximum	180.00	120.00	90.00	120.00
≤30mg [(n (%)]	7 (1.49)	0 (0.00)	0 (0.00)	0 (0.00)
>30-60mg [(n (%)]	53 (11.28)	8 (18.60)	0 (0.00)	2 (5.00)
>60-90mg [(n (%)]	152 (32.34)	12 (27.91)	1 (100.00)	11 (27.50)
>90-120mg [(n (%)]	38 (8.09)	4 (9.30)	0 (0.00)	3 (7.50)
>120mg* [(n (%)]	1 (0.21)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	219 (46.60)	19 (44.19)	0 (0.00)	24 (60.00)
Lumiracoxib				
n	2	0	0	1
Mean	.	.	.	.
Std. Dev.	.	.	.	.
Minimum	.	.	.	.
Median	.	.	.	.

Table 13
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Type of First Anti-Inflammatory Prescription for Treatment of AS
After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Type of First Anti-Inflammatory Prescription			
	COX-2 Inhibitor N=3,218	NSAID N=14,500	Multiple N=107	None N=9,556
Maximum	.	.	.	.
≤100mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>100-200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>200mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	2 (100.00)	0 (0.00)	0 (0.00)	1 (100.00)
Meloxicam				
n	372	28	0	22
Mean	12.46	12.35	.	14.38
Std. Dev.	4.05	3.71	.	5.95
Minimum	7.00	7.00	.	7.50
Median	15.00	15.00	.	15.00
Maximum	30.00	15.00	.	30.00
≤7.5mg [(n (%)]	90 (24.19)	7 (25.00)	0 (0.00)	3 (13.64)
>7.5-15mg [(n (%)]	170 (45.70)	13 (46.43)	0 (0.00)	8 (36.36)
>15mg* [(n (%)]	4 (1.08)	0 (0.00)	0 (0.00)	1 (4.55)
Missing [(n (%)]	108 (29.03)	8 (28.57)	0 (0.00)	10 (45.45)
Rofecoxib				
n	187	29	0	10
Mean	21.62	22.71	.	16.67
Std. Dev.	8.06	10.13	.	6.45
Minimum	12.00	12.00	.	12.50
Median	25.00	25.00	.	12.50
Maximum	50.00	50.00	.	25.00
≤12.5mg [(n (%)]	37 (19.79)	6 (20.69)	0 (0.00)	4 (40.00)
>12.5-25mg [(n (%)]	74 (39.57)	9 (31.03)	0 (0.00)	2 (20.00)
>25-50mg [(n (%)]	5 (2.67)	2 (6.90)	0 (0.00)	0 (0.00)
>50mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	71 (37.97)	12 (41.38)	0 (0.00)	4 (40.00)
Valdecoxib				
n	15	2	0	1
Mean	16.67	25.00	.	20.00
Std. Dev.	5.77	7.07	.	.

Table 13
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Type of First Anti-Inflammatory Prescription for Treatment of AS
After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Type of First Anti-Inflammatory Prescription			
	COX-2 Inhibitor N=3,218	NSAID N=14,500	Multiple N=107	None N=9,556
Minimum	10.00	20.00	.	20.00
Median	20.00	25.00	.	20.00
Maximum	20.00	30.00	.	20.00
≤10mg [(n (%)]	1 (6.67)	0 (0.00)	0 (0.00)	0 (0.00)
>10-20mg [(n (%)]	2 (13.33)	1 (50.00)	0 (0.00)	1 (100.00)
>20mg* [(n (%)]	0 (0.00)	1 (50.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	12 (80.00)	0 (0.00)	0 (0.00)	0 (0.00)
Non-Selective NSAIDS				
Aceclofenac				
n	1	38	0	4
Mean	200.00	184.62	.	200.00
Std. Dev.	.	36.79	.	0.00
Minimum	200.00	100.00	.	200.00
Median	200.00	200.00	.	200.00
Maximum	200.00	200.00	.	200.00
≤200mg [(n (%)]	1 (100.00)	26 (68.42)	0 (0.00)	4 (100.00)
>200mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	12 (31.58)	0 (0.00)	0 (0.00)
Acemetacin				
n	0	16	0	0
Mean	.	152.00	.	.
Std. Dev.	.	38.40	.	.
Minimum	.	120.00	.	.
Median	.	120.00	.	.
Maximum	.	240.00	.	.
≤180mg [(n (%)]	0 (0.00)	14 (87.50)	0 (0.00)	0 (0.00)
>180mg* [(n (%)]	0 (0.00)	1 (6.25)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	1 (6.25)	0 (0.00)	0 (0.00)
Azapropazone				
n	0	7	0	0
Mean	.	900.00	.	.
Std. Dev.	.	346.41	.	.

Table 13
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Type of First Anti-Inflammatory Prescription for Treatment of AS
After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Type of First Anti-Inflammatory Prescription			
	COX-2 Inhibitor N=3,218	NSAID N=14,500	Multiple N=107	None N=9,556
Minimum	.	600.00	.	.
Median	.	900.00	.	.
Maximum	.	1200.00	.	.
≤1200mg [(n (%)]	0 (0.00)	4 (57.14)	0 (0.00)	0 (0.00)
>1200mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	3 (42.86)	0 (0.00)	0 (0.00)
Dexketoprofen				
n	0	3	0	1
Mean	.	75.00	.	75.00
Std. Dev.	.	0.00	.	.
Minimum	.	75.00	.	75.00
Median	.	75.00	.	75.00
Maximum	.	75.00	.	75.00
≤50mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>50-75mg [(n (%)]	0 (0.00)	2 (66.67)	0 (0.00)	1 (100.00)
>75mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	1 (33.33)	0 (0.00)	0 (0.00)
Diclofenac				
n	129	3594	2	318
Mean	134.94	131.12	150.00	135.15
Std. Dev.	29.92	32.66	.	30.32
Minimum	50.00	25.00	150.00	1.35
Median	150.00	150.00	150.00	150.00
Maximum	200.00	450.00	150.00	225.00
≤50mg [(n (%)]	2 (1.55)	59 (1.64)	0 (0.00)	2 (0.63)
>50-75mg [(n (%)]	6 (4.65)	169 (4.70)	0 (0.00)	9 (2.83)
>75-100mg [(n (%)]	14 (10.85)	501 (13.94)	0 (0.00)	34 (10.69)
>100-150mg [(n (%)]	64 (49.61)	1,472 (40.96)	1 (50.00)	114 (35.85)
>150mg* [(n (%)]	2 (1.55)	46 (1.28)	0 (0.00)	5 (1.57)
Missing [(n (%)]	41 (31.78)	1,347 (37.48)	1 (50.00)	154 (48.43)
Etodolac				
n	2	76	0	10

Table 13
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Type of First Anti-Inflammatory Prescription for Treatment of AS
After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Type of First Anti-Inflammatory Prescription			
	COX-2 Inhibitor N=3,218	NSAID N=14,500	Multiple N=107	None N=9,556
Mean	600.00	605.56	.	544.44
Std. Dev.	0.00	111.19	.	113.04
Minimum	600.00	400.00	.	300.00
Median	600.00	600.00	.	600.00
Maximum	600.00	1200.00	.	600.00
≤300mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	1 (10.00)
>300-600mg [(n (%)]	2 (100.00)	70 (92.11)	0 (0.00)	8 (80.00)
>600mg* [(n (%)]	0 (0.00)	2 (2.63)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	4 (5.26)	0 (0.00)	1 (10.00)
Fenbufen				
n	0	27	0	1
Mean	.	841.30	.	900.00
Std. Dev.	.	161.42	.	.
Minimum	.	300.00	.	900.00
Median	.	900.00	.	900.00
Maximum	.	900.00	.	900.00
≤900mg [(n (%)]	0 (0.00)	23 (85.19)	0 (0.00)	1 (100.00)
>900mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	4 (14.81)	0 (0.00)	0 (0.00)
Fenoprofen				
n	0	2	0	0
Mean	.	2100.00	.	.
Std. Dev.	.	424.26	.	.
Minimum	.	1800.00	.	.
Median	.	2100.00	.	.
Maximum	.	2400.00	.	.
≤200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>200-400mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>400-600mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>600-800mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>800-1200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>1200-1600mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Table 13
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Type of First Anti-Inflammatory Prescription for Treatment of AS
After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Type of First Anti-Inflammatory Prescription			
	COX-2 Inhibitor N=3,218	NSAID N=14,500	Multiple N=107	None N=9,556
>1600-2000mg [(n (%)]	0 (0.00)	1 (50.00)	0 (0.00)	0 (0.00)
>2000-2400mg [(n (%)]	0 (0.00)	1 (50.00)	0 (0.00)	0 (0.00)
>2400-3200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>3200mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Flurbiprofen				
n	0	51	0	2
Mean	.	193.48	.	200.00
Std. Dev.	.	69.61	.	.
Minimum	.	50.00	.	200.00
Median	.	200.00	.	200.00
Maximum	.	450.00	.	200.00
≤50mg [(n (%)]	0 (0.00)	1 (1.96)	0 (0.00)	0 (0.00)
>50-100mg [(n (%)]	0 (0.00)	5 (9.80)	0 (0.00)	0 (0.00)
>100-150mg [(n (%)]	0 (0.00)	10 (19.61)	0 (0.00)	0 (0.00)
>150-200mg [(n (%)]	0 (0.00)	23 (45.10)	0 (0.00)	1 (50.00)
>200-250mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>250-300mg [(n (%)]	0 (0.00)	6 (11.76)	0 (0.00)	0 (0.00)
>300mg* [(n (%)]	0 (0.00)	1 (1.96)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	5 (9.80)	0 (0.00)	1 (50.00)
Ibuprofen				
n	57	1740	4	230
Mean	1362.86	1273.68	1000.00	1229.21
Std. Dev.	381.24	378.43	282.84	414.51
Minimum	400.00	300.00	800.00	400.00
Median	1200.00	1200.00	1000.00	1200.00
Maximum	2400.00	2400.00	1200.00	2400.00
≤400mg [(n (%)]	1 (1.75)	9 (0.52)	0 (0.00)	2 (0.87)
>400-600mg [(n (%)]	0 (0.00)	59 (3.39)	0 (0.00)	9 (3.91)
>600-800mg [(n (%)]	1 (1.75)	75 (4.31)	1 (25.00)	10 (4.35)
>800-1200mg [(n (%)]	21 (36.84)	556 (31.95)	1 (25.00)	52 (22.61)
>1200-1600mg [(n (%)]	4 (7.02)	102 (5.86)	0 (0.00)	8 (3.48)

Table 13
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Type of First Anti-Inflammatory Prescription for Treatment of AS
After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Type of First Anti-Inflammatory Prescription			
	COX-2 Inhibitor N=3,218	NSAID N=14,500	Multiple N=107	None N=9,556
>1600-2000mg [(n (%)]	6 (10.53)	117 (6.72)	0 (0.00)	13 (5.65)
>2000mg* [(n (%)]	2 (3.51)	29 (1.67)	0 (0.00)	3 (1.30)
Missing [(n (%)]	22 (38.60)	793 (45.57)	2 (50.00)	133 (57.83)
Indomethacin				
n	4	778	0	33
Mean	93.75	109.60	.	123.21
Std. Dev.	37.50	52.86	.	39.98
Minimum	75.00	25.00	.	50.00
Median	75.00	100.00	.	150.00
Maximum	150.00	800.00	.	200.00
≤25mg [(n (%)]	0 (0.00)	11 (1.41)	0 (0.00)	0 (0.00)
>25-50mg [(n (%)]	0 (0.00)	26 (3.34)	0 (0.00)	1 (3.03)
>50-75mg [(n (%)]	3 (75.00)	185 (23.78)	0 (0.00)	5 (15.15)
>150mg* [(n (%)]	0 (0.00)	18 (2.31)	0 (0.00)	1 (3.03)
>75-150mg [(n (%)]	1 (25.00)	253 (32.52)	0 (0.00)	14 (42.42)
Missing [(n (%)]	0 (0.00)	285 (36.63)	0 (0.00)	12 (36.36)
Ketoprofen				
n	3	97	0	3
Mean	200.00	186.08	.	237.50
Std. Dev.	0.00	70.08	.	229.81
Minimum	200.00	50.00	.	75.00
Median	200.00	200.00	.	237.50
Maximum	200.00	400.00	.	400.00
≤150mg [(n (%)]	0 (0.00)	22 (22.68)	0 (0.00)	1 (33.33)
>150-200mg [(n (%)]	2 (66.67)	59 (60.82)	0 (0.00)	0 (0.00)
>200mg* [(n (%)]	0 (0.00)	7 (7.22)	0 (0.00)	1 (33.33)
Missing [(n (%)]	1 (33.33)	9 (9.28)	0 (0.00)	1 (33.33)
Lornoxicam				
n	0	9	0	1
Mean	.	10.84	.	16.00
Std. Dev.	.	4.48	.	.
Minimum	.	8.00	.	16.00

Table 13
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Type of First Anti-Inflammatory Prescription for Treatment of AS
After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Type of First Anti-Inflammatory Prescription			
	COX-2 Inhibitor N=3,218	NSAID N=14,500	Multiple N=107	None N=9,556
Median	.	8.51	.	16.00
Maximum	.	16.00	.	16.00
≤12mg [(n (%)]	0 (0.00)	2 (22.22)	0 (0.00)	0 (0.00)
>12-16mg [(n (%)]	0 (0.00)	1 (11.11)	0 (0.00)	1 (100.00)
>16mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	6 (66.67)	0 (0.00)	0 (0.00)
Mefenamic Acid				
n	0	29	0	3
Mean	.	1254.63	.	1312.50
Std. Dev.	.	349.25	.	265.17
Minimum	.	750.00	.	1125.00
Median	.	1500.00	.	1312.50
Maximum	.	2000.00	.	1500.00
≤1000mg [(n (%)]	0 (0.00)	9 (31.03)	0 (0.00)	0 (0.00)
>1000-1500mg [(n (%)]	0 (0.00)	17 (58.62)	0 (0.00)	2 (66.67)
>1500mg* [(n (%)]	0 (0.00)	1 (3.45)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	2 (6.90)	0 (0.00)	1 (33.33)
Nabumetone				
n	1	71	0	5
Mean	1000.00	1158.73	.	1500.00
Std. Dev.	.	389.64	.	500.00
Minimum	1000.00	1000.00	.	1000.00
Median	1000.00	1000.00	.	1500.00
Maximum	1000.00	3000.00	.	2000.00
≤500mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>500-1000mg [(n (%)]	1 (100.00)	52 (73.24)	0 (0.00)	1 (20.00)
>1000mg* [(n (%)]	0 (0.00)	11 (15.49)	0 (0.00)	2 (40.00)
Missing [(n (%)]	0 (0.00)	8 (11.27)	0 (0.00)	2 (40.00)
Naproxen				
n	31	816	2	71
Mean	843.75	903.26	625.00	877.19
Std. Dev.	206.06	217.87	176.78	189.71

Table 13
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Type of First Anti-Inflammatory Prescription for Treatment of AS
After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Type of First Anti-Inflammatory Prescription			
	COX-2 Inhibitor N=3,218	NSAID N=14,500	Multiple N=107	None N=9,556
Minimum	500.00	125.00	500.00	500.00
Median	1000.00	1000.00	625.00	1000.00
Maximum	1000.00	3000.00	750.00	1000.00
≤250mg [(n (%)]	0 (0.00)	5 (0.61)	0 (0.00)	0 (0.00)
>250-500mg [(n (%)]	5 (16.13)	86 (10.54)	1 (50.00)	9 (12.68)
>500-1000mg [(n (%)]	19 (61.29)	557 (68.26)	1 (50.00)	48 (67.61)
>1000mg* [(n (%)]	0 (0.00)	11 (1.35)	0 (0.00)	0 (0.00)
Missing [(n (%)]	7 (22.58)	157 (19.24)	0 (0.00)	14 (19.72)
Phenylbutazone				
n	1	22	0	1
Mean	.	408.33	.	200.00
Std. Dev.	.	183.20	.	.
Minimum	.	200.00	.	200.00
Median	.	400.00	.	200.00
Maximum	.	900.00	.	200.00
≤300mg [(n (%)]	0 (0.00)	5 (22.73)	0 (0.00)	1 (100.00)
>300-400mg [(n (%)]	0 (0.00)	5 (22.73)	0 (0.00)	0 (0.00)
>400mg* [(n (%)]	0 (0.00)	2 (9.09)	0 (0.00)	0 (0.00)
Missing [(n (%)]	1 (100.00)	10 (45.45)	0 (0.00)	0 (0.00)
Piroxicam				
n	11	325	1	28
Mean	18.75	20.86	.	21.76
Std. Dev.	3.54	5.90	.	10.92
Minimum	10.00	8.57	.	10.00
Median	20.00	20.00	.	20.00
Maximum	20.00	40.00	.	60.00
≤10mg [(n (%)]	1 (9.09)	12 (3.69)	0 (0.00)	1 (3.57)
>10-20mg [(n (%)]	7 (63.64)	168 (51.69)	0 (0.00)	12 (42.86)
>20-30mg [(n (%)]	0 (0.00)	9 (2.77)	0 (0.00)	1 (3.57)
>30mg* [(n (%)]	0 (0.00)	12 (3.69)	0 (0.00)	1 (3.57)
Missing [(n (%)]	3 (27.27)	124 (38.15)	1 (100.00)	13 (46.43)
Sulindac				

Table 13
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Type of First Anti-Inflammatory Prescription for Treatment of AS
After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Type of First Anti-Inflammatory Prescription			
	COX-2 Inhibitor N=3,218	NSAID N=14,500	Multiple N=107	None N=9,556
n	0	9	0	0
Mean	.	350.00	.	.
Std. Dev.	.	141.42	.	.
Minimum	.	200.00	.	.
Median	.	400.00	.	.
Maximum	.	600.00	.	.
≤300mg [(n (%)]	0 (0.00)	3 (33.33)	0 (0.00)	0 (0.00)
>300-400mg [(n (%)]	0 (0.00)	4 (44.44)	0 (0.00)	0 (0.00)
>400mg* [(n (%)]	0 (0.00)	1 (11.11)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	1 (11.11)	0 (0.00)	0 (0.00)
Tenoxicam				
n	0	15	0	0
Mean	.	20.00	.	.
Std. Dev.	.	0.00	.	.
Minimum	.	20.00	.	.
Median	.	20.00	.	.
Maximum	.	20.00	.	.
≤20mg [(n (%)]	0 (0.00)	12 (80.00)	0 (0.00)	0 (0.00)
>20mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	3 (20.00)	0 (0.00)	0 (0.00)
Tiaprofenic Acid				
n	2	27	0	2
Mean	600.00	560.00	.	600.00
Std. Dev.	.	139.17	.	.
Minimum	600.00	300.00	.	600.00
Median	600.00	600.00	.	600.00
Maximum	600.00	900.00	.	600.00
≤600mg [(n (%)]	1 (50.00)	19 (70.37)	0 (0.00)	1 (50.00)
>600mg* [(n (%)]	0 (0.00)	1 (3.70)	0 (0.00)	0 (0.00)
Missing [(n (%)]	1 (50.00)	7 (25.93)	0 (0.00)	1 (50.00)
Tolmetin				
n	0	1	0	0

Table 13
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Type of First Anti-Inflammatory Prescription for Treatment of AS
After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Type of First Anti-Inflammatory Prescription			
	COX-2 Inhibitor N=3,218	NSAID N=14,500	Multiple N=107	None N=9,556
Mean	.	.	.	.
Std. Dev.	.	.	.	.
Minimum	.	.	.	.
Median	.	.	.	.
Maximum	.	.	.	.
≤200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>400-600mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>600-800mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>800-1200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>1200-1600mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>1600-1800mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>1800mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)

* Indicates doses above the maximum recommended dose for AS, or for other indications if AS indication is not labeled

Analyses of the total daily dose (TDD) of baseline non-steroidal anti-inflammatory treatment (defined as the most recent drug prescribed in the 6 months prior to entry), according to specific first type of non-steroidal anti-inflammatory treatment following entry in the AS cohort are shown in **Table 14**. Any recorded prescription for non-steroidal anti-inflammatory therapy regardless of frequency of occurrence during the 6 month baseline period prior to entry into the cohort is counted towards baseline non-steroidal anti-inflammatory use. For a given patient this may not have been their first ever treatment with a non-steroidal anti-inflammatory agent. Patients with multiple non-steroidal anti-inflammatory drugs as the most recent prescription prior to entry into the cohort are not included.

Among patients whose first non-steroidal anti-inflammatory treatment following entry in the AS cohort was etoricoxib (n=1,080), the numbers of patients with baseline histories of specific non-steroidal anti-inflammatory treatments were: 3 celecoxib, 459 etoricoxib, 8 meloxicam, 2 rofecoxib, 1 valdecoxib, 48 diclofenac, 33 ibuprofen, 2 indomethacin, 14 naproxen, and 3 piroxicam. Among the 459 patients with both baseline etoricoxib use and a first non-steroidal anti-inflammatory prescription following entry into the cohort for etoricoxib, the mean (SD) baseline TDD of etoricoxib was 87.1 mg (21.1 mg), the median baseline TDD was 90.0 mg, and the range was 30.0-180.0 mg (**Table 14**). About 8.3% had a TDD of >90 mg. Note that 215 of these 459 patients did not have dose information.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 14a** for UK CPRD + THIN, **Table 14b** for UK IMS, **Table 14c** for Germany IMS, and **Table 14d** for France IMS).

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
COX-2 Selective Inhibitors							
Celecoxib							
n	3	374	0	1	4	1	2
Mean	200.00	259.12	.	200.00	250.00	.	300.00
Std. Dev.	.	96.53	.	.	100.00	.	141.42
Minimum	200.00	28.58	.	200.00	200.00	.	200.00
Median	200.00	200.00	.	200.00	200.00	.	300.00
Maximum	200.00	400.00	.	200.00	400.00	.	400.00
≤100mg [(n (%)]	0 (0.00)	5 (1.34)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>100-200mg [(n (%)]	1 (33.33)	126 (33.69)	0 (0.00)	1 (100.00)	3 (75.00)	0 (0.00)	1 (50.00)
>200-400mg [(n (%)]	0 (0.00)	64 (17.11)	0 (0.00)	0 (0.00)	1 (25.00)	0 (0.00)	1 (50.00)
>400mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	2 (66.67)	179 (47.86)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)
Etoricoxib							
n	459	8	0	2	1	0	1
Mean	87.05	72.00	.	90.00	120.00	.	90.00
Std. Dev.	21.05	26.83	.	.	.	.	.
Minimum	30.00	30.00	.	90.00	120.00	.	90.00
Median	90.00	90.00	.	90.00	120.00	.	90.00
Maximum	180.00	90.00	.	90.00	120.00	.	90.00

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
≤30mg [(n (%)]	6 (1.31)	1 (12.50)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>30-60mg [(n (%)]	52 (11.33)	1 (12.50)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>60-90mg [(n (%)]	148 (32.24)	3 (37.50)	0 (0.00)	1 (50.00)	0 (0.00)	0 (0.00)	1 (100.00)
>90-120mg [(n (%)]	37 (8.06)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)
>120mg* [(n (%)]	1 (0.22)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	215 (46.84)	3 (37.50)	0 (0.00)	1 (50.00)	0 (0.00)	0 (0.00)	0 (0.00)
Lumiracoxib							
n	0	0	2	0	0	0	0
Mean	.	.	.	.	.	.	.
Std. Dev.	.	.	.	.	.	.	.
Minimum	.	.	.	.	.	.	.
Median	.	.	.	.	.	.	.
Maximum	.	.	.	.	.	.	.
≤100mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>100-200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>200mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	2 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Meloxicam							
n	8	2	0	355	7	0	2
Mean	12.50	15.00	.	12.48	11.25	.	15.00

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
Std. Dev.	3.87	.	.	4.07	4.11	.	.
Minimum	7.50	15.00	.	7.00	7.50	.	15.00
Median	15.00	15.00	.	15.00	11.25	.	15.00
Maximum	15.00	15.00	.	30.00	15.00	.	15.00
≤7.5mg [(n (%)]	2 (25.00)	0 (0.00)	0 (0.00)	85 (23.94)	3 (42.86)	0 (0.00)	0 (0.00)
>7.5-15mg [(n (%)]	4 (50.00)	1 (50.00)	0 (0.00)	162 (45.63)	3 (42.86)	0 (0.00)	1 (50.00)
>15mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	4 (1.13)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	2 (25.00)	1 (50.00)	0 (0.00)	104 (29.30)	1 (14.29)	0 (0.00)	1 (50.00)
Rofecoxib							
n	2	6	0	1	177	1	2
Mean	.	21.88	.	12.00	21.70	.	37.50
Std. Dev.	.	6.25	.	.	8.12	.	.
Minimum	.	12.50	.	12.00	12.00	.	37.50
Median	.	25.00	.	12.00	25.00	.	37.50
Maximum	.	25.00	.	12.00	50.00	.	37.50
≤12.5mg [(n (%)]	0 (0.00)	1 (16.67)	0 (0.00)	1 (100.00)	35 (19.77)	0 (0.00)	0 (0.00)
>12.5-25mg [(n (%)]	0 (0.00)	3 (50.00)	0 (0.00)	0 (0.00)	71 (40.11)	0 (0.00)	0 (0.00)
>25-50mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	5 (2.82)	0 (0.00)	1 (50.00)
>50mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	2 (100.00)	2 (33.33)	0 (0.00)	0 (0.00)	66 (37.29)	1 (100.00)	1 (50.00)

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
Valdecoxib							
n	1	1	0	1	0	12	0
Mean	.	.	.	.	.	16.67	.
Std. Dev.	.	.	.	.	.	5.77	.
Minimum	.	.	.	.	.	10.00	.
Median	.	.	.	.	.	20.00	.
Maximum	.	.	.	.	.	20.00	.
≤10mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (8.33)	0 (0.00)
>10-20mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (16.67)	0 (0.00)
>20mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	1 (100.00)	1 (100.00)	0 (0.00)	1 (100.00)	0 (0.00)	9 (75.00)	0 (0.00)
Non-Selective NSAIDS							
Aceclofenac							
n	0	0	0	1	0	0	0
Mean	.	.	.	200.00	.	.	.
Std. Dev.	.	.	.	.	.	.	.
Minimum	.	.	.	200.00	.	.	.
Median	.	.	.	200.00	.	.	.
Maximum	.	.	.	200.00	.	.	.
≤200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
>200mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Acemetacin							
n	0	0	0	0	0	0	0
Mean	.	.	.	.	.	.	.
Std. Dev.	.	.	.	.	.	.	.
Minimum	.	.	.	.	.	.	.
Median	.	.	.	.	.	.	.
Maximum	.	.	.	.	.	.	.
≤180mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>180mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Azapropazone							
n	0	0	0	0	0	0	0
Mean	.	.	.	.	.	.	.
Std. Dev.	.	.	.	.	.	.	.
Minimum	.	.	.	.	.	.	.
Median	.	.	.	.	.	.	.
Maximum	.	.	.	.	.	.	.
≤1200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
>1200mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Dexketoprofen							
n	0	0	0	0	0	0	0
Mean	.	.	.	.	.	.	.
Std. Dev.	.	.	.	.	.	.	.
Minimum	.	.	.	.	.	.	.
Median	.	.	.	.	.	.	.
Maximum	.	.	.	.	.	.	.
≤50mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>50-75mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>75mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Diclofenac							
n	48	29	0	31	20	1	13
Mean	136.57	133.33	.	142.86	122.50	150.00	137.50
Std. Dev.	27.50	31.85	.	23.90	37.26	.	29.19
Minimum	50.00	50.00	.	100.00	62.50	150.00	75.00
Median	150.00	150.00	.	150.00	100.00	150.00	150.00
Maximum	150.00	150.00	.	200.00	200.00	150.00	150.00

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
≤50mg [(n (%)]	1 (2.08)	1 (3.45)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>50-75mg [(n (%)]	1 (2.08)	3 (10.34)	0 (0.00)	0 (0.00)	2 (10.00)	0 (0.00)	2 (15.38)
>75-100mg [(n (%)]	3 (6.25)	1 (3.45)	0 (0.00)	4 (12.90)	6 (30.00)	0 (0.00)	0 (0.00)
>100-150mg [(n (%)]	22 (45.83)	19 (65.52)	0 (0.00)	16 (51.61)	6 (30.00)	1 (100.00)	10 (76.92)
>150mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	1 (3.23)	1 (5.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	21 (43.75)	5 (17.24)	0 (0.00)	10 (32.26)	5 (25.00)	0 (0.00)	1 (7.69)
Etodolac							
n	1	1	0	0	0	0	71
Mean	600.00	600.00	.	.	.	.	600.00
Std. Dev.	.	.	.	.	.	.	84.64
Minimum	600.00	600.00	.	.	.	.	400.00
Median	600.00	600.00	.	.	.	.	600.00
Maximum	600.00	600.00	.	.	.	.	1200.00
≤300mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>300-600mg [(n (%)]	1 (100.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	67 (94.37)
>600mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.41)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	3 (4.23)
Fenbufen							
n	0	0	0	0	0	0	0
Mean	.	.	.	.	.	.	.

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
Std. Dev.	.	.	.	.	.	.	.
Minimum	.	.	.	.	.	.	.
Median	.	.	.	.	.	.	.
Maximum	.	.	.	.	.	.	.
≤900mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>900mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Fenoprofen							
n	0	0	0	0	0	0	0
Mean	.	.	.	.	.	.	.
Std. Dev.	.	.	.	.	.	.	.
Minimum	.	.	.	.	.	.	.
Median	.	.	.	.	.	.	.
Maximum	.	.	.	.	.	.	.
≤200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>200-400mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>400-600mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>600-800mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>800-1200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>1200-1600mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
>1600-2000mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>2000-2400mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>2400-3200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>3200mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Flurbiprofen							
n	0	0	0	0	0	0	0
Mean	.	.	.	.	.	.	.
Std. Dev.	.	.	.	.	.	.	.
Minimum	.	.	.	.	.	.	.
Median	.	.	.	.	.	.	.
Maximum	.	.	.	.	.	.	.
≤50mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>50-100mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>100-150mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>150-200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>200-250mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>250-300mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>300mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
Ibuprofen							
n	33	11	0	7	6	0	3
Mean	1347.06	1222.22	.	1350.00	1680.00	.	1200.00
Std. Dev.	337.49	380.06	.	300.00	502.00	.	0.00
Minimum	800.00	400.00	.	1200.00	1200.00	.	1200.00
Median	1200.00	1200.00	.	1200.00	1800.00	.	1200.00
Maximum	2100.00	1800.00	.	1800.00	2400.00	.	1200.00
≤400mg [(n (%)]	0 (0.00)	1 (9.09)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>400-600mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>600-800mg [(n (%)]	1 (3.03)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>800-1200mg [(n (%)]	10 (30.30)	6 (54.55)	0 (0.00)	3 (42.86)	2 (33.33)	0 (0.00)	2 (66.67)
>1200-1600mg [(n (%)]	3 (9.09)	1 (9.09)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>1600-2000mg [(n (%)]	2 (6.06)	1 (9.09)	0 (0.00)	1 (14.29)	2 (33.33)	0 (0.00)	0 (0.00)
>2000mg* [(n (%)]	1 (3.03)	0 (0.00)	0 (0.00)	0 (0.00)	1 (16.67)	0 (0.00)	0 (0.00)
Missing [(n (%)]	16 (48.48)	2 (18.18)	0 (0.00)	3 (42.86)	1 (16.67)	0 (0.00)	1 (33.33)
Indomethacin							
n	2	0	0	2	0	0	0
Mean	75.00	.	.	112.50	.	.	.
Std. Dev.	0.00	.	.	53.03	.	.	.
Minimum	75.00	.	.	75.00	.	.	.

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
Median	75.00	.	.	112.50	.	.	.
Maximum	75.00	.	.	150.00	.	.	.
≤25mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>25-50mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>50-75mg [(n (%)]	2 (100.00)	0 (0.00)	0 (0.00)	1 (50.00)	0 (0.00)	0 (0.00)	0 (0.00)
>150mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>75-150mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	1 (50.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Ketoprofen							
n	0	0	0	2	1	0	0
Mean	.	.	.	200.00	200.00	.	.
Std. Dev.	.	.	.	.	.	.	.
Minimum	.	.	.	200.00	200.00	.	.
Median	.	.	.	200.00	200.00	.	.
Maximum	.	.	.	200.00	200.00	.	.
≤150mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>150-200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	1 (50.00)	1 (100.00)	0 (0.00)	0 (0.00)
>200mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	1 (50.00)	0 (0.00)	0 (0.00)	0 (0.00)
Lornoxicam							

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
n	0	0	0	0	0	0	0
Mean	.	.	.	.	.	.	.
Std. Dev.	.	.	.	.	.	.	.
Minimum	.	.	.	.	.	.	.
Median	.	.	.	.	.	.	.
Maximum	.	.	.	.	.	.	.
≤12mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>12-16mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>16mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Mefenamic Acid							
n	0	0	0	0	0	0	0
Mean	.	.	.	.	.	.	.
Std. Dev.	.	.	.	.	.	.	.
Minimum	.	.	.	.	.	.	.
Median	.	.	.	.	.	.	.
Maximum	.	.	.	.	.	.	.
≤1000mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>1000-1500mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>1500mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Nabumetone							
n	0	0	0	1	0	0	0
Mean	.	.	.	1000.00	.	.	.
Std. Dev.	.	.	.	.	.	.	.
Minimum	.	.	.	1000.00	.	.	.
Median	.	.	.	1000.00	.	.	.
Maximum	.	.	.	1000.00	.	.	.
≤500mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>500-1000mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
>1000mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Naproxen							
n	14	7	0	8	2	0	3
Mean	850.00	750.00	.	900.00	1000.00	.	916.67
Std. Dev.	210.82	250.00	.	136.93	0.00	.	144.34
Minimum	500.00	500.00	.	750.00	1000.00	.	750.00
Median	1000.00	750.00	.	1000.00	1000.00	.	1000.00
Maximum	1000.00	1000.00	.	1000.00	1000.00	.	1000.00
≤250mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
>250-500mg [(n (%)]	2 (14.29)	3 (42.86)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>500-1000mg [(n (%)]	8 (57.14)	4 (57.14)	0 (0.00)	5 (62.50)	2 (100.00)	0 (0.00)	3 (100.00)
>1000mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	4 (28.57)	0 (0.00)	0 (0.00)	3 (37.50)	0 (0.00)	0 (0.00)	0 (0.00)
Phenylbutazone							
n	0	0	1	0	0	0	0
Mean	.	.	.	.	.	.	.
Std. Dev.	.	.	.	.	.	.	.
Minimum	.	.	.	.	.	.	.
Median	.	.	.	.	.	.	.
Maximum	.	.	.	.	.	.	.
≤300mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>300-400mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>400mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Piroxicam							
n	3	2	0	4	1	1	0
Mean	15.00	20.00	.	20.00	20.00	20.00	.
Std. Dev.	7.07	0.00	.	0.00	.	.	.
Minimum	10.00	20.00	.	20.00	20.00	20.00	.

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
Median	15.00	20.00	.	20.00	20.00	20.00	.
Maximum	20.00	20.00	.	20.00	20.00	20.00	.
≤10mg [(n (%)]	1 (33.33)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>10-20mg [(n (%)]	1 (33.33)	2 (100.00)	0 (0.00)	2 (50.00)	1 (100.00)	1 (100.00)	0 (0.00)
>20-30mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>30mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	1 (33.33)	0 (0.00)	0 (0.00)	2 (50.00)	0 (0.00)	0 (0.00)	0 (0.00)
Sulindac							
n	0	0	0	0	0	0	0
Mean	.	.	.	.	.	.	.
Std. Dev.	.	.	.	.	.	.	.
Minimum	.	.	.	.	.	.	.
Median	.	.	.	.	.	.	.
Maximum	.	.	.	.	.	.	.
≤300mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>300-400mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>400mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Tenoxicam							
n	0	0	0	0	0	0	0

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
Mean	.	.	.	.	.	.	.
Std. Dev.	.	.	.	.	.	.	.
Minimum	.	.	.	.	.	.	.
Median	.	.	.	.	.	.	.
Maximum	.	.	.	.	.	.	.
≤20mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>20mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Tiaprofenic Acid							
n	0	1	0	0	1	0	0
Mean	.	600.00	.	.	.	.	.
Std. Dev.	.	.	.	.	.	.	.
Minimum	.	600.00	.	.	.	.	.
Median	.	600.00	.	.	.	.	.
Maximum	.	600.00	.	.	.	.	.
≤600mg [(n (%)]	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>600mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)
Tolmetin							
n	0	0	0	0	0	0	0

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
Mean	.	.	.	.	.	.	.
Std. Dev.	.	.	.	.	.	.	.
Minimum	.	.	.	.	.	.	.
Median	.	.	.	.	.	.	.
Maximum	.	.	.	.	.	.	.
≤200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>400-600mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>600-800mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>800-1200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>1200-1600mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>1600-1800mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>1800mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

* Indicates doses above the maximum recommended dose for AS, or for other indications if AS indication is not labeled

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
Most Recent Baseline Drug Total Daily Dose: n (%)	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
COX-2 Selective Inhibitors							
Celecoxib							
n	10	6	2	7	0	1	27
Mean	240.00	200.00	200.00	200.00	.	200.00	260.00
Std. Dev.	89.44	0.00	0.00	0.00	.	.	96.61
Minimum	200.00	200.00	200.00	200.00	.	200.00	200.00
Median	200.00	200.00	200.00	200.00	.	200.00	200.00
Maximum	400.00	200.00	200.00	200.00	.	200.00	400.00
≤100mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>100-200mg [(n (%)]	4 (40.00)	2 (33.33)	2 (100.00)	7 (100.00)	0 (0.00)	1 (100.00)	7 (25.93)
>200-400mg [(n (%)]	1 (10.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	3 (11.11)
>400mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	5 (50.00)	4 (66.67)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	17 (62.96)
Etoricoxib							
n	11	15	4	9	3	1	40
Mean	78.00	97.50	90.00	72.00	75.00	90.00	91.88
Std. Dev.	16.43	21.21	0.00	26.83	21.21	.	17.21
Minimum	60.00	60.00	90.00	60.00	60.00	90.00	60.00
Median	90.00	90.00	90.00	60.00	75.00	90.00	90.00

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
Most Recent Baseline Drug Total Daily Dose: n (%)	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
Maximum	90.00	120.00	90.00	120.00	90.00	90.00	120.00
≤30mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>30-60mg [(n (%)]	2 (18.18)	1 (6.67)	0 (0.00)	4 (44.44)	1 (33.33)	0 (0.00)	2 (5.00)
>60-90mg [(n (%)]	3 (27.27)	4 (26.67)	3 (75.00)	0 (0.00)	1 (33.33)	1 (100.00)	11 (27.50)
>90-120mg [(n (%)]	0 (0.00)	3 (20.00)	0 (0.00)	1 (11.11)	0 (0.00)	0 (0.00)	3 (7.50)
>120mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	6 (54.55)	7 (46.67)	1 (25.00)	4 (44.44)	1 (33.33)	0 (0.00)	24 (60.00)
Lumiracoxib							
n	0	0	0	0	0	0	1
Mean	.	.	.	.	.	.	.
Std. Dev.	.	.	.	.	.	.	.
Minimum	.	.	.	.	.	.	.
Median	.	.	.	.	.	.	.
Maximum	.	.	.	.	.	.	.
≤100mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>100-200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>200mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)
Meloxicam							

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
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By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
Most Recent Baseline Drug Total Daily Dose: n (%)	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
n	13	8	2	3	0	0	22
Mean	12.50	10.64	15.00	15.00	.	.	14.38
Std. Dev.	3.75	4.08	0.00	.	.	.	5.95
Minimum	7.50	7.00	15.00	15.00	.	.	7.50
Median	15.00	7.50	15.00	15.00	.	.	15.00
Maximum	15.00	15.00	15.00	15.00	.	.	30.00
≤7.5mg [(n (%)]	3 (23.08)	4 (50.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	3 (13.64)
>7.5-15mg [(n (%)]	6 (46.15)	3 (37.50)	2 (100.00)	1 (33.33)	0 (0.00)	0 (0.00)	8 (36.36)
>15mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (4.55)
Missing [(n (%)]	4 (30.77)	1 (12.50)	0 (0.00)	2 (66.67)	0 (0.00)	0 (0.00)	10 (45.45)
Rofecoxib							
n	11	7	3	2	4	0	10
Mean	27.08	15.38	25.00	18.50	20.83	.	16.67
Std. Dev.	12.29	5.75	.	9.19	7.22	.	6.45
Minimum	12.50	12.50	25.00	12.00	12.50	.	12.50
Median	25.00	12.50	25.00	18.50	25.00	.	12.50
Maximum	50.00	24.00	25.00	25.00	25.00	.	25.00
≤12.5mg [(n (%)]	1 (9.09)	3 (42.86)	0 (0.00)	1 (50.00)	1 (25.00)	0 (0.00)	4 (40.00)
>12.5-25mg [(n (%)]	4 (36.36)	1 (14.29)	1 (33.33)	1 (50.00)	2 (50.00)	0 (0.00)	2 (20.00)

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
Most Recent Baseline Drug Total Daily Dose: n (%)	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
>25-50mg [(n (%)]	1 (9.09)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>50mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	5 (45.45)	3 (42.86)	2 (66.67)	0 (0.00)	1 (25.00)	0 (0.00)	4 (40.00)
Valdecoxib							
n	1	1	0	0	0	0	1
Mean	30.00	20.00	.	.	.	.	20.00
Std. Dev.	.	.	.	.	.	.	.
Minimum	30.00	20.00	.	.	.	.	20.00
Median	30.00	20.00	.	.	.	.	20.00
Maximum	30.00	20.00	.	.	.	.	20.00
≤10mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>10-20mg [(n (%)]	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)
>20mg* [(n (%)]	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Non-Selective NSAIDS							
Aceclofenac							
n	1	0	0	0	37	0	4
Mean	200.00	.	.	.	184.00	.	200.00
Std. Dev.	.	.	.	.	37.42	.	0.00

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
Most Recent Baseline Drug Total Daily Dose: n (%)	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
Minimum	200.00	.	.	.	100.00	.	200.00
Median	200.00	.	.	.	200.00	.	200.00
Maximum	200.00	.	.	.	200.00	.	200.00
≤200mg [(n (%)]	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	25 (67.57)	0 (0.00)	4 (100.00)
>200mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	12 (32.43)	0 (0.00)	0 (0.00)
Acemetacin							
n	0	0	0	0	16	0	0
Mean	.	.	.	.	152.00	.	.
Std. Dev.	.	.	.	.	38.40	.	.
Minimum	.	.	.	.	120.00	.	.
Median	.	.	.	.	120.00	.	.
Maximum	.	.	.	.	240.00	.	.
≤180mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	14 (87.50)	0 (0.00)	0 (0.00)
>180mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (6.25)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (6.25)	0 (0.00)	0 (0.00)
Azapropazone							
n	2	1	0	0	4	0	0
Mean	900.00	600.00	.	.	1200.00	.	.

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
Most Recent Baseline Drug Total Daily Dose: n (%)	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
Std. Dev.	424.26	.	.	.	.	.	.
Minimum	600.00	600.00	.	.	1200.00	.	.
Median	900.00	600.00	.	.	1200.00	.	.
Maximum	1200.00	600.00	.	.	1200.00	.	.
≤1200mg [(n (%)]	2 (100.00)	1 (100.00)	0 (0.00)	0 (0.00)	1 (25.00)	0 (0.00)	0 (0.00)
>1200mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	3 (75.00)	0 (0.00)	0 (0.00)
Dexketoprofen							
n	0	0	0	0	3	0	1
Mean	.	.	.	.	75.00	.	75.00
Std. Dev.	.	.	.	.	0.00	.	.
Minimum	.	.	.	.	75.00	.	75.00
Median	.	.	.	.	75.00	.	75.00
Maximum	.	.	.	.	75.00	.	75.00
≤50mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>50-75mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (66.67)	0 (0.00)	1 (100.00)
>75mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (33.33)	0 (0.00)	0 (0.00)
Diclofenac							

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
Most Recent Baseline Drug Total Daily Dose: n (%)	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
n	3326	122	36	60	37	2	318
Mean	130.50	134.01	142.59	139.44	141.67	150.00	135.15
Std. Dev.	33.09	29.60	18.10	22.29	29.60	.	30.32
Minimum	25.00	50.00	100.00	75.00	50.00	150.00	1.35
Median	150.00	150.00	150.00	150.00	150.00	150.00	150.00
Maximum	450.00	200.00	150.00	150.00	200.00	150.00	225.00
≤50mg [(n (%)]	57 (1.71)	1 (0.82)	0 (0.00)	0 (0.00)	1 (2.70)	0 (0.00)	2 (0.63)
>50-75mg [(n (%)]	158 (4.75)	7 (5.74)	0 (0.00)	2 (3.33)	0 (0.00)	0 (0.00)	9 (2.83)
>75-100mg [(n (%)]	478 (14.37)	8 (6.56)	4 (11.11)	6 (10.00)	5 (13.51)	0 (0.00)	34 (10.69)
>100-150mg [(n (%)]	1,329 (39.96)	51 (41.80)	23 (63.89)	37 (61.67)	22 (59.46)	1 (50.00)	114 (35.85)
>150mg* [(n (%)]	43 (1.29)	1 (0.82)	0 (0.00)	0 (0.00)	2 (5.41)	0 (0.00)	5 (1.57)
Missing [(n (%)]	1,261 (37.91)	54 (44.26)	9 (25.00)	15 (25.00)	7 (18.92)	1 (50.00)	154 (48.43)
Etodolac							
n	3	1	0	0	1	0	10
Mean	600.00	1200.00	.	.	400.00	.	544.44
Std. Dev.	0.00	.	.	.	.	.	113.04
Minimum	600.00	1200.00	.	.	400.00	.	300.00
Median	600.00	1200.00	.	.	400.00	.	600.00
Maximum	600.00	1200.00	.	.	400.00	.	600.00

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
Most Recent Baseline Drug Total Daily Dose: n (%)	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
≤300mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (10.00)
>300-600mg [(n (%)]	2 (66.67)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	8 (80.00)
>600mg* [(n (%)]	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	1 (33.33)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (10.00)
Fenbufen							
n	2	1	0	0	24	0	1
Mean	900.00	600.00	.	.	847.50	.	900.00
Std. Dev.	0.00	.	.	.	163.41	.	.
Minimum	900.00	600.00	.	.	300.00	.	900.00
Median	900.00	600.00	.	.	900.00	.	900.00
Maximum	900.00	600.00	.	.	900.00	.	900.00
≤900mg [(n (%)]	2 (100.00)	1 (100.00)	0 (0.00)	0 (0.00)	20 (83.33)	0 (0.00)	1 (100.00)
>900mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	4 (16.67)	0 (0.00)	0 (0.00)
Fenoprofen							
n	0	0	0	0	2	0	0
Mean	.	.	.	.	2100.00	.	.
Std. Dev.	.	.	.	.	424.26	.	.
Minimum	.	.	.	.	1800.00	.	.

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
Most Recent Baseline Drug Total Daily Dose: n (%)	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
Median	.	.	.	.	2100.00	.	.
Maximum	.	.	.	.	2400.00	.	.
≤200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>200-400mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>400-600mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>600-800mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>800-1200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>1200-1600mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>1600-2000mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (50.00)	0 (0.00)	0 (0.00)
>2000-2400mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (50.00)	0 (0.00)	0 (0.00)
>2400-3200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>3200mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Flurbiprofen							
n	0	0	0	1	50	0	2
Mean	.	.	.	200.00	193.33	.	200.00
Std. Dev.	.	.	.	.	70.39	.	.
Minimum	.	.	.	200.00	50.00	.	200.00
Median	.	.	.	200.00	200.00	.	200.00

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
Most Recent Baseline Drug Total Daily Dose: n (%)	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
Maximum	.	.	.	200.00	450.00	.	200.00
≤50mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (2.00)	0 (0.00)	0 (0.00)
>50-100mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	5 (10.00)	0 (0.00)	0 (0.00)
>100-150mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	10 (20.00)	0 (0.00)	0 (0.00)
>150-200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)	22 (44.00)	0 (0.00)	1 (50.00)
>200-250mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>250-300mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	6 (12.00)	0 (0.00)	0 (0.00)
>300mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (2.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	5 (10.00)	0 (0.00)	1 (50.00)
Ibuprofen							
n	135	1512	15	40	35	4	230
Mean	1363.29	1266.10	1577.78	1193.55	1211.76	1000.00	1229.21
Std. Dev.	351.98	382.92	551.76	255.52	268.99	282.84	414.51
Minimum	600.00	300.00	800.00	600.00	800.00	800.00	400.00
Median	1200.00	1200.00	1600.00	1200.00	1200.00	1000.00	1200.00
Maximum	2400.00	2400.00	2400.00	1800.00	1800.00	1200.00	2400.00
≤400mg [(n (%)]	0 (0.00)	9 (0.60)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.87)
>400-600mg [(n (%)]	3 (2.22)	53 (3.51)	0 (0.00)	3 (7.50)	0 (0.00)	0 (0.00)	9 (3.91)
>600-800mg [(n (%)]	4 (2.96)	67 (4.43)	1 (6.67)	0 (0.00)	3 (8.57)	1 (25.00)	10 (4.35)

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
Most Recent Baseline Drug Total Daily Dose: n (%)	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
>800-1200mg [(n (%)]	42 (31.11)	473 (31.28)	3 (20.00)	25 (62.50)	11 (31.43)	1 (25.00)	52 (22.61)
>1200-1600mg [(n (%)]	9 (6.67)	88 (5.82)	2 (13.33)	1 (2.50)	2 (5.71)	0 (0.00)	8 (3.48)
>1600-2000mg [(n (%)]	20 (14.81)	93 (6.15)	1 (6.67)	2 (5.00)	1 (2.86)	0 (0.00)	13 (5.65)
>2000mg* [(n (%)]	1 (0.74)	26 (1.72)	2 (13.33)	0 (0.00)	0 (0.00)	0 (0.00)	3 (1.30)
Missing [(n (%)]	56 (41.48)	703 (46.49)	6 (40.00)	9 (22.50)	18 (51.43)	2 (50.00)	133 (57.83)
Indomethacin							
n	17	10	744	4	3	0	33
Mean	127.27	120.00	108.96	121.88	112.50	.	123.21
Std. Dev.	89.59	41.08	52.11	35.90	53.03	.	39.98
Minimum	50.00	75.00	25.00	75.00	75.00	.	50.00
Median	112.50	150.00	100.00	131.25	112.50	.	150.00
Maximum	375.00	150.00	800.00	150.00	150.00	.	200.00
≤25mg [(n (%)]	0 (0.00)	0 (0.00)	11 (1.48)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>25-50mg [(n (%)]	1 (5.88)	0 (0.00)	25 (3.36)	0 (0.00)	0 (0.00)	0 (0.00)	1 (3.03)
>50-75mg [(n (%)]	4 (23.53)	2 (20.00)	177 (23.79)	1 (25.00)	1 (33.33)	0 (0.00)	5 (15.15)
>150mg* [(n (%)]	1 (5.88)	0 (0.00)	17 (2.28)	0 (0.00)	0 (0.00)	0 (0.00)	1 (3.03)
>75-150mg [(n (%)]	5 (29.41)	3 (30.00)	241 (32.39)	3 (75.00)	1 (33.33)	0 (0.00)	14 (42.42)
Missing [(n (%)]	6 (35.29)	5 (50.00)	273 (36.69)	0 (0.00)	1 (33.33)	0 (0.00)	12 (36.36)
Ketoprofen							

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
Most Recent Baseline Drug Total Daily Dose: n (%)	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
n	4	3	0	4	86	0	3
Mean	212.50	100.00	.	131.25	190.91	.	237.50
Std. Dev.	143.61	50.00	.	80.04	63.08	.	229.81
Minimum	50.00	50.00	.	50.00	50.00	.	75.00
Median	200.00	100.00	.	137.50	200.00	.	237.50
Maximum	400.00	150.00	.	200.00	400.00	.	400.00
≤150mg [(n (%)]	1 (25.00)	3 (100.00)	0 (0.00)	2 (50.00)	16 (18.60)	0 (0.00)	1 (33.33)
>150-200mg [(n (%)]	2 (50.00)	0 (0.00)	0 (0.00)	2 (50.00)	55 (63.95)	0 (0.00)	0 (0.00)
>200mg* [(n (%)]	1 (25.00)	0 (0.00)	0 (0.00)	0 (0.00)	6 (6.98)	0 (0.00)	1 (33.33)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	9 (10.47)	0 (0.00)	1 (33.33)
Lornoxicam							
n	0	0	0	1	8	0	1
Mean	.	.	.	.	10.84	.	16.00
Std. Dev.	.	.	.	.	4.48	.	.
Minimum	.	.	.	.	8.00	.	16.00
Median	.	.	.	.	8.51	.	16.00
Maximum	.	.	.	.	16.00	.	16.00
≤12mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (25.00)	0 (0.00)	0 (0.00)
>12-16mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (12.50)	0 (0.00)	1 (100.00)

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
Most Recent Baseline Drug Total Daily Dose: n (%)	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
>16mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)	5 (62.50)	0 (0.00)	0 (0.00)
Mefenamic Acid							
n	2	5	1	1	20	0	3
Mean	1250.00	1175.00	1125.00	750.00	1312.50	.	1312.50
Std. Dev.	353.55	325.96	.	.	364.43	.	265.17
Minimum	1000.00	750.00	1125.00	750.00	750.00	.	1125.00
Median	1250.00	1125.00	1125.00	750.00	1500.00	.	1312.50
Maximum	1500.00	1500.00	1125.00	750.00	2000.00	.	1500.00
≤1000mg [(n (%)]	1 (50.00)	2 (40.00)	0 (0.00)	1 (100.00)	5 (25.00)	0 (0.00)	0 (0.00)
>1000-1500mg [(n (%)]	1 (50.00)	3 (60.00)	1 (100.00)	0 (0.00)	12 (60.00)	0 (0.00)	2 (66.67)
>1500mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (5.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (10.00)	0 (0.00)	1 (33.33)
Nabumetone							
n	2	4	1	3	61	0	5
Mean	1000.00	1500.00	2000.00	1750.00	1101.85	.	1500.00
Std. Dev.	0.00	1000.00	.	353.55	281.16	.	500.00
Minimum	1000.00	1000.00	2000.00	1500.00	1000.00	.	1000.00
Median	1000.00	1000.00	2000.00	1750.00	1000.00	.	1500.00

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
Most Recent Baseline Drug Total Daily Dose: n (%)	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
Maximum	1000.00	3000.00	2000.00	2000.00	2000.00	.	2000.00
≤500mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>500-1000mg [(n (%)]	2 (100.00)	3 (75.00)	0 (0.00)	0 (0.00)	47 (77.05)	0 (0.00)	1 (20.00)
>1000mg* [(n (%)]	0 (0.00)	1 (25.00)	1 (100.00)	2 (66.67)	7 (11.48)	0 (0.00)	2 (40.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	1 (33.33)	7 (11.48)	0 (0.00)	2 (40.00)
Naproxen							
n	50	13	9	733	8	2	71
Mean	901.16	781.25	937.50	904.98	850.00	625.00	877.19
Std. Dev.	164.93	247.76	176.78	221.73	223.61	176.78	189.71
Minimum	500.00	500.00	500.00	125.00	500.00	500.00	500.00
Median	1000.00	875.00	1000.00	1000.00	1000.00	625.00	1000.00
Maximum	1000.00	1000.00	1000.00	3000.00	1000.00	750.00	1000.00
≤250mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	5 (0.68)	0 (0.00)	0 (0.00)	0 (0.00)
>250-500mg [(n (%)]	4 (8.00)	3 (23.08)	1 (11.11)	77 (10.50)	1 (12.50)	1 (50.00)	9 (12.68)
>500-1000mg [(n (%)]	39 (78.00)	5 (38.46)	7 (77.78)	499 (68.08)	4 (50.00)	1 (50.00)	48 (67.61)
>1000mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	11 (1.50)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	7 (14.00)	5 (38.46)	1 (11.11)	141 (19.24)	3 (37.50)	0 (0.00)	14 (19.72)
Phenylbutazone							
n	1	2	0	0	19	0	1

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
Most Recent Baseline Drug Total Daily Dose: n (%)	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
Mean	.	.	.	.	408.33	.	200.00
Std. Dev.	.	.	.	.	183.20	.	.
Minimum	.	.	.	.	200.00	.	200.00
Median	.	.	.	.	400.00	.	200.00
Maximum	.	.	.	.	900.00	.	200.00
≤300mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	5 (26.32)	0 (0.00)	1 (100.00)
>300-400mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	5 (26.32)	0 (0.00)	0 (0.00)
>400mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (10.53)	0 (0.00)	0 (0.00)
Missing [(n (%)]	1 (100.00)	2 (100.00)	0 (0.00)	0 (0.00)	7 (36.84)	0 (0.00)	0 (0.00)
Piroxicam							
n	10	10	1	2	302	1	28
Mean	25.71	21.43	15.00	20.00	20.75	.	21.76
Std. Dev.	13.85	3.78	.	0.00	5.67	.	10.92
Minimum	8.57	20.00	15.00	20.00	10.00	.	10.00
Median	20.00	20.00	15.00	20.00	20.00	.	20.00
Maximum	40.00	30.00	15.00	20.00	40.00	.	60.00
≤10mg [(n (%)]	1 (10.00)	0 (0.00)	0 (0.00)	0 (0.00)	11 (3.64)	0 (0.00)	1 (3.57)
>10-20mg [(n (%)]	2 (20.00)	6 (60.00)	1 (100.00)	2 (100.00)	157 (51.99)	0 (0.00)	12 (42.86)
>20-30mg [(n (%)]	0 (0.00)	1 (10.00)	0 (0.00)	0 (0.00)	8 (2.65)	0 (0.00)	1 (3.57)

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
Most Recent Baseline Drug Total Daily Dose: n (%)	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
>30mg* [(n (%)]	2 (20.00)	0 (0.00)	0 (0.00)	0 (0.00)	10 (3.31)	0 (0.00)	1 (3.57)
Missing [(n (%)]	5 (50.00)	3 (30.00)	0 (0.00)	0 (0.00)	116 (38.41)	1 (100.00)	13 (46.43)
Sulindac							
n	0	1	0	0	8	0	0
Mean	.	200.00	.	.	371.43	.	.
Std. Dev.	.	.	.	.	138.01	.	.
Minimum	.	200.00	.	.	200.00	.	.
Median	.	200.00	.	.	400.00	.	.
Maximum	.	200.00	.	.	600.00	.	.
≤300mg [(n (%)]	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)	2 (25.00)	0 (0.00)	0 (0.00)
>300-400mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	4 (50.00)	0 (0.00)	0 (0.00)
>400mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (12.50)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (12.50)	0 (0.00)	0 (0.00)
Tenoxicam							
n	0	0	0	0	15	0	0
Mean	.	.	.	.	20.00	.	.
Std. Dev.	.	.	.	.	0.00	.	.
Minimum	.	.	.	.	20.00	.	.
Median	.	.	.	.	20.00	.	.

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
Most Recent Baseline Drug Total Daily Dose: n (%)	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
Maximum	.	.	.	.	20.00	.	.
≤20mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	12 (80.00)	0 (0.00)	0 (0.00)
>20mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	3 (20.00)	0 (0.00)	0 (0.00)
Tiaprofenic Acid							
n	0	1	1	0	25	0	2
Mean	.	.	600.00	.	557.89	.	600.00
Std. Dev.	.	.	.	.	142.66	.	.
Minimum	.	.	600.00	.	300.00	.	600.00
Median	.	.	600.00	.	600.00	.	600.00
Maximum	.	.	600.00	.	900.00	.	600.00
≤600mg [(n (%)]	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	18 (72.00)	0 (0.00)	1 (50.00)
>600mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (4.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)	6 (24.00)	0 (0.00)	1 (50.00)
Tolmetin							
n	0	0	0	0	1	0	0
Mean	.	.	.	.	.	.	.
Std. Dev.	.	.	.	.	.	.	.
Minimum	.	.	.	.	.	.	.

Table 14
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
Most Recent Baseline Drug Total Daily Dose: n (%)	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
Median	.	.	.	.	.	.	.
Maximum	.	.	.	.	.	.	.
≤200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>400-600mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>600-800mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>800-1200mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>1200-1600mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>1600-1800mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
>1800mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)

10.2.6 Baseline Other Medication Use

Baseline medication use (during the 6 months prior to entry into the cohort) other than non-steroidal anti-inflammatory therapy, for the cohort overall is provided in **Table 15.** Any recorded prescription regardless of frequency of occurrence during the 6 month baseline period prior to entry into the cohort is counted towards baseline medication use.

About 18.3% of the cohort had a baseline history of narcotic pain medications. About 11.8% had a baseline history of anti-rheumatic therapy (DMARDS or oral steroids). Approximately 22.4% used gastro-protective medications during the baseline period and about the same used cardiovascular medications, the most common of which were diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, calcium channel blockers, and statins. About 0.8% of the cohort used oral anticoagulants during baseline, and about 4.9% used oral anti-platelet drugs (including low dose aspirin). Note, over the counter low dose aspirin is not captured in the databases.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 15a** for UK CPRD + THIN, **Table 15b** for UK IMS, **Table 15c** for Germany IMS, and **Table 15d** for France IMS).

Table 15
AS Cohort Other Baseline Medication Use
(Assessed During the 6 Months Prior to Entry into the AS Cohort)
(Excluding Anti-Inflammatory Treatment)
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Medication: n (%)	N=27,381
Narcotic Pain Medications	**5,007 (18.29)**
Rheumatic Disease Treatments	**3,221 (11.76)**
Disease Modifying Anti-Rheumatic Drugs	1,718 (6.27)
Tumor Necrosis Factor Inhibitors	1 (0.00)
Oral Corticosteroids	1,988 (7.26)
Gastrointestinal Drugs	**6,132 (22.40)**
Histamine 2-Receptor Antagonists	889 (3.25)
Prostaglandin Analogues (incl. misoprostol + NSAID)	515 (1.88)
Proton Pump Inhibitors	4,941 (18.05)
Other Ulcer-healing Drugs	103 (0.38)
Cardiovascular / Lipid-Modifying Medications	**5,661 (20.67)**
Cardiac Glycosides	258 (0.94)
Diuretics	1,740 (6.35)
Beta-Blockers	1,378 (5.03)
Angiotensin-Converting Enzyme Inhibitors	1,381 (5.04)
Angiotensin-II Receptor Antagonists	1,522 (5.56)
Nitrates	428 (1.56)
Calcium-Channel Blockers	1,140 (4.16)
Oral Anticoagulants	226 (0.83)
Oral Antiplatelet Drugs (Including Low Dose Aspirin)	1,340 (4.89)
Anion-Exchange Resins	17 (0.06)
Ezetimibe	67 (0.24)
Fibrates	165 (0.60)
Statins	1,620 (5.92)
Nicotinic Acid	83 (0.30)
Oral Contraceptives	**742 (2.71)**
Estrogen Replacement Therapy	**305 (1.11)**
Prescription Aspirin (≥300 mg/day)	**80 (0.29)**

Baseline medication usage (during the 6 months prior to entry into the cohort) other than non-steroidal anti-inflammatory therapy, according to the type of first non-steroidal anti-inflammatory therapy following entry into the AS cohort (COX-2 inhibitor, non-selective NSAID, multiple, or none) is shown in **Table 16**. Any recorded prescription regardless of frequency of occurrence during the 6 month baseline period prior to entry into the cohort is counted towards baseline medication use.

Those whose first prescription for a non-steroidal anti-inflammatory following entry into the cohort was a COX-2 inhibitor more frequently had a baseline history of narcotic pain medication, DMARD or corticosteroid use, gastroprotective drug use, and to a lesser extent cardiovascular / lipid modifying medications than did those whose first prescription for a non-steroidal anti-inflammatory following entry into the cohort was an NSAID.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 16a** for UK CPRD + THIN, **Table 16b** for UK IMS, **Table 16c** for Germany IMS, and **Table 16d** for France IMS).

Table 16
AS Cohort Other Baseline Medication Use
(Assessed During the 6 Months Prior to Entry into the AS Cohort)
By Type of First Anti-Inflammatory Prescription for Treatment of AS
After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Type of First Anti-Inflammatory Prescription			
	COX-2 Inhibitor N=3,218	NSAID N=14,500	Multiple N=107	None N=9,556
Narcotic Pain Medications	**931 (28.93)**	**3,060 (21.10)**	**21 (19.63)**	**995 (10.41)**
Rheumatic Disease Treatments	**529 (16.44)**	**1,401 (9.66)**	**14 (13.08)**	**1,277 (13.36)**
Disease Modifying Anti-Rheumatic Drugs	327 (10.16)	834 (5.75)	11 (10.28)	546 (5.71)
Tumor Necrosis Factor Inhibitors	0 (0.00)	1 (0.01)	0 (0.00)	0 (0.00)
Oral Corticosteroids	298 (9.26)	757 (5.22)	3 (2.80)	930 (9.73)
Gastrointestinal Drugs	**949 (29.49)**	**2,949 (20.34)**	**27 (25.23)**	**2,207 (23.10)**
Histamine 2-Receptor Antagonists	136 (4.23)	583 (4.02)	6 (5.61)	164 (1.72)
Prostaglandin Analogues (incl. misoprostol + NSAID)	39 (1.21)	429 (2.96)	6 (5.61)	41 (0.43)
Proton Pump Inhibitors	810 (25.17)	2,099 (14.48)	16 (14.95)	2,016 (21.10)
Other Ulcer-healing Drugs	10 (0.31)	38 (0.26)	1 (0.93)	54 (0.57)
Cardiovascular / Lipid-Modifying Medications	**682 (21.19)**	**2,961 (20.42)**	**18 (16.82)**	**2,000 (20.93)**
Cardiac Glycosides	26 (0.81)	118 (0.81)	2 (1.87)	112 (1.17)
Diuretics	222 (6.90)	923 (6.37)	7 (6.54)	588 (6.15)
Beta-Blockers	169 (5.25)	755 (5.21)	7 (6.54)	447 (4.68)
Angiotensin-Converting Enzyme Inhibitors	186 (5.78)	727 (5.01)	5 (4.67)	463 (4.85)
Angiotensin-II Receptor Antagonists	163 (5.07)	729 (5.03)	1 (0.93)	629 (6.58)
Nitrates	60 (1.86)	223 (1.54)	0 (0.00)	145 (1.52)
Calcium-Channel Blockers	148 (4.60)	619 (4.27)	4 (3.74)	369 (3.86)
Oral Anticoagulants	24 (0.75)	64 (0.44)	0 (0.00)	138 (1.44)
Oral Antiplatelet Drugs (Including Low Dose Aspirin)	169 (5.25)	649 (4.48)	4 (3.74)	518 (5.42)
Anion-Exchange Resins	3 (0.09)	9 (0.06)	0 (0.00)	5 (0.05)
Ezetimibe	7 (0.22)	39 (0.27)	0 (0.00)	21 (0.22)
Fibrates	13 (0.40)	68 (0.47)	0 (0.00)	84 (0.88)
Statins	227 (7.05)	809 (5.58)	5 (4.67)	579 (6.06)
Nicotinic Acid	6 (0.19)	58 (0.40)	0 (0.00)	19 (0.20)
Oral Contraceptives	**96 (2.98)**	**390 (2.69)**	**4 (3.74)**	**252 (2.64)**
Estrogen Replacement Therapy	**46 (1.43)**	**202 (1.39)**	**0 (0.00)**	**57 (0.60)**
Prescription Aspirin (≥300 mg/day)	**10 (0.31)**	**50 (0.34)**	**0 (0.00)**	**20 (0.21)**

Baseline medication usage (during the 6 months prior to entry into the cohort), other than non-steroidal anti-inflammatory therapy, according to the specific first non-steroidal anti-inflammatory prescription following entry into the AS cohort is shown in **Table 17**. Any recorded prescription regardless of frequency of occurrence during the 6 month baseline period prior to entry into the cohort is counted towards baseline medication use.

Of those whose first prescription for a non-steroidal anti-inflammatory following entry into the cohort was etoricoxib (n=1,080), approximately 26.9% used narcotic pain medications, 11-12% DMARDS or oral corticosteroids, 26.4% gastroprotective medications, and 19.3% cardiovascular medications. About 0.7% and 3.6% used oral anticoagulants and anti-platelet drugs (including low dose aspirin), respectively, during the baseline period.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 17a** for UK CPRD + THIN, **Table 17b** for UK IMS, **Table 17c** for Germany IMS, and **Table 17d** for France IMS).

Table 17
AS Cohort Other Baseline Medication Use
(Assessed During the 6 Months Prior to Entry into the AS Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
Narcotic Pain Medications	**290 (26.85)**	**265 (31.21)**	**2 (16.67)**	**215 (26.61)**	**154 (35.24)**	**5 (15.63)**	**88 (45.83)**
Rheumatic Disease Treatments	**199 (18.43)**	**142 (16.73)**	**1 (8.33)**	**123 (15.22)**	**56 (12.81)**	**8 (25.00)**	**24 (12.50)**
Disease Modifying Anti-Rheumatic Drugs	128 (11.85)	95 (11.19)	0 (0.00)	64 (7.92)	33 (7.55)	7 (21.88)	16 (8.33)
Tumor Necrosis Factor Inhibitors	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Oral Corticosteroids	124 (11.48)	64 (7.54)	1 (8.33)	75 (9.28)	29 (6.64)	5 (15.63)	13 (6.77)
Gastrointestinal Drugs	**285 (26.39)**	**267 (31.45)**	**3 (25.00)**	**256 (31.68)**	**133 (30.43)**	**5 (15.63)**	**54 (28.13)**
Histamine 2-Receptor Antagonists	25 (2.31)	32 (3.77)	0 (0.00)	44 (5.45)	32 (7.32)	3 (9.38)	15 (7.81)
Prostaglandin Analogues (incl. misoprostol + NSAID)	7 (0.65)	13 (1.53)	0 (0.00)	5 (0.62)	13 (2.97)	1 (3.13)	1 (0.52)
Proton Pump Inhibitors	261 (24.17)	229 (26.97)	3 (25.00)	216 (26.73)	98 (22.43)	3 (9.38)	41 (21.35)
Other Ulcer-healing Drugs	3 (0.28)	3 (0.35)	0 (0.00)	1 (0.12)	2 (0.46)	1 (3.13)	0 (0.00)
Cardiovascular / Lipid-Modifying Medications	**208 (19.26)**	**168 (19.79)**	**6 (50.00)**	**175 (21.66)**	**118 (27.00)**	**7 (21.88)**	**40 (20.83)**
Cardiac Glycosides	7 (0.65)	5 (0.59)	0 (0.00)	3 (0.37)	10 (2.29)	1 (3.13)	0 (0.00)
Diuretics	65 (6.02)	55 (6.48)	0 (0.00)	56 (6.93)	45 (10.30)	1 (3.13)	11 (5.73)
Beta-Blockers	56 (5.19)	40 (4.71)	3 (25.00)	36 (4.46)	32 (7.32)	2 (6.25)	11 (5.73)
Angiotensin-Converting Enzyme Inhibitors	61 (5.65)	40 (4.71)	1 (8.33)	42 (5.20)	39 (8.92)	3 (9.38)	15 (7.81)
Angiotensin-II Receptor Antagonists	58 (5.37)	48 (5.65)	1 (8.33)	38 (4.70)	18 (4.12)	0 (0.00)	4 (2.08)
Nitrates	15 (1.39)	15 (1.77)	1 (8.33)	14 (1.73)	14 (3.20)	1 (3.13)	5 (2.60)
Calcium-Channel Blockers	40 (3.70)	36 (4.24)	1 (8.33)	47 (5.82)	23 (5.26)	1 (3.13)	14 (7.29)
Oral Anticoagulants	8 (0.74)	3 (0.35)	0 (0.00)	8 (0.99)	4 (0.92)	1 (3.13)	0 (0.00)
Oral Antiplatelet Drugs (Including Low Dose Aspirin)	39 (3.61)	53 (6.24)	1 (8.33)	44 (5.45)	31 (7.09)	1 (3.13)	13 (6.77)

Table 17
AS Cohort Other Baseline Medication Use
(Assessed During the 6 Months Prior to Entry into the AS Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Etoricoxib N=1,080	Celecoxib N=849	Lumiracoxib N=12	Meloxicam N=808	Rofecoxib N=437	Valdecoxib N=32	Etodolac N=192
Anion-Exchange Resins	1 (0.09)	0 (0.00)	0 (0.00)	2 (0.25)	0 (0.00)	0 (0.00)	0 (0.00)
Ezetimibe	3 (0.28)	3 (0.35)	0 (0.00)	1 (0.12)	0 (0.00)	0 (0.00)	0 (0.00)
Fibrates	4 (0.37)	2 (0.24)	0 (0.00)	5 (0.62)	2 (0.46)	0 (0.00)	0 (0.00)
Statins	77 (7.13)	61 (7.18)	3 (25.00)	59 (7.30)	25 (5.72)	2 (6.25)	11 (5.73)
Nicotinic Acid	4 (0.37)	0 (0.00)	0 (0.00)	1 (0.12)	1 (0.23)	0 (0.00)	0 (0.00)
Oral Contraceptives	**32 (2.96)**	**21 (2.47)**	**0 (0.00)**	**30 (3.71)**	**12 (2.75)**	**1 (3.13)**	**5 (2.60)**
Estrogen Replacement Therapy	**10 (0.93)**	**13 (1.53)**	**0 (0.00)**	**13 (1.61)**	**9 (2.06)**	**1 (3.13)**	**4 (2.08)**
Prescription Aspirin (≥300 mg/day)	**3 (0.28)**	**3 (0.35)**	**0 (0.00)**	**2 (0.25)**	**2 (0.46)**	**0 (0.00)**	**0 (0.00)**

Table 17
AS Cohort Other Baseline Medication Use
(Assessed During the 6 Months Prior to Entry into the AS Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
Narcotic Pain Medications	**1,297 (19.94)**	**625 (17.87)**	**260 (21.22)**	**468 (29.20)**	**322 (21.80)**	**21 (19.63)**	**995 (10.41)**
Rheumatic Disease Treatments	**584 (8.98)**	**300 (8.58)**	**158 (12.90)**	**156 (9.73)**	**179 (12.12)**	**14 (13.08)**	**1,277 (13.36)**
Disease Modifying Anti-Rheumatic Drugs	337 (5.18)	161 (4.60)	109 (8.90)	106 (6.61)	105 (7.11)	11 (10.28)	546 (5.71)
Tumor Necrosis Factor Inhibitors	0 (0.00)	0 (0.00)	1 (0.08)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Oral Corticosteroids	324 (4.98)	195 (5.57)	70 (5.71)	63 (3.93)	92 (6.23)	3 (2.80)	930 (9.73)
Gastrointestinal Drugs	**1,340 (20.60)**	**586 (16.75)**	**249 (20.33)**	**385 (24.02)**	**335 (22.68)**	**27 (25.23)**	**2,207 (23.10)**
Histamine 2-Receptor Antagonists	234 (3.60)	101 (2.89)	66 (5.39)	66 (4.12)	101 (6.84)	6 (5.61)	164 (1.72)
Prostaglandin Analogues (incl. misoprostol + NSAID)	341 (5.24)	11 (0.31)	21 (1.71)	33 (2.06)	22 (1.49)	6 (5.61)	41 (0.43)
Proton Pump Inhibitors	861 (13.24)	488 (13.95)	168 (13.71)	314 (19.59)	227 (15.37)	16 (14.95)	2,016 (21.10)
Other Ulcer-healing Drugs	17 (0.26)	9 (0.26)	3 (0.24)	0 (0.00)	9 (0.61)	1 (0.93)	54 (0.57)
Cardiovascular / Lipid-Modifying Medications	**1,257 (19.32)**	**841 (24.04)**	**242 (19.76)**	**272 (16.97)**	**309 (20.92)**	**18 (16.82)**	**2,000 (20.93)**
Cardiac Glycosides	55 (0.85)	30 (0.86)	11 (0.90)	4 (0.25)	18 (1.22)	2 (1.87)	112 (1.17)
Diuretics	396 (6.09)	282 (8.06)	61 (4.98)	82 (5.12)	91 (6.16)	7 (6.54)	588 (6.15)
Beta-Blockers	312 (4.80)	195 (5.57)	67 (5.47)	84 (5.24)	86 (5.82)	7 (6.54)	447 (4.68)
Angiotensin-Converting Enzyme Inhibitors	292 (4.49)	217 (6.20)	53 (4.33)	85 (5.30)	65 (4.40)	5 (4.67)	463 (4.85)
Angiotensin-II Receptor Antagonists	336 (5.17)	232 (6.63)	52 (4.24)	44 (2.74)	61 (4.13)	1 (0.93)	629 (6.58)
Nitrates	82 (1.26)	64 (1.83)	18 (1.47)	21 (1.31)	33 (2.23)	0 (0.00)	145 (1.52)
Calcium-Channel Blockers	239 (3.67)	149 (4.26)	63 (5.14)	77 (4.80)	77 (5.21)	4 (3.74)	369 (3.86)

Table 17
AS Cohort Other Baseline Medication Use
(Assessed During the 6 Months Prior to Entry into the AS Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS After Entry into the AS Cohort
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Specific First Anti-Inflammatory Prescription						
	Diclofenac N=6,505	Ibuprofen N=3,498	Indomethacin N=1,225	Naproxen N=1,603	Other Non-Selective NSAIDs N=1,477	Multiple N=107	None N=9,556
Oral Anticoagulants	21 (0.32)	21 (0.60)	5 (0.41)	8 (0.50)	9 (0.61)	0 (0.00)	138 (1.44)
Oral Antiplatelet Drugs (Including Low Dose Aspirin)	270 (4.15)	168 (4.80)	39 (3.18)	80 (4.99)	79 (5.35)	4 (3.74)	518 (5.42)
Anion-Exchange Resins	2 (0.03)	3 (0.09)	1 (0.08)	2 (0.12)	1 (0.07)	0 (0.00)	5 (0.05)
Ezetimibe	16 (0.25)	12 (0.34)	4 (0.33)	4 (0.25)	3 (0.20)	0 (0.00)	21 (0.22)
Fibrates	27 (0.42)	17 (0.49)	6 (0.49)	8 (0.50)	10 (0.68)	0 (0.00)	84 (0.88)
Statins	331 (5.09)	227 (6.49)	64 (5.22)	102 (6.36)	74 (5.01)	5 (4.67)	579 (6.06)
Nicotinic Acid	32 (0.49)	13 (0.37)	5 (0.41)	1 (0.06)	7 (0.47)	0 (0.00)	19 (0.20)
Oral Contraceptives	**162 (2.49)**	**99 (2.83)**	**22 (1.80)**	**55 (3.43)**	**47 (3.18)**	**4 (3.74)**	**252 (2.64)**
Estrogen Replacement Therapy	**92 (1.41)**	**45 (1.29)**	**10 (0.82)**	**23 (1.43)**	**28 (1.90)**	**0 (0.00)**	**57 (0.60)**
Prescription Aspirin (≥300 mg/day)	**21 (0.32)**	**11 (0.31)**	**3 (0.24)**	**8 (0.50)**	**7 (0.47)**	**0 (0.00)**	**20 (0.21)**

10.2.7 Duration of Follow-Up

The mean (SD) duration of follow-up for the cohort overall during the study period was 7.9 (5.5) years. The median follow-up was 6.6 years, with a minimum of 0 and a maximum of 27.7 years **Table 18**. (Note: the earliest date that a patient met the inclusion / exclusion criteria based on historical data is 1986.)

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 18a** for UK CPRD + THIN, **Table 18b** for UK IMS, **Table 18c** for Germany IMS, and **Table 18d** for France IMS).

Table 18
AS Cohort Duration of Follow-up
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Characteristic	
Duration of follow-up (years)	
Mean	7.85
Std. Dev.	5.48
Minimum	0.00
Median	6.63
Maximum	27.67

10.2.8 Duration of First Course of Non-steroidal Anti-inflammatory Treatment

Univariate statistics for the duration (in days) of the first course of therapy with a non-steroidal anti-inflammatory drug for AS after entry into the cohort are shown in **Table 19**. A course of non-steroidal anti-inflammatory treatment may include more than one successive prescription for the same medication. Patients who received multiple prescriptions for different non-steroidal anti-inflammatory drugs as their first course of non-steroidal anti-inflammatory treatment are excluded.

For those whose first course of non-steroidal anti-inflammatory treatment was etoricoxib, the mean (SD) duration of the first course of therapy was 104.5(170.8) days. The median duration was 59 days and the minimum and maximum were 15 and 1,868 days, respectively.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 19a** for UK CPRD + THIN, **Table 19b** for UK IMS, **Table 19c** for Germany IMS, and **Table 19d** for France IMS).

Table 19
Duration of First Course of Anti-Inflammatory Treatment for AS After Entry into the Cohort[†]
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Duration of Exposure (Days)				
	Mean	Std. Dev.	Minimum	Median	Maximum
COX-2 Selective Inhibitors					
Celecoxib	119.15	224.83	15.00	54.00	2177.00
Etoricoxib	104.54	170.78	15.00	59.00	1868.00
Lumiracoxib	24.00	15.12	15.00	15.00	64.00
Meloxicam	125.72	265.07	15.00	64.00	4685.00
Rofecoxib	95.63	145.97	15.00	44.00	1492.00
Valdecoxib	43.79	44.04	15.00	24.00	175.00
Non-Selective NSAIDS					
Diclofenac	76.28	164.50	14.00	42.00	3676.00
Etodolac	162.96	257.57	15.00	70.50	1965.00
Ibuprofen	52.41	96.16	14.00	39.00	2461.00
Indomethacin	178.94	470.29	14.00	64.00	6597.00
Naproxen	96.63	198.28	14.50	42.00	3741.00
Other non-selective NSAIDs[‡]	99.78	276.59	14.00	42.00	5005.00

[†] The first course of anti-inflammatory treatment is 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.

[‡] Aceclofenac, Acemetacin, Azapropazone, Dexketoprofen, Fenbufen, Fenoprofen, Feprazone, Flurbiprofen, Ketoprofen, Lornoxicam, Mefenamic acid, Nabumetone, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac, Tenoxicam, Tiaprofenic acid, Tolfenamic Acid , Tolmetin.

10.2.9 Duration of All Courses of Non-steroidal Anti-inflammatory Treatment

Univariate statistics for the total cumulative duration (in days) of therapy with non-steroidal anti-inflammatory drugs during the study period are shown in **Table 20**. This measure is the sum of the duration of all treatments courses for a given drug, regardless of whether the prescriptions were sequential. It thus provides an estimate of total cumulative exposure to a given product over the study period. Because a patient may have received more than one type of non-steroidal anti-inflammatory during follow-up, the patient's drug exposure may appear in more than one row. Patients who received multiple prescriptions for different non-steroidal anti-inflammatory drugs on one or more dates during the study period are excluded.

Among those who received etoricoxib at any time during the study period, the mean (SD) total cumulative duration was 391.5 (631.2) days. The median cumulative duration was 105days and the minimum and maximum were 15and 3,968days, respectively.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 20a** for UK CPRD + THIN, **Table 20b** for UK IMS, **Table 20c** for Germany IMS, and **Table 20d** for France IMS).

Table 20
Duration of Total (Cumulative) Anti-Inflammatory Treatment
At Any Time During Follow-up[†]
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

	Duration of Exposure (Days)				
	Mean	Std. Dev.	Minimum	Median	Maximum
COX-2 Selective Inhibitors					
Celecoxib	356.01	621.47	15.00	100.00	5049.00
Etoricoxib	391.48	631.24	15.00	105.00	3968.00
Lumiracoxib	66.81	110.69	15.00	19.50	437.00
Meloxicam	431.63	768.05	15.00	91.50	6197.00
Rofecoxib	265.34	358.99	15.00	89.00	2082.00
Valdecoxib	91.29	115.82	15.00	44.00	566.00
Non-Selective NSAIDS					
Diclofenac	368.70	714.29	14.33	84.00	7036.50
Etodolac	457.81	775.82	15.00	118.00	4971.00
Ibuprofen	187.08	426.64	14.50	44.00	8309.00
Indomethacin	709.77	1185.98	14.22	173.83	7694.00
Naproxen	358.02	682.89	14.15	90.00	8101.00
Other non-selective NSAIDs[‡]	397.20	840.17	14.11	76.00	7338.00

[†] The first course of anti-inflammatory treatment is 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.

[‡] Aceclofenac, Acemetacin, Azapropazone, Dexketoprofen, Fenbufen, Fenoprofen, Feprazone, Flurbiprofen, Ketoprofen, Lornoxicam,Mefenamic acid, Nabumetone, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac, Tenoxicam, Tiaprofenic acid, Tolfenamic Acid , Tolmetin.

10.2.10 Baseline Disease Risk Scores

As described in **Section 9.8**, summary disease risk scores (DRS) will be used to control for multiple risk factors for each outcome of interest in the case-control analysis that will address objective 3 for this study.

Baseline DRS were calculated for all patients as described in the protocol using logistic regression modelling. To be included in a given DRS model, a patient must have non-missing values for all variables in the model. Therefore, not all patients contributed data to each model. Because many patients did not have BMI values, BMI was treated as a categorical value (<25, 25-29.9, ≥30, or missing). In that way even patients with missing BMI data could contribute to the DRS models. Also, for patients in all the IMS databases, there were no data for alcohol use, blood pressure, and smoking status and therefore the model to derive the various DRS for patients in the IMS databases did not include these variables. In addition, due to small numbers of patients with certain characteristics (which made the models unstable), some of the pre-specified variables were dropped from the models as follows:

- History of renal failure from the model to predict risk of hypertension (for CPRD and THIN databases)
- History of diabetes from the model to predict risk of acute renal impairment / failure (for CPRD and THIN databases)
- History of peripheral arterial disease and history of haemorrhagic stroke from the model to predict vascular events + sudden death (for all databases)
- History of drug treatments for rheumatic diseases (oral corticosteroids and DMARDs) were combined into one variable (for all databases)

In future analyses these variables will be included in the models if there are sufficient numbers of patients with these characteristics.

Due to the differences in the models used to derive the DRS as described above, the baseline values are presented here separately for CPRD and THIN combined, and for the IMS databases combined. **Table 21** shows univariate statistics for the baseline DRS overall among the cohort members for patients in the UK CPRD and THIN databases combined (N=10,336) and the UK, Germany and France IMS databases combined (N=17,063). The numbers of patients contributing data are shown for each DRS model. The DRS can range from negative (less risk) to positive (more risk) values, and the greater the DRS value the greater the baseline risk of the outcome of interest. Because the models used to develop the DRS varied between the databases, the DRS for the CPRD and THIN patients are not directly comparable with those for the IMS patients.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 21a** for UK CPRD + THIN, **Table 21b** for UK IMS, **Table 21c** for Germany IMS, and **Table 21d** for France IMS). For the UK IMS and France IMS data, the numbers of patients with events is too small to calculate a DRS for any of the clinical outcomes except hypertension and congestive heart failure.

Table 21
AS Cohort Baseline Disease Risk Scores
(Assessed During the 6 Months Prior to Entry into the Cohort)

	Disease Risk Score				
	GI ulcers / bleeding	Vascular Events & Sudden / Unexplained Death	Hypertension	Congestive Heart Failure	Acute renal impairment / failure
UK (CPRD + THIN combined)					
N	10336	10336	10336	10336	10336
Mean	1.57	3.01	1.47	3.49	2.18
Std. Dev	0.57	1.01	0.94	1.25	0.80
Minimum	-1.06	0.67	-11.39	0.44	0.19
Median	1.55	2.96	1.39	3.33	2.07
Maximum	4.74	6.98	5.20	9.36	6.75
UK, Germany & France (IMS combined)					
N	17063	17063	17063	17063	17063
Mean	1.06	1.95	2.12	3.39	1.53
Std. Dev	0.48	0.85	1.43	1.33	0.62
Minimum	-0.10	0.14	-0.17	0.14	0.11
Median	0.98	1.77	1.57	3.16	1.42
Maximum	9.53	11.82	8.38	10.80	10.22

Baseline DRS according to the first type of treatment for AS (COX-2, NSAID, multiple non-steroidal anti-inflammatory agents, or none) after entry into the cohort for patients in the UK CPRD and THIN databases combined and the UK, Germany and France IMS databases combined are shown in **Table 22**. For a given patient this may not have been their first ever treatment with a non-steroidal anti-inflammatory agent. The numbers of patients contributing data are shown for each DRS model.

For the UK CPRD + THIN databases, patients receiving a COX-2 inhibitor as their first type of treatment for AS after entry into the cohort had similar mean and median baseline DRS for all types of events compared with patients receiving a non-selective NSAID as their first type of treatment for AS after entry into the cohort with small numeric differences in both directions. The clinical importance of the slight differences is unknown.

For the UK, Germany and France IMS databases, patients who received a COX-2 inhibitor as their first type of treatment for AS after entry into the cohort had similar mean and median baseline DRS for all types of events compared with patients who received a non-selective NSAID as their first type of treatment for AS after entry into the cohort, with the scores for the patients on COX-2 inhibitors slightly numerically higher for all types of events. The clinical importance of these slight differences is unknown.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 22a** for UK CPRD + THIN, **Table 22b** for UK IMS, **Table 22c** for Germany IMS, and **Table 22d** for France IMS). For the UK IMS and France IMS data, the numbers of patients with events is too small to calculate a risk score for any of the clinical outcomes except hypertension and congestive heart failure.

Table 22
AS Cohort Baseline Disease Risk Scores
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Type of First Anti-Inflammatory Prescription for Treatment of AS after Entry into the Cohort
UK CPRD+THIN

Disease Risk Score	Specific First Anti-Inflammatory Prescription			
	COX-2 Inhibitor	NSAID	Multiple	None
GI ulcers / bleeding				
N	1636.00	6629.00	55.00	2016.00
Mean	1.56	1.54	1.57	1.65
Std. Dev	0.57	0.54	0.56	0.64
Minimum	-1.06	-1.04	0.55	-0.87
Median	1.54	1.52	1.45	1.64
Maximum	3.67	4.49	3.06	4.74
Vascular & Sudden / Unexplained Death				
N	1636.00	6629.00	55.00	2016.00
Mean	2.91	2.95	2.77	3.30
Std. Dev	0.99	0.95	0.98	1.16
Minimum	0.67	0.68	0.82	0.69
Median	2.82	2.90	2.64	3.34
Maximum	6.69	6.55	5.48	6.98
Hypertension				
N	1636.00	6629.00	55.00	2016.00
Mean	1.42	1.48	1.47	1.50
Std. Dev	0.86	0.90	0.81	1.11
Minimum	-2.09	-11.39	0.03	-10.86
Median	1.33	1.40	1.37	1.42
Maximum	4.53	5.20	3.97	4.89
Congestive Heart Failure*				
N	1636.00	6629.00	55.00	2016.00
Mean	3.35	3.40	3.21	3.89
Std. Dev	1.20	1.17	1.14	1.44
Minimum	0.82	0.44	1.16	0.62
Median	3.19	3.26	3.11	3.90
Maximum	8.20	9.36	6.57	8.88
Acute renal impairment / failure				
N	1636.00	6629.00	55.00	2016.00
Mean	2.13	2.12	1.94	2.44
Std. Dev	0.77	0.75	0.76	0.91
Minimum	0.51	0.19	0.62	0.19
Median	2.02	2.02	1.96	2.42
Maximum	5.13	6.09	4.72	6.75

Table 22
AS Cohort Baseline Disease Risk Scores
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Type of First Anti-Inflammatory Prescription for Treatment of AS after Entry into the Cohort
UK, Germany & France (IMS) Combined

Disease Risk Score	Specific First Anti-Inflammatory Prescription			
	COX-2 Inhibitor	NSAID	Multiple	None
GI ulcers / bleeding				
N	1581.00	7881.00	53.00	7548.00
Mean	1.10	1.06	1.10	1.04
Std. Dev	0.53	0.49	0.38	0.46
Minimum	0.11	0.07	0.50	-0.10
Median	1.00	0.98	1.07	0.98
Maximum	5.15	9.53	2.22	5.32
Vascular & Sudden / Unexplained Death				
N	1581.00	7881.00	53.00	7548.00
Mean	1.98	1.95	2.12	1.94
Std. Dev	0.86	0.86	1.03	0.84
Minimum	0.22	0.14	0.80	0.19
Median	1.79	1.76	1.83	1.78
Maximum	6.80	11.82	5.66	8.00
Hypertension				
N	1581.00	7881.00	53.00	7548.00
Mean	2.17	2.16	2.29	2.08
Std. Dev	1.45	1.47	1.43	1.38
Minimum	0.17	0.12	0.84	-0.17
Median	1.60	1.57	1.62	1.58
Maximum	8.38	8.29	5.73	7.76
Congestive Heart Failure*				
N	1581.00	7881.00	53.00	7548.00
Mean	3.45	3.36	3.56	3.41
Std. Dev	1.33	1.33	1.39	1.33
Minimum	0.93	0.14	1.58	0.24
Median	3.20	3.12	3.16	3.20
Maximum	9.91	10.80	8.52	10.74
Acute renal impairment / failure				
N	1581.00	7881.00	53.00	7548.00
Mean	1.55	1.53	1.58	1.52
Std. Dev	0.61	0.63	0.57	0.62
Minimum	0.39	0.11	0.73	0.18
Median	1.43	1.42	1.40	1.44
Maximum	6.60	10.22	3.17	7.02

Baseline DRS according to the specific first non-steroidal anti-inflammatory treatment for AS after entry into the cohort for patients in the UK CPRD and THIN databases combined and the UK, Germany and France IMS databases combined are shown in **Table 23**. For a given patient this may not have been their first ever treatment with a non-steroidal anti-inflammatory agent.
The numbers of patients contributing data to the models are shown for each model.

For the UK CPRD + THIN databases, in general, patients receiving etoricoxib as their first treatment for AS after entry into the cohort (n=518) had slightly lower baseline mean and median DRS for all types of events than did patients receiving celecoxib (n=410) as their first treatment for AS after entry into the cohort (**Table 23**). The clinical importance of these differences is unknown; however this suggests that in these databases patients receiving etoricoxib were at lesser risk of all clinical outcomes at baseline than patients receiving celecoxib.

For the UK, Germany and France IMS databases, patients receiving etoricoxib as their first treatment for AS after entry into the cohort (n=562) had slightly lower baseline mean and median baseline DRS for all types of events compared with patients receiving celecoxib (n=439) as their first treatment for AS after entry into the cohort (**Table 23**). The clinical importance of these differences is unknown; however this suggests that in these databases patients receiving etoricoxib were at lesser risk of all clinical outcomes at baseline than patients receiving celecoxib.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 23a** for UK CPRD + THIN, **Table 23b** for UK IMS, **Table 23c** for Germany IMS, and **Table 23d** for France IMS). For the UK IMS and France IMS data, the numbers of patients with events is too small to calculate a risk score for any of the clinical outcomes except hypertension and congestive heart failure.

Table 23
AS Cohort Baseline Disease Risk Scores
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS after Entry into the Cohort
UK CPRD+THIN

Disease Risk Score	Specific First Anti-Inflammatory Prescription						
	Etoricoxib	Celecoxib	Lumiracoxib	Meloxicam	Rofecoxib	Valdecoxib	Etodolac
GI ulcers / bleeding							
N	518.00	410.00	2.00	435.00	261.00	10.00	164.00
Mean	1.42	1.64	1.72	1.57	1.69	1.41	1.54
Std. Dev	0.54	0.58	0.03	0.55	0.61	0.65	0.51
Minimum	-1.06	-0.30	1.70	-0.67	-0.31	0.69	0.44
Median	1.40	1.66	1.72	1.57	1.69	1.27	1.53
Maximum	2.98	3.59	1.74	3.67	3.59	2.76	2.67
Vascular & Sudden / Unexplained Death							
N	518.00	410.00	2.00	435.00	261.00	10.00	164.00
Mean	2.63	3.03	2.97	2.97	3.19	2.59	2.96
Std. Dev	0.92	0.99	1.54	0.97	1.04	0.81	1.00
Minimum	0.67	0.73	1.88	0.89	0.68	1.13	1.05
Median	2.44	2.96	2.97	2.93	3.14	2.61	2.92
Maximum	5.99	6.68	4.06	6.69	6.25	3.49	5.33
Hypertension							
N	518.00	410.00	2.00	435.00	261.00	10.00	164.00
Mean	1.18	1.54	1.34	1.49	1.63	1.04	1.45
Std. Dev	0.79	0.87	0.14	0.86	0.89	0.57	0.90
Minimum	-0.31	-0.53	1.25	-0.79	-2.09	0.39	-0.24
Median	1.09	1.42	1.34	1.41	1.59	0.91	1.33
Maximum	4.49	4.11	1.44	4.53	4.41	1.95	4.18
Congestive Heart Failure*							

Table 23
AS Cohort Baseline Disease Risk Scores
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS after Entry into the Cohort
UK CPRD+THIN

Disease Risk Score	Specific First Anti-Inflammatory Prescription						
	Etoricoxib	Celecoxib	Lumiracoxib	Meloxicam	Rofecoxib	Valdecoxib	Etodolac
N	518.00	410.00	2.00	435.00	261.00	10.00	164.00
Mean	3.04	3.44	3.76	3.42	3.70	3.14	3.41
Std. Dev	1.14	1.18	1.96	1.19	1.26	1.19	1.16
Minimum	0.98	1.09	2.38	1.15	0.82	1.29	0.71
Median	2.84	3.24	3.76	3.28	3.66	3.07	3.27
Maximum	7.21	7.43	5.15	6.75	8.20	5.07	6.26
Acute renal impairment / failure							
N	518.00	410.00	2.00	435.00	261.00	10.00	164.00
Mean	1.95	2.20	2.29	2.17	2.31	1.96	2.22
Std. Dev	0.71	0.77	1.71	0.76	0.79	0.61	0.80
Minimum	0.65	0.84	1.08	0.51	0.71	1.12	0.71
Median	1.78	2.12	2.29	2.09	2.17	1.86	2.09
Maximum	4.79	5.07	3.49	4.45	5.13	3.13	4.96

Table 23
AS Cohort Baseline Disease Risk Scores
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS after Entry into the Cohort
UK CPRD+THIN

Disease Risk Score	Specific First Anti-Inflammatory Prescription						
	Diclofenac	Ibuprofen	Indometacin	Naproxen	Other Non-Selective NSAIDs	Multiple	None
GI ulcers / bleeding							
N	2760.00	1180.00	588.00	1218.00	719.00	55.00	2016.00
Mean	1.51	1.59	1.58	1.49	1.64	1.57	1.65
Std. Dev	0.53	0.55	0.50	0.56	0.56	0.56	0.64
Minimum	-1.01	-0.50	0.12	-1.04	-0.04	0.55	-0.87
Median	1.48	1.58	1.57	1.47	1.65	1.45	1.64
Maximum	4.00	3.92	3.41	4.49	3.63	3.06	4.74
Vascular & Sudden / Unexplained Death							
N	2760.00	1180.00	588.00	1218.00	719.00	55.00	2016.00
Mean	2.88	3.19	2.90	2.81	3.14	2.77	3.30
Std. Dev	0.93	1.03	0.84	0.92	0.96	0.98	1.16
Minimum	0.69	0.74	0.87	0.68	0.76	0.82	0.69
Median	2.82	3.17	2.83	2.76	3.11	2.64	3.34
Maximum	6.17	5.90	5.61	5.97	6.55	5.48	6.98
Hypertension							
N	2760.00	1180.00	588.00	1218.00	719.00	55.00	2016.00
Mean	1.45	1.61	1.55	1.32	1.60	1.47	1.50
Std. Dev	0.88	0.98	0.84	0.78	1.01	0.81	1.11
Minimum	-11.39	-9.57	-0.08	-1.16	-9.68	0.03	-10.86
Median	1.37	1.51	1.45	1.26	1.61	1.37	1.42

Table 23
AS Cohort Baseline Disease Risk Scores
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS after Entry into the Cohort
UK CPRD+THIN

	Specific First Anti-Inflammatory Prescription						
Disease Risk Score	Diclofenac	Ibuprofen	Indometacin	Naproxen	Other Non-Selective NSAIDs	Multiple	None
Maximum	5.20	5.00	4.54	3.87	4.77	3.97	4.89
Congestive Heart Failure*							
N	2760.00	1180.00	588.00	1218.00	719.00	55.00	2016.00
Mean	3.31	3.66	3.36	3.25	3.63	3.21	3.89
Std. Dev	1.13	1.30	1.03	1.12	1.18	1.14	1.44
Minimum	0.89	0.44	1.00	0.75	1.03	1.16	0.62
Median	3.14	3.57	3.25	3.12	3.55	3.11	3.90
Maximum	8.22	9.36	7.08	6.59	8.09	6.57	8.88
Acute renal impairment / failure							
N	2760.00	1180.00	588.00	1218.00	719.00	55.00	2016.00
Mean	2.06	2.27	2.05	2.04	2.24	1.94	2.44
Std. Dev	0.73	0.83	0.65	0.70	0.80	0.76	0.91
Minimum	0.42	0.19	0.65	0.44	0.53	0.62	0.19
Median	1.96	2.20	1.96	1.95	2.13	1.96	2.42
Maximum	6.09	5.39	4.46	4.77	6.07	4.72	6.75

Table 23
AS Cohort Baseline Disease Risk Scores
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS after Entry into the Cohort
UK, Germany & France (IMS) Combined

Disease Risk Score	Specific First Anti-Inflammatory Prescription						
	Etoricoxib	Celecoxib	Lumiracoxib	Meloxicam	Rofecoxib	Valdecoxib	Etodolac
GI ulcers / bleeding							
N	562.00	439.00	10.00	373.00	175.00	22.00	28.00
Mean	1.08	1.09	1.64	1.11	1.17	1.05	1.19
Std. Dev	0.49	0.49	1.15	0.57	0.59	0.34	0.59
Minimum	0.11	0.32	0.83	0.23	0.34	0.56	0.56
Median	0.97	1.00	1.22	1.00	1.05	0.98	1.01
Maximum	4.83	5.15	4.72	4.86	4.41	1.73	3.42
Vascular & Sudden / Unexplained Death							
N	562.00	439.00	10.00	373.00	175.00	22.00	28.00
Mean	1.95	1.96	2.81	1.94	2.15	2.02	1.92
Std. Dev	0.84	0.81	1.24	0.85	1.05	0.67	0.84
Minimum	0.22	0.58	1.43	0.56	0.60	0.99	0.92
Median	1.77	1.82	2.53	1.73	1.87	1.79	1.82
Maximum	6.80	6.20	5.53	5.58	6.11	3.47	4.95
Hypertension							
N	562.00	439.00	10.00	373.00	175.00	22.00	28.00
Mean	2.17	2.10	2.88	2.06	2.46	2.32	1.79
Std. Dev	1.50	1.35	1.25	1.36	1.71	1.52	1.09
Minimum	0.17	0.60	1.30	0.46	0.51	0.85	0.81
Median	1.59	1.62	2.58	1.53	1.68	1.71	1.61
Maximum	8.38	7.21	5.04	6.91	6.54	6.00	6.64
Congestive Heart Failure*							

Table 23
AS Cohort Baseline Disease Risk Scores
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS after Entry into the Cohort
UK, Germany & France (IMS) Combined

Disease Risk Score	Specific First Anti-Inflammatory Prescription						
	Etoricoxib	Celecoxib	Lumiracoxib	Meloxicam	Rofecoxib	Valdecoxib	Etodolac
N	562.00	439.00	10.00	373.00	175.00	22.00	28.00
Mean	3.43	3.47	4.46	3.32	3.71	3.54	3.11
Std. Dev	1.29	1.23	1.25	1.27	1.78	0.97	0.95
Minimum	0.93	1.22	2.51	0.99	0.97	2.23	1.52
Median	3.18	3.29	4.11	3.00	3.29	3.38	3.17
Maximum	8.70	9.18	6.12	9.91	9.82	6.20	5.86
Acute renal impairment / failure							
N	562.00	439.00	10.00	373.00	175.00	22.00	28.00
Mean	1.57	1.55	1.90	1.49	1.61	1.60	1.49
Std. Dev	0.67	0.53	0.40	0.56	0.70	0.48	0.51
Minimum	0.39	0.50	1.24	0.41	0.43	1.00	0.83
Median	1.44	1.45	1.90	1.38	1.45	1.51	1.44
Maximum	6.17	5.47	2.40	5.45	6.60	3.01	3.25

Table 23
AS Cohort Baseline Disease Risk Scores
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS after Entry into the Cohort
UK, Germany & France (IMS) Combined

	Specific First Anti-Inflammatory Prescription						
Disease Risk Score	Diclofenac	Ibuprofen	Indometacin	Naproxen	Other Non-Selective NSAIDs	Multiple	None
GI ulcers / bleeding							
N	3750.00	2321.00	638.00	387.00	757.00	53.00	7548.00
Mean	1.08	1.05	1.08	1.03	1.05	1.10	1.04
Std. Dev	0.49	0.48	0.52	0.52	0.50	0.38	0.46
Minimum	0.07	0.08	0.16	0.28	0.26	0.50	-0.10
Median	0.99	0.97	0.99	0.93	0.97	1.07	0.98
Maximum	9.53	5.03	4.67	4.02	4.67	2.22	5.32
Vascular & Sudden / Unexplained Death							
N	3750.00	2321.00	638.00	387.00	757.00	53.00	7548.00
Mean	1.98	1.95	1.94	1.75	1.88	2.12	1.94
Std. Dev	0.87	0.89	0.81	0.76	0.73	1.03	0.84
Minimum	0.14	0.19	0.16	0.31	0.50	0.80	0.19
Median	1.78	1.78	1.76	1.65	1.72	1.83	1.78
Maximum	11.82	6.98	5.72	5.23	5.11	5.66	8.00
Hypertension							
N	3750.00	2321.00	638.00	387.00	757.00	53.00	7548.00
Mean	2.19	2.23	2.12	1.77	1.99	2.29	2.08
Std. Dev	1.49	1.54	1.40	1.17	1.30	1.43	1.38
Minimum	0.12	0.31	0.38	0.40	0.43	0.84	-0.17
Median	1.59	1.59	1.57	1.45	1.51	1.62	1.58

Table 23
AS Cohort Baseline Disease Risk Scores
(Assessed During the 6 Months Prior to Entry into the Cohort)
By Specific First Anti-Inflammatory Prescription for Treatment of AS after Entry into the Cohort
UK, Germany & France (IMS) Combined

	Specific First Anti-Inflammatory Prescription						
Disease Risk Score	Diclofenac	Ibuprofen	Indometacin	Naproxen	Other Non-Selective NSAIDs	Multiple	None
Maximum	8.29	7.85	6.14	7.33	6.58	5.73	7.76
Congestive Heart Failure*							
N	3750.00	2321.00	638.00	387.00	757.00	53.00	7548.00
Mean	3.41	3.36	3.39	2.98	3.30	3.56	3.41
Std. Dev	1.33	1.39	1.28	1.11	1.22	1.39	1.33
Minimum	0.14	0.69	0.69	0.73	0.87	1.58	0.24
Median	3.16	3.12	3.12	2.84	3.04	3.16	3.20
Maximum	10.80	10.14	9.65	7.34	9.59	8.52	10.74
Acute renal impairment / failure							
N	3750.00	2321.00	638.00	387.00	757.00	53.00	7548.00
Mean	1.56	1.52	1.53	1.39	1.48	1.58	1.52
Std. Dev	0.65	0.66	0.54	0.50	0.53	0.57	0.62
Minimum	0.11	0.30	0.39	0.34	0.36	0.73	0.18
Median	1.44	1.42	1.44	1.32	1.38	1.40	1.44
Maximum	10.22	6.98	5.25	3.82	5.64	3.17	7.02

10.2.11 Baseline Characteristics of Patients Prescribed Etoricoxib 'Off-Label'

As described in the protocol, an analysis was done using data for patients whose first course of non-steroidal anti-inflammatory therapy for AS was etoricoxib, celecoxib or etodolac 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 (in France, no patients were treated with etoricoxib for the period of this study). During this time period none of these three drugs had an approved indication for AS and patients in the AS cohort were presumably equally likely to have received any of these three drugs 'off-label'. Patients with approved indications for these drugs (OA, or RA for etoricoxib, celecoxib and etodolac, and gout for etoricoxib) are excluded from this analysis; it is assumed they received these drugs for those indications.

The baseline characteristics of this group overall (n=569) are shown in **Table 24**. Compared with the total cohort as described in **Section 10.2.3** Baseline Characteristics **(**see **Table 3)**, these patients are similar in age, gender distribution, BMI, and mean / median blood pressure values. A greater proportion of the 'off-label' patients entered the cohort before the COX-2 Urgent Safety Restriction (65.4% vs. 41.5%)

These data for the separate countries / databases (except for France, where no patients were treated with etoricoxib for this study period) are found in the **Annexes** specific to each under separate cover (**Table 24a** for UK CPRD + THIN, **Table 24b** for UK IMS, **Table 24c** for Germany IMS).

Table 24
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
Among Patients Whose First Anti-Inflammatory Prescription for Treatment of AS
After Entry Was Etoricoxib, Celecoxib or Etodolac 'Off-Label'[†]
UK (CPRD, THIN & IMS) and Germany (IMS)

Characteristic	N=569
Age (years)	
Mean	48.23
Std. Dev.	16.04
Minimum	15.00
Median	47.00
Maximum	99.00
Age<65 Years n (%)	471 (82.78)
Age≥65 Years n (%)	98 (17.22)
Gender: n (%)	
Male	354 (62.21)
Female	215 (37.79)
Smoking status (most recent): n (%) **	
Non-Smoker	175 (30.76)
Current Smoker	127 (22.32)
Ex-Smoker	65 (11.42)
Missing	202 (35.50)
Alcohol status (most recent): n (%) **	
Non-Alcohol Use	59 (10.37)
Current Alcohol Use	254 (44.64)
Ex-Alcohol Use	6 (1.05)
Missing	250 (43.94)
Body mass index (kg/m2) (most recent) **	
Mean	26.12
Std. Dev.	4.79
Minimum	16.10
Median	25.90
Maximum	45.30
Year of entry into cohort: n (%)	
1989	0 (0.00)
1990	2 (0.35)
1991	2 (0.35)
1992	1 (0.18)
1993	1 (0.18)
1994	2 (0.35)
1995	2 (0.35)
1996	4 (0.70)

Table 24
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
Among Patients Whose First Anti-Inflammatory Prescription for Treatment of AS
After Entry Was Etoricoxib, Celecoxib or Etodolac 'Off-Label'[†]
UK (CPRD, THIN & IMS) and Germany (IMS)

Characteristic	N=569
1997	4 (0.70)
1998	2 (0.35)
1999	5 (0.88)
2000	1 (0.18)
2001	20 (3.51)
2002	66 (11.60)
2003	115 (20.21)
2004	135 (23.73)
2005	95 (16.70)
2006	112 (19.68)
2007	0 (0.00)
2008	0 (0.00)
2009	0 (0.00)
2010	0 (0.00)
2011	0 (0.00)
2012	0 (0.00)
2013	0 (0.00)
Cohort entry before cox-2 Urgent Safety Restriction (17Feb05): n (%)	
Yes	372 (65.38)
No	197 (34.62)
Total number of prior health care encounters*	
Mean	6.09
Std. Dev.	5.87
Minimum	1.00
Median	4.00
Maximum	61.00
**Referral to Rheumatologist: n (%) ** **	
Yes	41 (7.21)
No	373 (65.55)
Missing	155 (27.24)
**X-ray of the sacrum or spine: n (%) ** **	
Yes	5 (0.88)
No	409 (71.88)
Missing	155 (27.24)
**Both Referral to Rheumatologist and X-ray of the sacrum or spine: n (%) ** **	
Yes	0 (0.00)

Table 24
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
Among Patients Whose First Anti-Inflammatory Prescription for Treatment of AS
After Entry Was Etoricoxib, Celecoxib or Etodolac 'Off-Label'[†]
UK (CPRD, THIN & IMS) and Germany (IMS)

Characteristic	N=569
No	414 (72.76)
Missing	155 (27.24)
Mean SBP (mmHg) (most recent) **	
Mean	130.70
Std. Dev.	16.80
Minimum	90.00
Median	130.00
Maximum	190.00
<120	82 (14.41)
120-139	164 (28.82)
≥140	129 (22.67)
Missing	194 (34.09)
Mean DBP (mmHg) (most recent) **	
Mean	78.07
Std. Dev.	9.47
Minimum	50.00
Median	80.00
Maximum	108.00
<80	168 (29.53)
80-89	159 (27.94)
≥90	48 (8.44)
Missing	194 (34.09)

[†] See methods. Includes patients from the UK and Germany whose first course of anti-inflammatory therapy for AS was etoricoxib, celecoxib or etodolac 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. Patients with common indications for the drugs other than AS (OA, RA, or gout for etoricoxib, OA or RA for celecoxib and etodolac) are excluded from this analysis.

* Total number of visits to GP and referrals to specialists in the 6 months prior to cohort entry

The group of patients prescribed etoricoxib 'off-label' as their first non-steroidal anti-inflammatory agent (n=218, **Table 25**) following entry into the cohort were similar to all patients whose first prescription for non-steroidal anti-inflammatory treatment after entry into the cohort was etoricoxib as described in **Section 10.2.3** Baseline Characteristics **(**see **Table 5)**, except that a greater proportion entered the cohort before the COX-2 Urgent Safety Restriction (51.4% vs. 12.7%)**.** For a given patient this may not have been their first ever treatment with a non-steroidal anti-inflammatory agent.

These data for the separate countries / databases (except for France, where no patients were treated with etoricoxib for this study period) are found in the **Annexes** specific to each under separate cover (**Table 25a** for UK CPRD + THIN, **Table 25b** for UK IMS, **Table 25c** for Germany IMS).

Table 25
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
Among Patients Whose First Anti-Inflammatory Prescription for Treatment of AS
After Entry Was Etoricoxib, Celecoxib or Etodolac 'Off-Label'[†]
UK (CPRD, THIN & IMS) and Germany (IMS)

Characteristic	Specific First Anti-Inflammatory Prescription		
	Etoricoxib N=218	Celecoxib N=282	Etodolac N=69
Age (years)			
Mean	45.99	49.53	49.99
Std. Dev.	15.65	15.92	17.14
Minimum	17.00	15.00	15.00
Median	45.00	49.50	51.00
Maximum	87.00	99.00	89.00
Age<65 Years n (%)	187 (85.78)	231 (81.91)	53 (76.81)
Age≥65 Years n (%)	31 (14.22)	51 (18.09)	16 (23.19)
Gender: n (%)			
Male	138 (63.30)	167 (59.22)	49 (71.01)
Female	80 (36.70)	115 (40.78)	20 (28.99)
Smoking status (most recent): n (%) **			
Non-Smoker	61 (27.98)	83 (29.43)	31 (44.93)
Current Smoker	52 (23.85)	57 (20.21)	18 (26.09)
Ex-Smoker	17 (7.80)	38 (13.48)	10 (14.49)
Missing	88 (40.37)	104 (36.88)	10 (14.49)
Alcohol status (most recent): n (%) **			
Non-Alcohol Use	19 (8.72)	31 (10.99)	9 (13.04)
Current Alcohol Use	89 (40.83)	123 (43.62)	42 (60.87)
Ex-Alcohol Use	2 (0.92)	4 (1.42)	0 (0.00)
Missing	108 (49.54)	124 (43.97)	18 (26.09)
Body mass index (kg/m2) (most recent) **			
Mean	26.14	26.30	25.34
Std. Dev.	4.82	4.78	4.75
Minimum	16.80	16.29	16.10
Median	26.05	26.05	25.20
Maximum	45.10	45.30	44.18
Year of entry into cohort: n (%)			
1989	0 (0.00)	0 (0.00)	0 (0.00)
1990	0 (0.00)	2 (0.71)	0 (0.00)
1991	0 (0.00)	2 (0.71)	0 (0.00)
1992	0 (0.00)	1 (0.35)	0 (0.00)

Table 25
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
Among Patients Whose First Anti-Inflammatory Prescription for Treatment of AS
After Entry Was Etoricoxib, Celecoxib or Etodolac 'Off-Label'[†]
UK (CPRD, THIN & IMS) and Germany (IMS)

Characteristic	Specific First Anti-Inflammatory Prescription		
	Etoricoxib N=218	Celecoxib N=282	Etodolac N=69
1993	0 (0.00)	1 (0.35)	0 (0.00)
1994	1 (0.46)	1 (0.35)	0 (0.00)
1995	0 (0.00)	2 (0.71)	0 (0.00)
1996	0 (0.00)	4 (1.42)	0 (0.00)
1997	2 (0.92)	2 (0.71)	0 (0.00)
1998	1 (0.46)	1 (0.35)	0 (0.00)
1999	1 (0.46)	4 (1.42)	0 (0.00)
2000	1 (0.46)	0 (0.00)	0 (0.00)
2001	5 (2.29)	14 (4.96)	1 (1.45)
2002	12 (5.50)	38 (13.48)	16 (23.19)
2003	34 (15.60)	68 (24.11)	13 (18.84)
2004	51 (23.39)	72 (25.53)	12 (17.39)
2005	47 (21.56)	35 (12.41)	13 (18.84)
2006	63 (28.90)	35 (12.41)	14 (20.29)
2007	0 (0.00)	0 (0.00)	0 (0.00)
2008	0 (0.00)	0 (0.00)	0 (0.00)
2009	0 (0.00)	0 (0.00)	0 (0.00)
2010	0 (0.00)	0 (0.00)	0 (0.00)
2011	0 (0.00)	0 (0.00)	0 (0.00)
2012	0 (0.00)	0 (0.00)	0 (0.00)
2013	0 (0.00)	0 (0.00)	0 (0.00)
Cohort entry before cox-2 Urgent Safety Restriction (17Feb05): n (%)			
Yes	112 (51.38)	217 (76.95)	43 (62.32)
No	106 (48.62)	65 (23.05)	26 (37.68)
Total number of prior health care encounters*			
Mean	6.26	5.59	7.59
Std. Dev.	6.13	5.38	6.67
Minimum	1.00	1.00	1.00
Median	5.00	4.00	6.00
Maximum	61.00	43.00	38.00
Referral to Rheumatologist: n (%) **			
Yes	12 (5.50)	21 (7.45)	8 (11.59)

Table 25
AS Cohort Baseline Characteristics
(Assessed During the 6 Months Prior to Entry into the Cohort)
Among Patients Whose First Anti-Inflammatory Prescription for Treatment of AS
After Entry Was Etoricoxib, Celecoxib or Etodolac 'Off-Label'†
UK (CPRD, THIN & IMS) and Germany (IMS)

Characteristic	Specific First Anti-Inflammatory Prescription		
	Etoricoxib N=218	Celecoxib N=282	Etodolac N=69
No	132 (60.55)	185 (65.60)	56 (81.16)
Missing	74 (33.94)	76 (26.95)	5 (7.25)
X-ray of the sacrum or spine: n (%) **			
Yes	0 (0.00)	3 (1.06)	2 (2.90)
No	144 (66.06)	203 (71.99)	62 (89.86)
Missing	74 (33.94)	76 (26.95)	5 (7.25)
Both Referral to Rheumatologist and X-ray of the sacrum or spine: n (%) **			
Yes	0 (0.00)	0 (0.00)	0 (0.00)
No	144 (66.06)	206 (73.05)	64 (92.75)
Missing	74 (33.94)	76 (26.95)	5 (7.25)
Mean SBP (mmHg) (most recent) **			
Mean	128.16	132.05	131.95
Std. Dev.	15.01	17.24	18.64
Minimum	96.00	90.00	90.00
Median	130.00	130.00	134.00
Maximum	163.00	190.00	170.00
<120	29 (13.30)	40 (14.18)	13 (18.84)
120-139	63 (28.90)	79 (28.01)	22 (31.88)
≥140	37 (16.97)	69 (24.47)	23 (33.33)
Missing	89 (40.83)	94 (33.33)	11 (15.94)
Mean DBP (mmHg) (most recent) **			
Mean	77.36	78.78	77.34
Std. Dev.	8.35	9.58	11.29
Minimum	59.00	55.00	50.00
Median	80.00	80.00	80.00
Maximum	108.00	105.00	104.00
<80	61 (27.98)	79 (28.01)	28 (40.58)
80-89	60 (27.52)	80 (28.37)	19 (27.54)
≥90	8 (3.67)	29 (10.28)	11 (15.94)
Missing	89 (40.83)	94 (33.33)	11 (15.94)

† See methods. Includes patients from the UK and Germany whose first course of anti-inflammatory therapy for AS was Etoricoxib, Celecoxib or Etodolac 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. Patients with common indications for the drugs other than AS (OA, RA, or gout for Etoricoxib, OA or RA for Celecoxib and Etodolac) are excluded from this analysis.
* Total number of visits to GP and referrals to specialists in the 6 months prior to cohort entry

Patients prescribed etoricoxib 'off-label' as their first non-steroidal anti-inflammatory agent following entry into the cohort (n=218, **Table 26**) overall had fewer baseline comorbidities than all patients whose first prescription for non-steroidal anti-inflammatory treatment after entry into the cohort was etoricoxib, as described in **Section 10.2.4** Baseline Medical History (see **Table 10**). For a given patient this may not have been their first ever treatment with a non-steroidal anti-inflammatory agent.

The same applies to patients to other baseline medical history (assessed during the period 6 to 12 months prior to entry into the cohort) among patients with at least one year of medical records (See **Table 27** and **Section 10.2.4** Baseline Medical History**, Table 11)**

These data for the separate countries / databases (except for France, where no patients were treated with etoricoxib for this study period) are found in the **Annexes** specific to each under separate cover (**Tables 26a and 27a** for UK CPRD + THIN, **Tables 26b and 27b** for UK IMS, **Tables 26c and 27c** for Germany IMS).

Table 26
AS Cohort Baseline Medical History
(Assessed During the 6 Months Prior to Entry into the Cohort)
Among Patients Whose First Anti-Inflammatory Prescription for Treatment of AS
After Entry Was Etoricoxib, Celecoxib or Etodolac 'Off-Label'[†]
(Patients with at Least One Year of Registration)
UK (CPRD, THIN & IMS) and Germany (IMS)

Characteristic	Specific First Anti-Inflammatory Prescription		
	Etoricoxib N=218	Celecoxib N=282	Etodolac N=69
Medical History[‡]: n (%)			
Osteoarthritis	0 (0.00)	0 (0.00)	0 (0.00)
Rheumatoid Arthritis	0 (0.00)	0 (0.00)	0 (0.00)
Gout	0 (0.00)	0 (0.00)	0 (0.00)
Arthritis NOS	17 (7.80)	16 (5.67)	6 (8.70)
GI PUB	2 (0.92)	3 (1.06)	0 (0.00)
MI	0 (0.00)	0 (0.00)	0 (0.00)
UAP	0 (0.00)	1 (0.35)	0 (0.00)
Acute or Subacute CHD (excluding MI or UAP)	2 (0.92)	1 (0.35)	1 (1.45)
Atherosclerotic Cardiovascular Disease	0 (0.00)	2 (0.71)	0 (0.00)
Ischemic CVD or TIA	0 (0.00)	0 (0.00)	0 (0.00)
Hemorrhagic CVD	0 (0.00)	0 (0.00)	0 (0.00)
DVT or PE	3 (1.38)	1 (0.35)	0 (0.00)
Edema	1 (0.46)	1 (0.35)	0 (0.00)
Renal Disease	2 (0.92)	0 (0.00)	0 (0.00)
Acute Renal Failure	0 (0.00)	0 (0.00)	0 (0.00)
Hypertension (diagnosis only)	18 (8.26)	16 (5.67)	4 (5.80)
CHF	1 (0.46)	0 (0.00)	0 (0.00)
IBD	3 (1.38)	6 (2.13)	0 (0.00)
PAD	1 (0.46)	0 (0.00)	0 (0.00)
Dyslipidemia	8 (3.67)	7 (2.48)	0 (0.00)
DM (diagnosis or medication)	8 (3.67)	9 (3.19)	4 (5.80)

[†] See methods. Includes patients from the UK and Germany whose first course of anti-inflammatory therapy for AS was etoricoxib, celecoxib or etodolac 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. Patients with common indications for the drugs other than AS (OA, RA, or gout for etoricoxib, OA or RA for celecoxib and etodolac) are excluded from this analysis.

[‡] NOS = Not Otherwise Specified; PUB = Perforation, Ulcer, Bleeding; MI = Myocardial Infarction; UAP = Unstable Angina Pectoris; CHD = Coronary Heart Disease; CVD = Cerebrovascular Disease; TIA = Transient Ischemic Attack; DVT = Deep Venous Thrombosis; PE = Pulmonary Embolism; CHF = Congestive Heart Failure or Left Ventricular Dysfunction; IBD = Inflammatory Bowel Disease; PAD = Peripheral Arterial Disease; DM = Diabetes Mellitus;

Table 27
AS Cohort Baseline Medical History
(Assessed During the Period 6 to 12 Months Prior to Entry into the Cohort)
(Patients with at Least One Year of Registration)
Among Patients Whose First Anti-Inflammatory Prescription for Treatment of AS
After Entry Was Etoricoxib, Celecoxib or Etodolac 'Off-Label'[†]
UK (CPRD, THIN & IMS) and Germany (IMS)

Characteristic	Specific First Anti-Inflammatory Prescription		
	Etoricoxib N=184	Celecoxib N=239	Etodolac N=60
Medical History[‡] n (%)			
Osteoarthritis	0 (0.00)	0 (0.00)	0 (0.00)
Rheumatoid Arthritis	0 (0.00)	0 (0.00)	0 (0.00)
Gout	0 (0.00)	0 (0.00)	0 (0.00)
Arthritis NOS	8 (4.35)	5 (2.09)	1 (1.67)
GI PUB	1 (0.54)	4 (1.67)	0 (0.00)
MI	1 (0.54)	0 (0.00)	0 (0.00)
UAP	0 (0.00)	1 (0.42)	0 (0.00)
Acute or Subacute CHD (excluding MI or UAP)	0 (0.00)	4 (1.67)	0 (0.00)
Atherosclerotic Cardiovascular Disease	0 (0.00)	0 (0.00)	0 (0.00)
Ischemic CVD or TIA	0 (0.00)	1 (0.42)	0 (0.00)
Hemorrhagic CVD	0 (0.00)	0 (0.00)	0 (0.00)
DVT or PE	1 (0.54)	1 (0.42)	0 (0.00)
Edema	2 (1.09)	0 (0.00)	0 (0.00)
Renal Disease	1 (0.54)	0 (0.00)	0 (0.00)
Acute Renal Failure	0 (0.00)	0 (0.00)	0 (0.00)
Hypertension (diagnosis only)	12 (6.52)	8 (3.35)	3 (5.00)
CHF	0 (0.00)	1 (0.42)	0 (0.00)
IBD	2 (1.09)	3 (1.26)	1 (1.67)
PAD	0 (0.00)	0 (0.00)	0 (0.00)
Dyslipidemia	4 (2.17)	3 (1.26)	1 (1.67)
DM (diagnosis or medication)	4 (2.17)	5 (2.09)	4 (6.67)

[†] See methods. Includes patients from the UK and Germany whose first course of anti-inflammatory therapy for AS was etoricoxib, celecoxib or etodolac 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. Patients with common indications for the drugs other than AS (OA, RA, or gout for etoricoxib, OA or RA for celecoxib and etodolac) are excluded from this analysis.

[‡] NOS = Not Otherwise Specified; PUB = Perforation, Ulcer, Bleeding; MI = Myocardial Infarction; UAP = Unstable Angina Pectoris; CHD = Coronary Heart Disease; CVD = Cerebrovascular Disease; TIA = Transient Ischemic Attack; DVT = Deep Venous Thrombosis; PE = Pulmonary Embolism; CHF = Congestive Heart Failure or Left Ventricular Dysfunction; IBD = Inflammatory Bowel Disease; PAD = Peripheral Arterial Disease; DM = Diabetes Mellitus;

Patients prescribed etoricoxib 'off-label' as their first non-steroidal anti-inflammatory agent following entry into the cohort (n=218) most frequently had a baseline history of prior etoricoxib use (n=85), followed by diclofenac (n=18) (**Table 28**). For a given patient this may not have been their first ever treatment with a non-steroidal anti-inflammatory agent.

Among the 85 patients with both baseline etoricoxib use and a first non-steroidal anti-inflammatory prescription following entry into the cohort for etoricoxib 'off-label', the mean (SD) baseline TDD of etoricoxib was 90.0 mg (18.1 mg), the median baseline TDD was 90 mg, and the range was 60-120 mg (**Table 28**). Note that for 30 of these 85 patients, etoricoxib TDD data were missing.

These data for the separate countries / databases (except for France, where no patients were treated with etoricoxib for this study period) are found in the **Annexes** specific to each under separate cover (**Table 28a** for UK CPRD + THIN, **Table 28b** for UK IMS, **Table 28c** for Germany IMS).

Table 28
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
Among Patients Whose First Anti-Inflammatory Prescription for Treatment of AS
After Entry Was Etoricoxib, Celecoxib or Etodolac 'Off-Label'[†]
UK (CPRD, THIN & IMS) and Germany (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription		
	Etoricoxib N=218	Celecoxib N=282	Etodolac N=69
COX-2 Selective Inhibitors			
Celecoxib			
n	0	125	2
Mean	.	250.57	300.00
Std. Dev.	.	93.62	141.42
Minimum	.	100.00	200.00
Median	.	200.00	300.00
Maximum	.	400.00	400.00
≤100mg [(n (%)]	0 (0.00)	2 (1.60)	0 (0.00)
>100-200mg [(n (%)]	0 (0.00)	62 (49.60)	1 (50.00)
>200-400mg [(n (%)]	0 (0.00)	24 (19.20)	1 (50.00)
>400mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	37 (29.60)	0 (0.00)
Etoricoxib			
n	85	1	1
Mean	90.00	90.00	90.00
Std. Dev.	18.26	.	.
Minimum	60.00	90.00	90.00
Median	90.00	90.00	90.00
Maximum	120.00	90.00	90.00
≤30mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
>30-60mg [(n (%)]	10 (11.76)	0 (0.00)	0 (0.00)
>60-90mg [(n (%)]	35 (41.18)	1 (100.00)	1 (100.00)
>90-120mg [(n (%)]	10 (11.76)	0 (0.00)	0 (0.00)
>120mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	30 (35.29)	0 (0.00)	0 (0.00)
Meloxicam			
n	1	0	0
Mean	7.50	.	.
Std. Dev.	.	.	.
Minimum	7.50	.	.
Median	7.50	.	.

Table 28
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
Among Patients Whose First Anti-Inflammatory Prescription for Treatment of AS
After Entry Was Etoricoxib, Celecoxib or Etodolac 'Off-Label'†
UK (CPRD, THIN & IMS) and Germany (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription		
	Etoricoxib N=218	Celecoxib N=282	Etodolac N=69
Maximum	7.50	.	.
≤7.5mg [(n (%)]	1 (100.00)	0 (0.00)	0 (0.00)
>7.5-15mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
>15mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
Rofecoxib			
n	2	3	2
Mean	.	25.00	37.50
Std. Dev.	.	0.00	.
Minimum	.	25.00	37.50
Median	.	25.00	37.50
Maximum	.	25.00	37.50
≤12.5mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
>12.5-25mg [(n (%)]	0 (0.00)	3 (100.00)	0 (0.00)
>25-50mg [(n (%)]	0 (0.00)	0 (0.00)	1 (50.00)
>50mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	2 (100.00)	0 (0.00)	1 (50.00)
Valdecoxib			
n	0	1	0
Mean	.	.	.
Std. Dev.	.	.	.
Minimum	.	.	.
Median	.	.	.
Maximum	.	.	.
≤10mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
>10-20mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
>20mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	1 (100.00)	0 (0.00)
Non-Selective NSAIDS			
Diclofenac			
n	18	11	4
Mean	141.07	140.00	150.00

Table 28
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
Among Patients Whose First Anti-Inflammatory Prescription for Treatment of AS
After Entry Was Etoricoxib, Celecoxib or Etodolac 'Off-Label'†
UK (CPRD, THIN & IMS) and Germany (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription		
	Etoricoxib N=218	Celecoxib N=282	Etodolac N=69
Std. Dev.	23.22	24.15	0.00
Minimum	75.00	75.00	150.00
Median	150.00	150.00	150.00
Maximum	150.00	150.00	150.00
≤50mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
>50-75mg [(n (%)]	1 (5.56)	1 (9.09)	0 (0.00)
>75-100mg [(n (%)]	1 (5.56)	0 (0.00)	0 (0.00)
>100-150mg [(n (%)]	12 (66.67)	9 (81.82)	4 (100.00)
>150mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	4 (22.22)	1 (9.09)	0 (0.00)
Etodolac			
n	0	0	31
Mean	.	.	600.00
Std. Dev.	.	.	0.00
Minimum	.	.	600.00
Median	.	.	600.00
Maximum	.	.	600.00
≤300mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
>300-600mg [(n (%)]	0 (0.00)	0 (0.00)	30 (96.77)
>600mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	1 (3.23)
Ibuprofen			
n	4	3	1
Mean	1200.00	1200.00	.
Std. Dev.	0.00	0.00	.
Minimum	1200.00	1200.00	.
Median	1200.00	1200.00	.
Maximum	1200.00	1200.00	.
≤400mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
>400-600mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
>600-800mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
>800-1200mg [(n (%)]	4 (100.00)	2 (66.67)	0 (0.00)

Table 28
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
Among Patients Whose First Anti-Inflammatory Prescription for Treatment of AS
After Entry Was Etoricoxib, Celecoxib or Etodolac 'Off-Label'†
UK (CPRD, THIN & IMS) and Germany (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription		
	Etoricoxib N=218	Celecoxib N=282	Etodolac N=69
>1200-1600mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
>1600-2000mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
>2000mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	1 (33.33)	1 (100.00)
Indomethacin			
n	1	0	0
Mean	75.00	.	.
Std. Dev.	.	.	.
Minimum	75.00	.	.
Median	75.00	.	.
Maximum	75.00	.	.
≤25mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
>25-50mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
>50-75mg [(n (%)]	1 (100.00)	0 (0.00)	0 (0.00)
>150mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
>75-150mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
Naproxen			
n	1	0	1
Mean	.	.	1000.00
Std. Dev.	.	.	.
Minimum	.	.	1000.00
Median	.	.	1000.00
Maximum	.	.	1000.00
≤250mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
>250-500mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
>500-1000mg [(n (%)]	0 (0.00)	0 (0.00)	1 (100.00)
>1000mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	1 (100.00)	0 (0.00)	0 (0.00)
Piroxicam			
n	0	1	0
Mean	.	20.00	.

Table 28
AS Cohort Baseline NSAIDs/COX-2 Selective Inhibitor Use Total Daily Dose
(Assessed During the 6 Months Prior to Entry into the Cohort)
Among Patients Whose First Anti-Inflammatory Prescription for Treatment of AS
After Entry Was Etoricoxib, Celecoxib or Etodolac 'Off-Label'†
UK (CPRD, THIN & IMS) and Germany (IMS)

Most Recent Baseline Drug Total Daily Dose	Specific First Anti-Inflammatory Prescription		
	Etoricoxib N=218	Celecoxib N=282	Etodolac N=69
Std. Dev.	.	.	.
Minimum	.	20.00	.
Median	.	20.00	.
Maximum	.	20.00	.
≤10mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
>10-20mg [(n (%)]	0 (0.00)	1 (100.00)	0 (0.00)
>20-30mg [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
>30mg* [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)
Missing [(n (%)]	0 (0.00)	0 (0.00)	0 (0.00)

† See methods. Includes patients from the UK and Germany whose first course of anti-inflammatory therapy for AS was etoricoxib, celecoxib or etodolac 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. Patients with common indications for the drugs other than AS (OA, RA, or gout for etoricoxib, OA or RA for celecoxib and etodolac) are excluded from this analysis.

* Indicates doses above the maximum recommended dose for AS, or for other indications if AS indication is not labeled

Baseline medication usage, other than non-steroidal anti-inflammatory therapy, among patients whose first non-steroidal anti-inflammatory treatment following entry in the AS cohort was etoricoxib, celecoxib or etodolac 'off-label' is shown in **Table 29**. For a given patient this may not have been their first ever treatment with a non-steroidal anti-inflammatory agent.

Those whose first prescription for a non-steroidal anti-inflammatory following entry into the cohort was etoricoxib 'off-label' (n=218) less frequently had a baseline history of narcotic pain medication and cardiovascular drug use than did those prescribed celecoxib or etodolac 'off-label'. They also less frequently had a baseline history of GI drugs and rheumatic disease treatments and more frequently had a history of oral contraceptive use than patients prescribed celecoxib 'off-label'. Otherwise those whose first prescription for a non-steroidal anti-inflammatory following entry into the cohort was etoricoxib 'off-label' had similar baseline medication use compared with those prescribed celecoxib or etodolac 'off-label'.

These data for the separate countries / databases (except for France, where no patients were treated with etoricoxib for this study period) are found in the **Annexes** specific to each under separate cover (**Table 29a** for UK CPRD + THIN, **Table 29b** for UK IMS, **Table 29c** for Germany IMS).

Table 29
AS Cohort Other Baseline Medication Use
(Assessed During the 6 Months Prior to Entry into the Cohort)
Among Patients Whose First Anti-Inflammatory Prescription for Treatment of AS
After Entry Was Etoricoxib, Celecoxib or Etodolac 'Off-Label'†
UK (CPRD, THIN & IMS) and Germany (IMS)

	Specific First Anti-Inflammatory Prescription		
	Etoricoxib N=218	Celecoxib N=282	Etodolac N=69
Narcotic Pain Medications	**64 (29.36)**	**125 (44.33)**	**31 (44.93)**
Rheumatic Disease Treatments	**20 (9.17)**	**34 (12.06)**	**9 (13.04)**
Disease Modifying Anti-Rheumatic Drugs	14 (6.42)	21 (7.45)	5 (7.25)
Oral Corticosteroids	10 (4.59)	15 (5.32)	7 (10.14)
Gastrointestinal Drugs	**52 (23.85)**	**98 (34.75)**	**13 (18.84)**
Histamine 2-Receptor Antagonists	8 (3.67)	18 (6.38)	5 (7.25)
Prostaglandin Analogues (incl. misoprostol + NSAID)	5 (2.29)	8 (2.84)	1 (1.45)
Proton Pump Inhibitors	44 (20.18)	76 (26.95)	8 (11.59)
Cardiovascular / Lipid-Modifying Medications	**40 (18.35)**	**60 (21.28)**	**17 (24.64)**
Cardiac Glycosides	1 (0.46)	3 (1.06)	0 (0.00)
Diuretics	16 (7.34)	18 (6.38)	5 (7.25)
Beta-Blockers	13 (5.96)	19 (6.74)	7 (10.14)
Angiotensin-Converting Enzyme Inhibitors	13 (5.96)	13 (4.61)	5 (7.25)
Angiotensin-II Receptor Antagonists	10 (4.59)	11 (3.90)	1 (1.45)
Nitrates	3 (1.38)	10 (3.55)	2 (2.90)
Calcium-Channel Blockers	10 (4.59)	14 (4.96)	5 (7.25)
Oral Anticoagulants	1 (0.46)	2 (0.71)	0 (0.00)
Oral Antiplatelet Drugs (Including Low Dose Aspirin)	11 (5.05)	23 (8.16)	5 (7.25)
Anion-Exchange Resins	1 (0.46)	0 (0.00)	0 (0.00)
Ezetimibe	1 (0.46)	0 (0.00)	0 (0.00)
Statins	12 (5.50)	23 (8.16)	7 (10.14)
Oral Contraceptives	**12 (5.50)**	**7 (2.48)**	**2 (2.90)**
Estrogen Replacement Therapy	**4 (1.83)**	**9 (3.19)**	**1 (1.45)**
Prescription Aspirin (≥300 mg/day)	**2 (0.92)**	**1 (0.35)**	**0 (0.00)**

† See methods. Includes patients from the UK and Germany whose first course of anti-inflammatory therapy for AS was etoricoxib, celecoxib or etodolac 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. Patients with common indications for the drugs other than AS (OA, RA, or gout for etoricoxib, OA or RA for celecoxib and etodolac) are excluded from this analysis.

* Total number of visits to GP and referrals to specialists in the 6 months prior to cohort entry

10.3 Outcome Data

This section describes the methods and results of comparative analyses of the clinical outcomes of hypertension and the combination of all vascular events (ischemic / thrombotic cardiac or peripheral vascular events and ischemic / thrombotic / haemorrhagic cerebrovascular events) plus sudden death, according to exposure to the study drugs of interest.

10.3.1 Incidences of Clinical Outcomes

There were 104 events in 92 men while currently exposed to etoricoxib. Ten men with more than one event included:

Pt. ID PPD on 90 mg with essential hypertension in PPD and acute MI in PPD
Pt. ID PPD on 90 mg with acute MI in PPD and essential hypertension in PPD
Pt. ID PPD on 90 mg with essential hypertension in PPD and two venous thromboemboli in PPD
Pt. ID PPD on 120 mg with unspecified essential hypertension in PPD and renal impairment in PPD
Pt. ID PPD on 120 mg with cerebral infarction and essential hypertension in PPD and a duodenal ulcer in PPD
Pt. ID PPD on 90 mg with gastric ulcer in PPD and essential hypertension in PPD
Pt. ID PPD on 120 mg with essential hypertension in PPD and a pulmonary embolus in PPD
Pt. ID PPD on 90 mg with essential hypertension and other cerebrovascular disease in PPD
Pt. ID PPD on 90 mg with essential hypertension in PPD and an acute MI in PPD
Pt. ID PPD on 90 mg with a cerebral infarction in PPD and an unspecified type of stroke in PPD

There were 73 events in 60 women while currently exposed to etoricoxib. Eleven women with more than one event included:
Pt. ID PPD on 60 mg of etoricoxib with unspecified renal failure in PPD and an occlusion/stenosis of the carotid artery in PPD
Pt. ID PPD on 90 mg of etoricoxib with acute MI in PPD and phlebitis/thrombosis of the leg in PPD
Pt. ID PPD on 90 mg with essential hypertension in PPD cerebral artery stenosis in PPD and a myocardial infarction in PPD
Pt. ID PPD on 240 mg with essential hypertension and pulmonary embolism in PPD
Pt. ID PPD on 90 mg with essential hypertension in PPD and bleeding gastric ulcer in PPD

Pt. ID PPD on 90 mg with unspecified types of stroke in PPD
Pt. ID PPD on 60 mg with essential hypertension in PPD gastric ulcer in PPD and heart failure in PPD
Pt. ID PPD on 90 mg with heart failure in PPD and essential hypertension in PPD
Pt. ID PPD on 90 mg with essential hypertension in PPD and an unspecified cerebral infarction in PPD
Pt. ID PPD on 90 mg with heart failure in PPD and essential hypertension in PPD
Pt. ID PPD on 90 mg with GI haemorrhage and melaena in PPD

The following listing includes patients with events while currently exposed to etoricoxib:

Patient ID	Age at time of event	Specific diagnosis	Date of event (dd/mm/yyyy)	Baseline medical history of same event	Duration of exposure (days)	Current dose (mg/day)
PPD						


PPD

PPD

PPD

PPD

PPD

PPD

PPD

The numbers (%s) and incidences / 1000 patient-years of the clinical outcomes of interest are shown for those cohort members without a baseline history of such events in **Table 30**. For a given outcome, the events shown are incident events in patients without a recorded diagnosis for that outcome during the 6 months prior to entry into the cohort.

In the following narrative, the incidence of clinical outcomes are described according to the following guidelines from the World Health Organization [Guidelines for Preparing Core Clinical Safety Information on Drugs – Report of the CIOMS Working Group III. Geneva, WHO, 1995. (Chapter 5, Good Safety Information Practices)]:

very common	≥100/1000py
common	<100 but ≥10/1000py
uncommon	<10 but ≥1/1000py
rare	<1 but ≥0.1/1000py
very rare	<0.1/1000py

The incidence of gastrointestinal events was uncommon (4.4/1000py). The incidence of any vascular event / sudden death was common (12.0/1000py); although that specifically for cardiac events (MI or unstable angina) was uncommon (3.6/1000py). Other events of interest occurred uncommonly: ischemic / thrombotic cerebrovascular events (the combination of ischemic strokes, strokes not classified as ischemic or haemorrhagic, and TIAs) at a rate of 4.3/1000py; peripheral thromboembolic vascular events (mostly DVT) at a rate of 4.3/1000py; acute renal failure / impairment at a rate of 1.8/1000py; and congestive heart failure at a rate of 4.2/1000py. Hypertension diagnoses were common at a rate of 17.4/1000py.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 30a** for UK CPRD + THIN, **Table 30b** for UK IMS, **Table 30c** for Germany IMS, and **Table 30d** for France IMS).

Table 30
Number (%) of Patients and Incidence of Clinical Outcomes Overall During Follow-up*
Patients Without A Medical History of the Respective Outcome
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Clinical Outcome	n/N (%)	Incidence /1000 py‡ (95% CI)
Gastrointestinal Ulcer, Perforation or Bleeding	**904/27174 (3.33)**	**4.37 (4.09, 4.66)**
Vascular Events	**2417/27381 (8.83)**	**12.00 (11.52, 12.48)**
Ischemic / Thrombotic Cardiac Events:	765/27378 (2.79)	3.64 (3.39, 3.91)
Acute Myocardial Infarction	527/27201 (1.94)	2.50 (2.29, 2.72)
Unstable Angina Pectoris	275/27312 (1.01)	1.30 (1.15, 1.46)
Ischemic / Thrombotic Cerebrovascular Events:	896/27380 (3.27)	4.27 (3.99, 4.56)
Ischemic Stroke	264/27316 (0.97)	1.24 (1.09, 1.40)
Stroke NOS†	475/27258 (1.74)	2.25 (2.05, 2.46)
Transient Ischemic Attack	374/27320 (1.37)	1.76 (1.59, 1.95)
Hemorrhagic Cerebrovascular Events:	72/27375 (0.26)	0.34 (0.26, 0.42)
Hemorrhagic Stroke	72/27375 (0.26)	0.34 (0.26, 0.42)
Thromboembolic Peripheral Vascular Events	903/27381 (3.30)	4.30 (4.03, 4.60)
Deep Venous Thrombosis	752/27250 (2.76)	3.59 (3.34, 3.85)
Pulmonary Embolism	162/27339 (0.59)	0.76 (0.65, 0.88)
Arterial Embolism / Thrombosis	48/27374 (0.18)	0.22 (0.16, 0.30)
Sudden / Unexplained Death	166/27381 (0.61)	0.77 (0.66, 0.90)
Acute Renal Failure	**388/27283 (1.42)**	**1.83 (1.65, 2.02)**
Congestive Heart Failure / Left Ventricular Dysfunction	**875/27108 (3.23)**	**4.20 (3.93, 4.49)**
Hypertension	**3063/24624 (12.44)**	**17.43 (16.82, 18.06)**

* Each row is not mutually exclusive; an individual patient may be counted in more than one row, but is counted only once ina given row.
† NOS=not otherwise specified as ischemic or hemorrhagic.
‡ py=person years

The number (%) of patients and incidence/1000 patient-years for each of the clinical outcomes of interest are shown for those cohort members with a baseline history of such events in **Table 31**. For a given outcome, the events shown are incident events in patients with a recorded diagnosis for that outcome during the 6 months prior to entry into the cohort.

As expected, the incidences are higher in this population than in those without a history of prior events. However, the numerators and/or denominators for many of the calculations are small, making the corresponding incident rates unstable. In addition, these rates may be especially prone to error because it is likely that the outcome diagnosis codes will repeatedly appear in the medical records of these patients, making it difficult to distinguish prevalent disease from new incident diagnoses.

These data for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Table 31a** for UK CPRD + THIN, **Table 31b** for UK IMS, **Table 31c** for Germany IMS, and **Table 31d** for France IMS).

Table 31
Number (%) of Patients and Incidence of Clinical Outcomes Overall During Follow-up*
Patients with a Medical History of the Respective Outcome
UK (CPRD, THIN & IMS), Germany (IMS) and France (IMS)

Clinical Outcome	n/N (%)	Incidence /1000 py‡ (95% CI)
Gastrointestinal Ulcer, Perforation or Bleeding	**73/207 (35.27)**	**61.47 (48.18, 77.29)**
Vascular Events	**256/592 (43.24)**	**99.25 (87.46, 112.18)**
Ischemic / Thrombotic Cardiac Events:	93/246 (37.80)	79.64 (64.28, 97.57)
Acute Myocardial Infarction	61/180 (33.89)	68.70 (52.55, 88.25)
Unstable Angina Pectoris	34/69 (49.28)	108.68 (75.26, 151.86)
Ischemic / Thrombotic Cerebrovascular Events:	101/206 (49.03)	114.75 (93.46, 139.43)
Ischemic Stroke	33/65 (50.77)	158.12 (108.84, 222.05)
Stroke NOS†	66/123 (53.66)	123.47 (95.49, 157.08)
Transient Ischemic Attack	23/61 (37.70)	78.32 (49.65, 117.52)
Hemorrhagic Cerebrovascular Events:	3/6 (50.00)	195.77 (40.37, 572.12)
Hemorrhagic Stroke	3/6 (50.00)	195.77 (40.37, 572.12)
Thromboembolic Peripheral Vascular Events	70/169 (41.42)	102.31 (79.75, 129.26)
Deep Venous Thrombosis	53/131 (40.46)	92.27 (69.12, 120.70)
Pulmonary Embolism	19/42 (45.24)	152.52 (91.83, 238.18)
Arterial Embolism / Thrombosis	2/7 (28.57)	58.30 (7.06, 210.61)
Sudden / Unexplained Death	0 (0.00)	.
Acute Renal Failure	**44/98 (44.90)**	**108.33 (78.71, 145.43)**
Congestive Heart Failure / Left Ventricular Dysfunction	**187/273 (68.50)**	**311.90 (268.80, 359.95)**
Hypertension	**1889/2757 (68.52)**	**272.97 (260.79, 285.56)**

* Each row is not mutually exclusive; an individual patient may be counted in more than one row, but is counted only once ina given row.
† NOS=not otherwise specified as ischemic or hemorrhagic.
‡ py=person years

10.4. Main results (Case Control Analyses)

10.4.1 Case-Control Analysis Methods Specific to the 2013 and Subsequent Year Reports

A matched case-control analysis was conducted using conditional logistic regression to assess the association of the drugs of interest with the outcomes of hypertension and the combination of all vascular events (ischemic / thrombotic cardiac or peripheral vascular events and ischemic / thrombotic / haemorrhagic cerebrovascular events) plus sudden death. The resulting measures of association between etoricoxib, the other drugs of interest, and the outcomes are odds ratios (OR) and associated 95% confidence intervals (CI) for each drug relative to no exposure to any non-steroidal anti-inflammatory treatment.

The date of diagnosis of an outcome was designated the index date for the case. Up to 5 controls were matched to each case on age, gender, calendar year of entry into the AS cohort, and database. Additionally, we also matched controls to cases according to history of the outcome during the baseline period (in the 6 months prior to entering the cohort); although not specified in the protocol, this was done in order to perform a secondary analysis to include patients with a prior history of the outcome in the case-control analysis. Controls were assigned an index date that was the same as the case to which he/she was matched.

The conditional logistic regression models (in addition to the matching factors as described) also controlled for the patients' baseline disease risk scores (DRS) for the outcome of interest (as described in **Section 10.2.10** Baseline Disease Risk Score. The quartile of number of etoricoxib prescriptions for the practice attended by the patient, derived from the total number of etoricoxib prescriptions over the entire study period for each practice (intended to address potential confounding by different etoricoxib prescribing habits among the GPs) was included in the logistic models. Removal of this variable from the models had no meaningful effect on the risk estimates, but the models with the quartile variables are included in this report for completeness.

The primary case-control analyses were done in patients without a prior history of the relevant outcome. A secondary analysis was done in all patients (with and without a medical history of the outcome). Interpretation of the secondary analysis results is 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 re-recording of a prior diagnosis addressed during a follow-up clinical encounter.

Using the logistic regression model, odds ratios (OR) and associated 95% confidence intervals (CI) for exposure to etoricoxib and the other study drugs of interest, vs. non-exposure as a common referent group, were calculated. The models were run separately for each outcome in each country / database combination (when possible). In this update, there were sufficient data to perform the modelling for two outcomes: hypertension and vascular event + sudden death. Both outcomes were available in the CPRD+THIN and Germany IMS databases only. In addition, as specified in the protocol, when possible,

two-level modelling was used to fit the data from different countries / databases to get a combined summary odds ratio. In this update, this could be done only with the outcome of hypertension and vascular event + sudden death using the separate estimates from CPRD+THIN and Germany IMS databases.

The protocol specified that a multiplicity adjustment would be applied to any statistically significant "signals" to control the false discovery rate (FDR) at a desired low level. However, due to limited data and the lack of significant drug effects this procedure was not applied in this analysis.

The protocol indicated sensitivity analyses would 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 analysing only the UK data (CPRD, THIN, and IMS), and comparing the results to an analysis using only the UK CPRD 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.

Sensitivity analyses were done for the outcome of hypertension since there were more than 700 cases of hypertension both before and after the URS. None of the above sensitivity analyses were done for other endpoints because there were insufficient data. An additional sensitivity analysis was done as follows:

- By assessing a baseline history of each outcome in the 12 months prior to cohort entry (as opposed to the default of 6 months prior to cohort entry). The longer baseline period would have the potential effect of more accurately classifying cases and controls with respect to their baseline history of the event of interest, thereby potentially reducing error and increasing precision.

The protocol also indicated we would examine the potential for immeasurable time bias (due to inpatient exposure to the drugs of interest that is not captured in the databases) by assessing the record for each case and his/her selected controls for hospital admissions within the 6 months prior to the index date. This was done for the UK CPRD+THIN and the Germany IMS case-control sets.

In the UK CPRD+THIN case-control sets, for the patients without a prior history of event there were:

- for hypertension: 46 of 2,222 patients were hospitalized in 6 months prior to their index date; of these 1 had current exposure to etoricoxib on the index date
- for vascular events, 19 of 1,158 patients were hospitalized in 6 months prior to their index date; of these none had current exposure to etoricoxib on the index date

In the Germany IMS case-control sets, for the patients without a prior history of event there were:

- for hypertension: 230 of 2,369 patients were hospitalized in 6 months prior to their index date; of these 6 had current exposure to etoricoxib on the index date
- for vascular events, 260 of 1713 patients were hospitalized in 6 months prior to their index date; of these 12 had current exposure to etoricoxib on the index date

Therefore, although the duration of those hospitalizations is unknown, the potential for immeasurable time bias in the analysis of the UK CPRD+THIN databases is effectively ruled out.

10.4.2 Hypertension

Overall, in the primary analysis population (the subset of the cohort without a history of hypertension in the 6 months before entry into the AS cohort) there were a total of 3,066 hypertension cases and 14,926 controls from all the databases combined. Seven hundred forty-four (24.3%) of the cases and 3,001 (20.1%) of the controls were currently exposed to an NSAID or COX-2 inhibitor at the time of diagnosis. There were 1,316 cases from UK CPRD+THIN, 180 from UK IMS, 1,371 from Germany IMS, and 199 from France IMS. There were 6,434 controls from UK CPRD+THIN, 767 from UK IMS, 6,786 from Germany IMS, and 939 from France IMS.

10.4.2.1 Baseline Characteristics of hypertension cases and controls

Baseline characteristics (assessed during the 6 months prior to entry into the AS cohort) for the primary analysis cases and controls are shown for patients in the CPRD+THIN databases, the UK IMS database, the Germany IMS database, and the France IMS database in **Tables 32a, 32b, 32c,** and **32d**, respectively. As mentioned previously, the prevalence of baseline medical history diagnoses and baseline medication use may be lower than expected given the relatively short baseline assessment period (the 6 months prior to entry into the AS cohort).

For the patients from the UK CPRD+THIN databases, the cases were statistically significantly ($p<0.05$) more likely to have higher mean baseline systolic and diastolic blood pressures and to have used DMARDS than the controls. Cases also had statistically significantly higher mean baseline hypertension disease RS. Controls were statistically significantly more likely to have more prior medical encounters, to have CHF and DM and to have used various cardiovascular medications than cases (**Table 32a**).

For the patients from the UK IMS database, cases had statistically significantly ($p<0.05$) more prior health encounters and were more likely to be female than the controls. (**Table 32b**).

For the patients from the Germany IMS database, cases had statistically significantly ($p<0.05$) higher BMI and more health care encounters than controls. They were statistically significantly more likely to have a baseline history of MI, acute or subacute CHD, CHF, edema, IBD, acute renal failure, and diabetes mellitus and to use baseline non-selective NSAIDs, proton pump inhibitors, and a variety of cardiovascular medications. Cases also had statistically significantly higher mean baseline hypertension disease RS (**Table 32c**).

For the patients from the France IMS database, cases were statistically significantly ($p<0.05$) more likely to occur before the Urgent Safety Restriction than controls. They were more likely to use cardiovascular medications than were the controls. Cases also had statistically significantly higher mean baseline hypertension disease RS (**Table 32d**).

Table 32a (THIN/CPRD UK)
Baseline Characteristics for Hypertension Cases and Controls
(Assessed During the Six Months Prior to Cohort Entry Without History)

Baseline Characteristics	Cases N=1,316	Control N=6,434	p-value
Age (years)			
Mean (sd)	54.21 (12.56)	54.68 (12.01)	0.2129
Gender: n (%)			
Male	893 (67.86)	4,407 (68.50)	0.6500
Female	423 (32.14)	2,027 (31.50)	
Smoking status (most recent): n (%) **			
Non-Smoker	539 (40.96)	2,868 (44.58)	0.0003
Current Smoker	309 (23.48)	1,512 (23.50)	
Ex-Smoker	208 (15.81)	1,081 (16.80)	
Missing	260 (19.76)	973 (15.12)	
Alcohol status (most recent): n (%) **			
Non-Alcohol Use	181 (13.75)	777 (12.08)	0.0007
Current Alcohol Use	760 (57.75)	4,078 (63.38)	
Ex-Alcohol Use	12 (0.91)	78 (1.21)	
Missing	363 (27.58)	1,501 (23.33)	
Body mass index (kg/m2) (most recent) **			
Mean (sd)	27.40 (4.82)	27.59 (4.90)	0.2432
Cohort entry before cox-2 Urgent Safety Restriction (17Feb05): n (%)			
Yes	1,070 (81.31)	5,198 (80.79)	0.6636
No	246 (18.69)	1,236 (19.21)	
Total number of prior health care encounters*			
Mean (sd)	5.83 (4.95)	6.20 (5.03)	0.0161
Referral to Rheumatologist: n (%) **			
Yes	145 (11.02)	725 (11.27)	0.7935
No	1,171 (88.98)	5,709 (88.73)	
X-ray of the sacrum or spine: n (%) **			
Yes	42 (3.19)	226 (3.51)	0.5613
No	1,274 (96.81)	6,208 (96.49)	
Both Referral to Rheumatologist and X-ray of the sacrum or spine: n (%) **			
Yes	5 (0.38)	35 (0.54)	0.4492
No	1,311 (99.62)	6,399 (99.46)	
Blood pressure (most recent) (mmHg)			
Mean (sd) Systolic	140.80 (18.45)	138.20 (17.41)	<.0001
Mean (sd) Diastolic	83.10 (9.98)	81.83 (9.57)	<.0001
Medical History†: n (%)			
Osteoarthritis	92 (6.99)	482 (7.49)	0.5275

Table 32a (THIN/CPRD UK)
Baseline Characteristics for Hypertension Cases and Controls
(Assessed During the Six Months Prior to Cohort Entry Without History)

Baseline Characteristics	Cases N=1,316	Control N=6,434	p-value
Rheumatoid Arthritis	5 (0.38)	36 (0.56)	0.4132
Gout	3 (0.23)	27 (0.42)	0.3076
Arthritis NOS	55 (4.18)	216 (3.36)	0.1390
GI PUB	13 (0.99)	42 (0.65)	0.1871
MI	3 (0.23)	17 (0.26)	0.8133
UAP		5 (0.08)	0.5965
Acute or Subacute CHD (excluding MI or UAP)	16 (1.22)	127 (1.97)	0.0626
Atherosclerotic Cardiovascular Disease		1 (0.02)	1.0000
Ischemic CVD or TIA	5 (0.38)	22 (0.34)	0.8312
DVT or PE	1 (0.08)	5 (0.08)	1.0000
Renal Disease	2 (0.15)	14 (0.22)	0.6328
Acute Renal Failure		9 (0.14)	0.3727
CHF	2 (0.15)	38 (0.59)	0.0430
IBD	13 (0.99)	41 (0.64)	0.1636
PAD	1 (0.08)	15 (0.23)	0.2525
Dyslipidemia	13 (0.99)	88 (1.37)	0.2682
DM (diagnosis or medication)	60 (4.56)	406 (6.31)	0.0149
Medications: n (%)			
Anti-inflammatory Drugs	643 (48.86)	2,998 (46.60)	0.1338
Non-selective NSAID	556 (42.25)	2,607 (40.52)	0.2446
COX-2 selective inhibitor	87 (6.61)	391 (6.08)	0.4633
Narcotic Pain Medications	579 (44.00)	2,779 (43.19)	0.5915
Rheumatic Disease Treatments	150 (11.40)	597 (9.28)	0.0176
Disease Modifying Anti-Rheumatic Drugs	104 (7.90)	364 (5.66)	0.0018
Oral Corticosteroids	60 (4.56)	300 (4.66)	0.8709
Gastrointestinal Drugs	366 (27.81)	1,732 (26.92)	0.5069
Histamine 2-Receptor Antagonists	107 (8.13)	534 (8.30)	0.8393
Prostaglandin Analogues (incl. misoprostol + NSAID)	82 (6.23)	368 (5.72)	0.4698
Proton Pump Inhibitors	210 (15.96)	1,042 (16.20)	0.8309
Other Ulcer-healing Drugs	1 (0.08)	4 (0.06)	1.0000
Cardiovascular / Lipid-Modifying Medications	407 (30.93)	2,934 (45.60)	<.0001
Cardiac Glycosides	10 (0.76)	57 (0.89)	0.6527
Diuretics	137 (10.41)	1,144 (17.78)	<.0001
Beta-Blockers	150 (11.40)	1,168 (18.15)	<.0001
Angiotensin-Converting Enzyme Inhibitors	114 (8.66)	1,009 (15.68)	<.0001
Angiotensin-II Receptor Antagonists	29 (2.20)	280 (4.35)	0.0003

Table 32a (THIN/CPRD UK)
Baseline Characteristics for Hypertension Cases and Controls
(Assessed During the Six Months Prior to Cohort Entry Without History)

Baseline Characteristics	Cases N=1,316	Control N=6,434	p-value
Nitrates	48 (3.65)	329 (5.11)	0.0243
Calcium-Channel Blockers	113 (8.59)	1,012 (15.73)	<.0001
Oral Anticoagulants	15 (1.14)	110 (1.71)	0.1349
Oral Antiplatelet Drugs (Including Low Dose Aspirin)	105 (7.98)	736 (11.44)	0.0002
Anion-Exchange Resins	2 (0.15)	4 (0.06)	0.2708
Ezetimibe	2 (0.15)	28 (0.44)	0.1317
Fibrates	6 (0.46)	41 (0.64)	0.4402
Statins	100 (7.60)	820 (12.74)	<.0001
Oral Contraceptives	9 (0.68)	28 (0.44)	0.2330
Estrogen Replacement Therapy	44 (3.34)	240 (3.73)	0.4963
Prescription Aspirin (≥300 mg/day)	11 (0.84)	84 (1.31)	0.1583
Hypertension Disease Risk Score			
Mean (sd)	2.01 (0.76)	1.92 (0.73)	<.0001

* Total number of visits to GP and referrals to specialists in the 6 months prior to cohort entry

† NOS = Not Otherwise Specified; PUB = Perforation, Ulcer, Bleeding; MI = Myocardial Infarction; UAP = Unstable Angina Pectoris; CHD = Coronary Heart Disease; CVD = Cerebrovascular Disease; TIA = Transient Ischemic Attack; DVT = Deep Venous Thrombosis; PE = Pulmonary Embolism; CHF = Congestive Heart Failure or Left Ventricular Dysfunction; IBD = Inflammatory Bowel Disease; PAD = Peripheral Arterial Disease; DM = Diabetes Mellitus;

Table 32b (IMS-UK)
Baseline Characteristics for Hypertension Cases and Controls
(Assessed During the Six Months Prior to Cohort Entry Without History)

Baseline Characteristics	Cases N=180	Control N=767	p-value
Age (years)			
Mean (sd)	50.12 (13.83)	50.46 (12.34)	0.7581
Gender: n (%)			
Male	138 (76.67)	638 (83.18)	0.0409
Female	42 (23.33)	129 (16.82)	
Body mass index (kg/m2) (most recent) **			
Mean (sd)	28.62 (6.11)	29.22 (6.11)	0.2613
Cohort entry before cox-2 Urgent Safety Restriction (17Feb05): n (%)			
Yes	163 (90.56)	690 (89.96)	0.8102
No	17 (9.44)	77 (10.04)	
Total number of prior health care encounters*			
Mean (sd)	3.83 (4.69)	2.96 (3.25)	0.0192
Medical History†: n (%)			
Osteoarthritis	5 (2.78)	11 (1.43)	0.2081
Rheumatoid Arthritis	2 (1.11)	1 (0.13)	0.0943
Gout		2 (0.26)	1.0000
Arthritis NOS	8 (4.44)	23 (3.00)	0.3266
GI PUB	1 (0.56)	13 (1.69)	0.2543
MI		5 (0.65)	0.5899
Acute or Subacute CHD (excluding MI or UAP)	2 (1.11)	8 (1.04)	1.0000
Atherosclerotic Cardiovascular Disease	2 (1.11)	9 (1.17)	1.0000
DVT or PE	1 (0.56)	2 (0.26)	0.4691
Edema	1 (0.56)	4 (0.52)	1.0000
Renal Disease	2 (1.11)		0.0360
CHF	1 (0.56)	2 (0.26)	0.4691
IBD	4 (2.22)	10 (1.30)	0.3183
Dyslipidemia	2 (1.11)	1 (0.13)	0.0943
DM (diagnosis or medication)	5 (2.78)	20 (2.61)	0.8980
Medications: n (%)			
Anti-inflammatory Drugs	81 (45.00)	298 (38.85)	0.1298
Non-selective NSAID	70 (38.89)	263 (34.29)	0.2448
COX-2 selective inhibitor	11 (6.11)	35 (4.56)	0.3846
Narcotic Pain Medications	4 (2.22)	12 (1.56)	0.5378
Rheumatic Disease Treatments	9 (5.00)	46 (6.00)	0.6066
Disease Modifying Anti-Rheumatic Drugs	6 (3.33)	30 (3.91)	0.7151
Oral Corticosteroids	3 (1.67)	24 (3.13)	0.2887

Table 32b (IMS-UK)
Baseline Characteristics for Hypertension Cases and Controls (Assessed During the Six Months Prior to Cohort Entry Without History)

Baseline Characteristics	Cases N=180	Control N=767	p-value
Gastrointestinal Drugs	20 (11.11)	106 (13.82)	0.3355
Histamine 2-Receptor Antagonists	9 (5.00)	46 (6.00)	0.6066
Prostaglandin Analogues (incl. misoprostol + NSAID)	4 (2.22)	6 (0.78)	0.1029
Proton Pump Inhibitors	10 (5.56)	57 (7.43)	0.3770
Cardiovascular / Lipid-Modifying Medications	21 (11.67)	119 (15.51)	0.1905
Cardiac Glycosides		1 (0.13)	1.0000
Diuretics	9 (5.00)	37 (4.82)	0.9213
Beta-Blockers	1 (0.56)		0.1901
Angiotensin-Converting Enzyme Inhibitors		5 (0.65)	0.5899
Angiotensin-II Receptor Antagonists	6 (3.33)	61 (7.95)	0.0296
Calcium-Channel Blockers	4 (2.22)	9 (1.17)	0.2850
Oral Anticoagulants		2 (0.26)	1.0000
Oral Antiplatelet Drugs (Including Low Dose Aspirin)	8 (4.44)	20 (2.61)	0.1904
Ezetimibe		4 (0.52)	1.0000
Fibrates	1 (0.56)	1 (0.13)	0.3442
Statins	8 (4.44)	22 (2.87)	0.2772
Oral Contraceptives	5 (2.78)	5 (0.65)	0.0260
Hypertension Disease Risk Score			
Mean (sd)	2.15 (0.60)	2.10 (0.54)	0.3502

* Total number of visits to GP and referrals to specialists in the 6 months prior to cohort entry

† NOS = Not Otherwise Specified; PUB = Perforation, Ulcer, Bleeding; MI = Myocardial Infarction; UAP = Unstable Angina Pectoris; CHD = Coronary Heart Disease; CVD = Cerebrovascular Disease; TIA = Transient Ischemic Attack; DVT = Deep Venous Thrombosis; PE = Pulmonary Embolism; CHF = Congestive Heart Failure or Left Ventricular Dysfunction; IBD = Inflammatory Bowel Disease; PAD = Peripheral Arterial Disease; DM = Diabetes Mellitus;

Table 32c (IMS-Germany)
Baseline Characteristics for Hypertension Cases and Controls
(Assessed During the Six Months Prior to Cohort Entry Without History)

Baseline Characteristics	Cases N=1,371	Control N=6,786	p-value
Age (years)			
Mean (sd)	55.59 (13.41)	55.42 (12.96)	0.6636
Gender: n (%)			
Male	885 (64.55)	4,391 (64.71)	0.9126
Female	486 (35.45)	2,395 (35.29)	
Smoking status (most recent): n (%) **			
Non-Smoker	114 (8.32)	531 (7.82)	0.7750
Current Smoker	81 (5.91)	434 (6.40)	
Ex-Smoker	41 (2.99)	184 (2.71)	
Missing	1,135 (82.79)	5,637 (83.07)	
Body mass index (kg/m2) (most recent) **			
Mean (sd)	28.54 (4.96)	27.68 (4.64)	0.0001
Cohort entry before cox-2 Urgent Safety Restriction (17Feb05): n (%)			
Yes	686 (50.04)	3,350 (49.37)	0.6508
No	685 (49.96)	3,436 (50.63)	
Total number of prior health care encounters*			
Mean (sd)	3.93 (2.95)	3.61 (3.02)	0.0004
Medical History†: n (%)			
Osteoarthritis	61 (4.45)	236 (3.48)	0.0798
Rheumatoid Arthritis	60 (4.38)	260 (3.83)	0.3431
Gout	27 (1.97)	96 (1.41)	0.1243
Arthritis NOS	155 (11.31)	828 (12.20)	0.3527
GI PUB	24 (1.75)	125 (1.84)	0.8175
MI	26 (1.90)	64 (0.94)	0.0021
UAP	11 (0.80)	44 (0.65)	0.5252
Acute or Subacute CHD (excluding MI or UAP)	112 (8.17)	376 (5.54)	0.0002
Atherosclerotic Cardiovascular Disease	12 (0.88)	37 (0.55)	0.1492
Ischemic CVD or TIA	14 (1.02)	68 (1.00)	0.9485
DVT or PE	20 (1.46)	81 (1.19)	0.4181
Edema	11 (0.80)	27 (0.40)	0.0449
Renal Disease	36 (2.63)	146 (2.15)	0.2781
Acute Renal Failure	14 (1.02)	36 (0.53)	0.0338
CHF	36 (2.63)	120 (1.77)	0.0345
IBD	35 (2.55)	105 (1.55)	0.0089
PAD	17 (1.24)	84 (1.24)	0.9948
Dyslipidemia	158 (11.52)	664 (9.78)	0.0510

Table 32c (IMS-Germany)
Baseline Characteristics for Hypertension Cases and Controls
(Assessed During the Six Months Prior to Cohort Entry Without History)

Baseline Characteristics	Cases N=1,371	Control N=6,786	p-value
DM (diagnosis or medication)	142 (10.36)	565 (8.33)	0.0148
Medications: n (%)			
Anti-inflammatory Drugs	551 (40.19)	2,464 (36.31)	0.0066
Non-selective NSAID	479 (34.94)	2,163 (31.87)	0.0270
COX-2 selective inhibitor	72 (5.25)	301 (4.44)	0.1871
Narcotic Pain Medications	121 (8.83)	552 (8.13)	0.3961
Rheumatic Disease Treatments	129 (9.41)	561 (8.27)	0.1657
Disease Modifying Anti-Rheumatic Drugs	57 (4.16)	220 (3.24)	0.0878
Oral Corticosteroids	97 (7.08)	437 (6.44)	0.3856
Gastrointestinal Drugs	258 (18.82)	914 (13.47)	<.0001
Histamine 2-Receptor Antagonists	46 (3.36)	158 (2.33)	0.0264
Prostaglandin Analogues (incl. misoprostol + NSAID)	14 (1.02)	61 (0.90)	0.6654
Proton Pump Inhibitors	197 (14.37)	719 (10.60)	<.0001
Other Ulcer-healing Drugs	9 (0.66)	31 (0.46)	0.3345
Cardiovascular / Lipid-Modifying Medications	441 (32.17)	1,283 (18.91)	<.0001
Cardiac Glycosides	32 (2.33)	118 (1.74)	0.1346
Diuretics	113 (8.24)	228 (3.36)	<.0001
Beta-Blockers	78 (5.69)	150 (2.21)	<.0001
Angiotensin-Converting Enzyme Inhibitors	82 (5.98)	171 (2.52)	<.0001
Angiotensin-II Receptor Antagonists	154 (11.23)	308 (4.54)	<.0001
Nitrates	17 (1.24)	51 (0.75)	0.0696
Calcium-Channel Blockers	66 (4.81)	232 (3.42)	0.0120
Oral Anticoagulants	15 (1.09)	22 (0.32)	0.0001
Oral Antiplatelet Drugs (Including Low Dose Aspirin)	71 (5.18)	236 (3.48)	0.0025
Anion-Exchange Resins	1 (0.07)	7 (0.10)	1.0000
Ezetimibe	2 (0.15)	3 (0.04)	0.1989
Fibrates	11 (0.80)	54 (0.80)	0.9801
Statins	105 (7.66)	343 (5.05)	0.0001
Nicotinic Acid	17 (1.24)	63 (0.93)	0.2856
Oral Contraceptives	11 (0.80)	30 (0.44)	0.0854
Estrogen Replacement Therapy	4 (0.29)	30 (0.44)	0.4307
Prescription Aspirin (≥300 mg/day)	2 (0.15)	14 (0.21)	0.6446
Hypertension Disease Risk Score			
Mean (sd)	2.78 (1.08)	2.50 (0.93)	<.0001

* Total number of visits to GP and referrals to specialists in the 6 months prior to cohort entry

† NOS = Not Otherwise Specified; PUB = Perforation, Ulcer, Bleeding; MI = Myocardial Infarction; UAP = Unstable Angina Pectoris; CHD = Coronary Heart Disease; CVD = Cerebrovascular Disease; TIA = Transient Ischemic Attack; DVT = Deep Venous Thrombosis; PE = Pulmonary Embolism; CHF = Congestive Heart Failure or Left Ventricular Dysfunction; IBD = Inflammatory Bowel Disease; PAD = Peripheral Arterial Disease; DM = Diabetes Mellitus;

Table 32d (IMS-France)
Baseline Characteristics for Hypertension Cases and Controls
(Assessed During the Six Months Prior to Cohort Entry Without History)

Baseline Characteristics	Cases N=199	Control N=939	p-value
Age (years)			
Mean (sd)	54.77 (12.96)	54.97 (11.64)	0.8419
Gender: n (%)			
Male	106 (53.27)	498 (53.04)	0.9527
Female	93 (46.73)	441 (46.96)	
Body mass index (kg/m2) (most recent) **			
Mean (sd)			
Cohort entry before cox-2 Urgent Safety Restriction (17Feb05): n (%)			
Yes	77 (38.69)	294 (31.31)	0.0435
No	122 (61.31)	645 (68.69)	
Total number of prior health care encounters*			
Mean (sd)	3.45 (2.48)	3.41 (2.52)	0.8608
Medical History†: n (%)			
Osteoarthritis	3 (1.51)	10 (1.06)	0.4846
Rheumatoid Arthritis	7 (3.52)	42 (4.47)	0.5465
Gout	2 (1.01)		0.0305
Arthritis NOS	31 (15.58)	112 (11.93)	0.1582
GI PUB	1 (0.50)	4 (0.43)	1.0000
Acute or Subacute CHD (excluding MI or UAP)	1 (0.50)	9 (0.96)	1.0000
Atherosclerotic Cardiovascular Disease	1 (0.50)	4 (0.43)	1.0000
DVT or PE		3 (0.32)	1.0000
Edema	1 (0.50)	1 (0.11)	0.3193
Renal Disease	3 (1.51)	8 (0.85)	0.4188
CHF	2 (1.01)	3 (0.32)	0.2120
IBD	3 (1.51)	10 (1.06)	0.4846
PAD	1 (0.50)	3 (0.32)	0.5370
Dyslipidemia	11 (5.53)	32 (3.41)	0.1543
DM (diagnosis or medication)	19 (9.55)	61 (6.50)	0.1261
Medications: n (%)			
Anti-inflammatory Drugs	13 (6.53)	44 (4.69)	0.2779
Non-selective NSAID	11 (5.53)	37 (3.94)	0.3116
COX-2 selective inhibitor	2 (1.01)	7 (0.75)	0.6612
Narcotic Pain Medications	1 (0.50)	3 (0.32)	0.5370
Rheumatic Disease Treatments	39 (19.60)	185 (19.70)	0.9733
Disease Modifying Anti-Rheumatic Drugs	3 (1.51)	31 (3.30)	0.1770
Oral Corticosteroids	38 (19.10)	170 (18.10)	0.7425

Table 32d (IMS-France)
Baseline Characteristics for Hypertension Cases and Controls
(Assessed During the Six Months Prior to Cohort Entry Without History)

Baseline Characteristics	Cases N=199	Control N=939	p-value
Gastrointestinal Drugs	93 (46.73)	402 (42.81)	0.3107
Histamine 2-Receptor Antagonists	2 (1.01)	6 (0.64)	0.6349
Prostaglandin Analogues (incl. misoprostol + NSAID)	4 (2.01)	11 (1.17)	0.3461
Proton Pump Inhibitors	89 (44.72)	382 (40.68)	0.2930
Other Ulcer-healing Drugs	2 (1.01)	16 (1.70)	0.4729
Cardiovascular / Lipid-Modifying Medications	72 (36.18)	202 (21.51)	<.0001
Cardiac Glycosides	2 (1.01)	4 (0.43)	0.2830
Diuretics	18 (9.05)	54 (5.75)	0.0829
Beta-Blockers	7 (3.52)	18 (1.92)	0.1617
Angiotensin-Converting Enzyme Inhibitors	9 (4.52)	25 (2.66)	0.1615
Angiotensin-II Receptor Antagonists	39 (19.60)	80 (8.52)	<.0001
Calcium-Channel Blockers	8 (4.02)	23 (2.45)	0.2163
Oral Anticoagulants	1 (0.50)	2 (0.21)	0.4385
Oral Antiplatelet Drugs (Including Low Dose Aspirin)	10 (5.03)	46 (4.90)	0.9404
Anion-Exchange Resins	1 (0.50)	2 (0.21)	0.4385
Fibrates	10 (5.03)	31 (3.30)	0.2359
Statins	1 (0.50)	5 (0.53)	1.0000
Nicotinic Acid		8 (0.85)	0.3637
Oral Contraceptives	4 (2.01)	15 (1.60)	0.6799
Hypertension Disease Risk Score			
Mean (sd)	2.03 (1.23)	1.57 (0.98)	0.0002

* Total number of visits to GP and referrals to specialists in the 6 months prior to cohort entry

† NOS = Not Otherwise Specified; PUB = Perforation, Ulcer, Bleeding; MI = Myocardial Infarction; UAP = Unstable Angina Pectoris; CHD = Coronary Heart Disease; CVD = Cerebrovascular Disease; TIA = Transient Ischemic Attack; DVT = Deep Venous Thrombosis; PE = Pulmonary Embolism; CHF = Congestive Heart Failure or Left Ventricular Dysfunction; IBD = Inflammatory Bowel Disease; PAD = Peripheral Arterial Disease; DM = Diabetes Mellitus;

10.4.2.2 Incidence of Hypertension According to Current Exposure

The numbers of patients without a baseline medical history of hypertension with incident hypertension diagnoses, and the incidence rates (95% CI) of hypertension by current exposure status are shown in **Tables 33a, 33b, 33c, and 33d** for the CPRD+THIN, UK IMS, Germany IMS and France IMS databases, respectively.

The incidence rates/1000py of follow-up (95% CI) of hypertension in patients without current non-steroidal anti-inflammatory exposure were 17.4 (15.4, 19.7), 6.2 (4.2, 8.7), 14.1 (12.9, 15.4) and 10.3 (8.8, 11.9) in the UK CPRD+THIN, UK IMS, Germany IMS and France IMS databases, respectively (**Tables 33a, 33b, 33c,** and **33d**). It is not known why the rate in the UK IMS database is lower than the other estimates.

The incidence rate of hypertension / 1000py (95% confidence interval [CI])) with 'current' exposure to etoricoxib was 20.2 (14.4, 27.7), 10.3 (3.4, 24.1) and 39.9 (23.6, 63.0) in the UK CPRD+THIN, UK IMS, and Germany IMS, respectively. There were no cases of hypertension with current etoricoxib exposure in France. Due to the small numbers of exposed patients with hypertension and the limited person-time of exposure in the UK IMS and Germany IMS databases, the above rates are highly imprecise; the absolute rates and any apparent "trends" must be interpreted with caution. The hypertension rate (20.29/1000py) for 'current' etoricoxib in the CPRD+THIN database, which had the greatest number of cases with 'current' exposure to etoricoxib (39 patients with 1,926 person-year of exposure), was consistent with the rate for non-exposure and with the rates for most other non-steroidal anti-inflammatory treatments with reasonable amounts of data in that same database **(Table 33a).**

Table 33a (THIN/CPRD)
Hypertension Incidence Rates by Current Treatment
(Without History)

Treatment	n/N	P-Y of Exposure	Rate/ 1000 P-Y	95% CI
None*	257/7823	14751.7973	17.42	(15.36, 19.69)
Etoricoxib	39/1295	1926.7342	20.24	(14.39, 27.67)
Rofecoxib	20/679	563.3836	35.50	(21.68, 54.83)
Celecoxib	29/1121	1333.0932	21.75	(14.57, 31.24)
Valdecoxib	1/44	15.9616	62.65	(1.59, 349.06)
Lumiracoxib	0/11	3.4959	0.00	(0.00, 1055.20)
Meloxicam	37/1086	1517.7342	24.38	(17.16, 33.60)
Etodolac	22/448	547.8712	40.16	(25.17, 60.80)
Diclofenac	103/4193	5725.5562	17.99	(14.68, 21.82)
Ibuprofen	39/2208	1474.5479	26.45	(18.81, 36.16)
Naproxen	73/2762	2617.4000	27.89	(21.86, 35.07)
Indometacin	55/973	2211.3644	24.87	(18.74, 32.37)
Other Non-Selective NSAIDs†	48/1513	1817.7534	26.41	(19.47, 35.01)
Multiple COX-2 / NSAIDs	1/388	90.6274	11.03	(0.28, 61.48)

* No current COX-2 or NSAID

† Including Aceclofenac, Acemetacin, Azapropazone, Dexibuprofen, Dexfetoprofen, Fenbufen, Fenoprofen, Feprazone, Flurbiprofen, Ketoprofen, Lornoxicam, Mefenamic Acid, Nabumetone, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac, Tenoxicam, Tiaprofenic Acid, Tolfenamic Acid or Tolmetin

Table 33b (IMS-UK)
Hypertension Incidence Rates by Current Treatment
(Without History)

Treatment	n/N	P-Y of Exposure	Rate/ 1000 P-Y	95% CI
None*	32/1309	5193.1479	6.16	(4.21, 8.70)
Etoricoxib	5/204	484.8986	10.31	(3.35, 24.06)
Rofecoxib	5/157	128.9534	38.77	(12.59, 90.48)
Celecoxib	11/211	431.0603	25.52	(12.74, 45.66)
Valdecoxib	0/6	4.0575	0.00	(0.00, 909.14)
Lumiracoxib	0/1	0.3014	0.00	(0.00, 12240.37)
Meloxicam	6/262	930.3753	6.45	(2.37, 14.04)
Etodolac	0/86	155.7205	0.00	(0.00, 23.69)
Diclofenac	15/980	3360.5589	4.46	(2.50, 7.36)
Ibuprofen	1/434	402.9781	2.48	(0.06, 13.83)
Naproxen	7/582	1349.1753	5.19	(2.09, 10.69)
Indometacin	16/307	1629.5068	9.82	(5.61, 15.95)
Other Non-Selective NSAIDs†	10/330	1007.3644	9.93	(4.76, 18.26)
Multiple COX-2 / NSAIDs	0/84	12.0219	0.00	(0.00, 306.85)

* No current COX-2 or NSAID

† Including Aceclofenac, Acemetacin, Azapropazone, Dexibuprofen, Dexfetoprofen, Fenbufen, Fenoprofen, Feprazone, Flurbiprofen, Ketoprofen, Lornoxicam, Mefenamic Acid, Nabumetone, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac, Tenoxicam, Tiaprofenic Acid, Tolfenamic Acid or Tolmetin

Table 33c (IMS-Germany)
Hypertension Incidence Rates by Current Treatment
(Without History)

Treatment	n/N	P-Y of Exposure	Rate/ 1000 P-Y	95% CI
None*	485/8950	34445.3562	14.08	(12.85, 15.39)
Etoricoxib	18/930	451.5753	39.86	(23.62, 63.00)
Rofecoxib	4/233	83.3123	48.01	(13.08, 122.93)
Celecoxib	10/615	367.3315	27.22	(13.05, 50.06)
Valdecoxib	0/73	10.7452	0.00	(0.00, 343.30)
Lumiracoxib	0/16	0.8219	0.00	(0.00, 4488.14)
Meloxicam	8/455	277.1288	28.87	(12.46, 56.88)
Etodolac	.		.	.
Diclofenac	69/3794	2396.0137	28.80	(22.41, 36.45)
Ibuprofen	38/3188	1343.0740	28.29	(20.02, 38.83)
Naproxen	4/248	95.8219	41.74	(11.37, 106.88)
Indometacin	27/647	828.9507	32.57	(21.46, 47.39)
Other Non-Selective NSAIDs†	18/695	379.1205	47.48	(28.14, 75.04)
Multiple COX-2 / NSAIDs	0/243	29.3562	0.00	(0.00, 125.66)

* No current COX-2 or NSAID

† Including Aceclofenac, Acemetacin, Azapropazone, Dexibuprofen, Dexfetoprofen, Fenbufen, Fenoprofen, Feprazone, Flurbiprofen, Ketoprofen, Lornoxicam, Mefenamic Acid, Nabumetone, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac, Tenoxicam, Tiaprofenic Acid, Tolfenamic Acid or Tolmetin

Table 33d (IM S-France)
Hypertension Incidence Rates by Current Treatment
(Without History)

Treatment	n/N	P-Y of Exposure	Rate/ 1000 P-Y	95% CI
None*	174/2984	16941.8603	10.27	(8.80, 11.91)
Etoricoxib	0/5	2.9836	0.00	(0.00, 1236.40)
Rofecoxib	0/2	0.1370	0.00	(0.00, 26928.82)
Celecoxib	1/26	15.2356	65.64	(1.66, 365.70)
Valdecoxib	.		.	.
Lumiracoxib	.		.	.
Meloxicam	0/64	16.1726	0.00	(0.00, 228.09)
Etodolac	0/4	0.2740	0.00	(0.00, 13464.41)
Diclofenac	0/141	40.9205	0.00	(0.00, 90.15)
Ibuprofen	.		.	.
Naproxen	.		.	.
Indometacin	.		.	.
Other Non-Selective NSAIDs†	4/165	49.3945	80.98	(22.06, 207.34)
Multiple COX-2 / NSAIDs	0/1	0.0384	0.00	(0.00, 96174.36)

* No current COX-2 or NSAID

† Including Aceclofenac, Acemetacin, Azapropazone, Dexibuprofen, Dexfetoprofen, Fenbufen, Fenoprofen, Feprazone, Flurbiprofen, Ketoprofen, Lornoxicam, Mefenamic Acid, Nabumetone, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac, Tenoxicam, Tiaprofenic Acid, Tolfenamic Acid or Tolmetin

10.4.2.3 Association of NSAID / COX-2 Exposure with Hypertension

There were a total of 62 hypertension cases with current exposure to etoricoxib overall (39, 5, 18, and 0 in the CPRD+THIN, UK IMS, Germany IMS, and France IMS databases, respectively). The number (%) of hypertension cases and controls with current exposure by database are shown in **Table 34**. In the CPRD+THIN databases, the proportion of cases and controls with current exposure to etoricoxib on the index date were 3.0% and 2.3% respectively. In the UK IMS database these proportions were 2.8% and 1.3% respectively, while in the Germany IMS database they were 1.3% and 0.7% respectively.

The database with the largest number of hypertension cases with 'current' exposure to a non-steroidal anti-inflammatory drug was the UK CPRD+THIN databases (467 patients). This database also had the most cases of hypertension among patients with 'current' exposure to etoricoxib (39 patients).

Table 34
Number (%) of Hypertension Cases and Controls with Current Exposure by Database and Current Treatment
Patients without a Baseline Medical History of Hypertension

	CPRD + THIN				UK IMS				Germany IMS				France IMS			
	Cases N=1316		Controls N=6434		Cases N=180		Controls N=767		Cases N=1371		Controls N=6786		Cases N=199		Controls N=939	
Treatment	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
None*	849	64.51	4477	69.58	104	57.78	490	63.89	1175	85.70	6029	88.84	194	97.49	929	98.94
Etoricoxib	39	2.96	145	2.25	5	2.78	10	1.30	18	1.31	47	0.69	0	0.00	0	0.00
Rofecoxib	20	1.52	85	1.32	5	2.78	12	1.56	4	0.29	14	0.21	0	0.00	0	0.00
Celecoxib	29	2.20	155	2.41	11	6.11	21	2.74	10	0.73	41	0.60	1	0.50	4	0.43
Valdecoxib	1	0.08	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lumiracoxib	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.01	0	0.00	0	0.00
Meloxicam	37	2.81	201	3.12	6	3.33	21	2.74	8	0.58	37	0.55	0	0.00	1	0.11
Etodolac	22	1.67	64	0.99	0	0.00	1	0.13	0	0.00	0	0.00	0	0.00	0	0.00
Diclofenac	103	7.83	539	8.38	15	8.33	67	8.74	69	5.03	257	3.79	0	0.00	0	0.00
Ibuprofen	39	2.96	141	2.19	1	0.56	21	2.74	38	2.77	190	2.80	0	0.00	0	0.00
Naproxen	73	5.55	243	3.78	7	3.89	34	4.43	4	0.29	12	0.18	0	0.00	0	0.00
Indomethacin	55	4.18	197	3.06	16	8.89	53	6.91	27	1.97	104	1.53	0	0.00	0	0.00
Other Non-Selective NSAIDs†	48	3.65	176	2.74	10	5.56	37	4.82	18	1.31	49	0.72	4	2.01	5	0.53
Multiple COX-2 / NSAIDs	1	0.08	11	0.17	0	0.00	0	0.00	0	0.00	5	0.07	0	0.00	0	0.00

* No current COX-2 or NSAID

† Including Aceclofenac, Acemetacin, Azapropazone, Dexibuprofen, Dexfetoprofen, Fenbufen, Fenoprofen, Feprazone, Flurbiprofen, Ketoprofen, Lornoxicam,Mefenamic Acid, Nabumetone, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac, Tenoxicam, Tiaprofenic Acid, Tolfenamic Acid orTolmetin

10.4.2.4 Hypertension Case-control Analysis Results

The protocol specified that the case-control analysis would be conducted separately in each country / database for each outcome. However, because of insufficient data in the UK IMS and France IMS databases, the analyses were not possible. In addition, the protocol specified that two-level modelling would be used to fit the data from different countries / databases to get a combined summary odds ratio. This was done for the estimates of effect for etoricoxib and the other study drugs of interest using the CPRD+THIN databases and the Germany IMS database.

10.4.2.4.1 Primary Results

Combined CPRD+THIN and Germany IMS

The results of the protocol-specified primary case-control analysis (in patients without a history of hypertension in the 6 months before entry into the AS cohort; exposure to a given medication defined as the calculated duration of the prescription + 14 days), performed with two-level modelling using data from the UK CPRD+THIN and Germany IMS databases are shown in **Table 35**. The results, adjusted for baseline hypertension RS and the quartile of etoricoxib prescribing for the general practice, showed no association between 'current' (adjusted OR 1.35; 95% CI 0.68, 2.69), 'recent' (adjusted OR 1.23; 95% CI 0.61, 2.50) or 'prior' (adjusted OR 1.0; 95% CI 0.54, 1.86) exposure to etoricoxib and hypertension, compared with the referent group of no exposure. Although the estimates for 'current' and 'recent' etoricoxib exposure were slightly elevated, the 95% confidence interval for the estimates was wide. Similarly, in the primary analysis, no association is seen between 'current', recent' or 'prior' exposure to any of the other non-steroidal anti-inflammatory drugs of interest and hypertension, compared with the referent group of no exposure. In general, the confidence intervals are wide for all of the OR estimates, reflecting generally sparse data. Some estimates for specific drugs could not be computed due to the lack of data. Due to the imprecision of the data, comparison of the risk estimates for hypertension with etoricoxib exposure to that of the other study drugs of interest is not reliable. As expected, the baseline hypertension RS is positively associated with hypertension in this analysis (adjusted OR 1.38; 95% CI 1.28, 1.49), whereas the quartile of etoricoxib prescribing for the practice is not associated with the outcome (adjusted OR 0.96; 95% CI 0.91, 1.01).

The same conclusions apply to the results for etoricoxib from the sensitivity analyses that varied the baseline period and the exposure definition (**Tables 36, 37** and **38**). In general the same conclusions also apply to the results for the other study drugs from the sensitivity analyses as well. The above results specific to results for UK CPRD + THIN and Germany IMS databases separately can be found in the Annexes specific to each under separate cover (**Tables 35a-38a** for UK CPRD + THIN, **Tables 35c-38c** for Germany IMS).

In another sensitivity analyses stratified by index date for the case-control set occurring before or after the COX-2 Urgent Safety Restriction (i.e., <17Feb05 vs. ≥17Feb05), current etoricoxib exposure was not associated with hypertension in the post-Urgent Safety Restriction stratum. The adjusted OR ranged from 1.25 (95% CI 0.53, 3.00) to 1.59 (95% CI 0.76, 3.35), depending on the length of baseline period and the definition of the exposure time. The 95% CI for these point estimates were wide. The pre-Urgent Safety Restriction stratum did not have adequate cases to generate meaningful estimates in IMS Germany. In CPRD+THIN only, current etoricoxib exposure was not associated with hypertension in the pre-Urgent Safety Restriction stratum. The adjusted OR ranged from 1.48 (95% CI 0.40, 5.50) to 5.20 (95% CI 0.88, 30.55), depending on the length of baseline period and the definition of the exposure time. The 95% CI for these point estimates were wide.

Table 35 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model
for New Hypertension Diagnosis by Exposure Category
(Without History, 6 Month baseline, 14 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Non-exposure*	.	.	.
Etoricoxib			
Current	1.354	0.681	2.694
Recent	1.234	0.610	2.498
Prior	0.999	0.536	1.864
Rofecoxib			
Current	1.468	0.524	4.119
Recent	0.920	0.337	2.511
Prior	0.979	0.441	2.171
Celecoxib			
Current	0.848	0.393	1.833
Recent	1.286	0.617	2.682
Prior	1.175	0.629	2.195
Valdecoxib			
Current	.	.	.
Recent	.	.	.
Prior	3.393	0.213	54.056
Lumiracoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Meloxicam			
Current	1.122	0.556	2.262
Recent	0.935	0.452	1.934
Prior	1.086	0.606	1.946
Etodolac			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Diclofenac			

Table 35 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model for New Hypertension Diagnosis by Exposure Category (Without History, 6 Month baseline, 14 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Current	0.976	0.712	1.338
Recent	1.324	0.993	1.766
Prior	1.113	0.869	1.424
Ibuprofen			
Current	1.183	0.775	1.808
Recent	1.082	0.735	1.594
Prior	0.967	0.696	1.344
Naproxen			
Current	1.558	0.856	2.836
Recent	0.901	0.494	1.641
Prior	1.080	0.643	1.816
Indomethacin			
Current	1.341	0.728	2.471
Recent	0.967	0.522	1.790
Prior	1.123	0.609	2.072
Other Non-Selective NSAIDs[†]			
Current	1.399	0.786	2.489
Recent	0.916	0.529	1.588
Prior	1.269	0.783	2.057
Multiple COX-2 / NSAIDs			
Current	0.430	0.019	9.792
Recent	2.171	0.588	8.016
Prior	0.642	0.217	1.899
Hypertension Disease Risk Score[‡]	1.377	1.276	1.486
COX-2 / NSAID[‡]	.	.	.
Quartile of etoricoxib prescribing for practice#	0.959	0.910	1.011

* No current, recent or prior treatment defined 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).

[†] Including aceclofenac, acemetacin, azapropazone, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, feprazone, flurbiprofen, ketoprofen, lornoxicam, mefenamic acid, nabumetone, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, tolfenamic acid, or tolmetin

[‡] In the 6 months prior to the diagnosis date for cases and the same calendar date for his/her matched controls

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 using all databases combined.

Table 36 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model
for New Hypertension Diagnosis by Exposure Category
(Without History, 6 Month baseline, 28 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Non-exposure*	.	.	.
Etoricoxib			
Current	1.435	0.720	2.861
Recent	1.228	0.608	2.480
Prior	0.968	0.510	1.838
Rofecoxib			
Current	1.552	0.557	4.321
Recent	0.812	0.291	2.264
Prior	1.048	0.478	2.300
Celecoxib			
Current	1.007	0.484	2.094
Recent	0.993	0.466	2.119
Prior	1.361	0.735	2.519
Valdecoxib			
Current	.	.	.
Recent	.	.	.
Prior	2.722	0.159	46.532
Lumiracoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Meloxicam			
Current	1.088	0.540	2.195
Recent	0.960	0.464	1.986
Prior	1.041	0.574	1.888
Etodolac			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Diclofenac			

Table 36 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model for New Hypertension Diagnosis by Exposure Category (Without History, 6 Month baseline, 28 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Current	1.157	0.863	1.550
Recent	1.224	0.917	1.634
Prior	1.061	0.826	1.364
Ibuprofen			
Current	1.068	0.718	1.589
Recent	1.295	0.893	1.877
Prior	0.914	0.652	1.281
Naproxen			
Current	1.410	0.776	2.560
Recent	1.024	0.568	1.847
Prior	1.006	0.592	1.711
Indomethacin			
Current	1.458	0.791	2.687
Recent	0.861	0.456	1.626
Prior	1.143	0.616	2.121
Other Non-Selective NSAIDs[†]			
Current	1.359	0.780	2.368
Recent	0.956	0.557	1.641
Prior	1.220	0.741	2.008
Multiple COX-2 / NSAIDs			
Current	0.537	0.060	4.789
Recent	1.816	0.478	6.892
Prior	0.691	0.232	2.060
Hypertension Disease Risk Score[‡]	1.375	1.274	1.484
COX-2 / NSAID[‡]	.	.	.
Quartile of etoricoxib prescribing for practice#	0.958	0.909	1.010

* No current, recent or prior treatment defined as follows:
'Current' when the most recent exposure (calculated duration of the most recent prescription + 28 days) overlaps the 'index' date.
'Recent' when the most recent exposure (calculated duration of the most recent prescription + 28 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 + 28 days) ended on a date 61 to 180 days prior to the 'index' date (does not overlap index date).

[†] Including aceclofenac, acemetacin, azapropazone, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, feprazone, flurbiprofen, ketoprofen, lornoxicam, mefenamic acid, nabumetone, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, tolfenamic acid, or tolmetin

[‡] In the 6 months prior to the diagnosis date for cases and the same calendar date for his/her matched controls

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 using all databases combined.

Table 37 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model
for New Hypertension Diagnosis by Exposure Category
(Without History, 12 Month baseline, 14 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Non-exposure*	.	.	.
Etoricoxib			
Current	1.272	0.573	2.825
Recent	1.295	0.581	2.889
Prior	0.821	0.400	1.685
Rofecoxib			
Current	1.854	0.579	5.930
Recent	0.790	0.254	2.462
Prior	1.151	0.484	2.739
Celecoxib			
Current	0.959	0.371	2.477
Recent	1.503	0.615	3.674
Prior	1.094	0.523	2.288
Valdecoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Lumiracoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Meloxicam			
Current	1.309	0.575	2.978
Recent	0.767	0.314	1.872
Prior	1.033	0.514	2.078
Etodolac			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Diclofenac			

Table 37 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model for New Hypertension Diagnosis by Exposure Category (Without History, 12 Month baseline, 14 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Current	1.061	0.727	1.549
Recent	1.275	0.903	1.800
Prior	1.106	0.824	1.486
Ibuprofen			
Current	1.350	0.821	2.222
Recent	0.848	0.527	1.364
Prior	0.933	0.633	1.376
Naproxen			
Current	1.498	0.800	2.804
Recent	0.982	0.513	1.880
Prior	1.046	0.591	1.851
Indomethacin			
Current	1.489	0.699	3.169
Recent	1.181	0.571	2.442
Prior	0.899	0.433	1.870
Other Non-Selective NSAIDs[†]			
Current	0.977	0.482	1.982
Recent	1.236	0.646	2.366
Prior	1.496	0.854	2.619
Multiple COX-2 / NSAIDs			
Current	.	.	.
Recent	2.891	0.652	12.816
Prior	0.894	0.270	2.962
Hypertension Disease Risk Score[‡]	1.318	1.202	1.444
COX-2 / NSAID[‡]	.	.	.
Quartile of etoricoxib prescribing for practice#	0.948	0.891	1.008

* No current, recent or prior treatment defined 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).

† Including aceclofenac, acemetacin, azapropazone, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, feprazone, flurbiprofen, ketoprofen, lornoxicam, mefenamic acid, nabumetone, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, tolfenamic acid, or tolmetin

‡ In the 6 months prior to the diagnosis date for cases and the same calendar date for his/her matched controls

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 using all databases combined.

Table 38 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model
for New Hypertension Diagnosis by Exposure Category
(Without History, 12 Month baseline, 28 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Non-exposure*	.	.	.
Etoricoxib			
Current	1.284	0.581	2.837
Recent	1.186	0.527	2.670
Prior	0.824	0.396	1.713
Rofecoxib			
Current	1.477	0.492	4.433
Recent	0.818	0.267	2.507
Prior	1.259	0.541	2.928
Celecoxib			
Current	1.222	0.501	2.976
Recent	1.030	0.417	2.547
Prior	1.257	0.612	2.583
Valdecoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Lumiracoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Meloxicam			
Current	1.210	0.526	2.784
Recent	0.831	0.337	2.052
Prior	1.012	0.495	2.071
Etodolac			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Diclofenac			

Table 38 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model for New Hypertension Diagnosis by Exposure Category (Without History, 12 Month baseline, 28 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Current	1.192	0.834	1.703
Recent	1.243	0.880	1.755
Prior	1.053	0.781	1.420
Ibuprofen			
Current	1.167	0.728	1.871
Recent	1.168	0.742	1.838
Prior	0.786	0.524	1.179
Naproxen			
Current	1.330	0.704	2.510
Recent	1.169	0.610	2.241
Prior	0.957	0.526	1.743
Indomethacin			
Current	1.405	0.665	2.968
Recent	1.119	0.516	2.428
Prior	0.964	0.466	1.998
Other Non-Selective NSAIDs[†]			
Current	0.986	0.496	1.959
Recent	1.032	0.538	1.978
Prior	1.655	0.941	2.910
Multiple COX-2 / NSAIDs			
Current	0.488	0.041	5.745
Recent	2.146	0.498	9.249
Prior	0.866	0.254	2.953
Hypertension Disease Risk Score[‡]	1.318	1.203	1.444
COX-2 / NSAID[‡]	.	.	.
Quartile of etoricoxib prescribing for practice#	0.945	0.888	1.005

* No current, recent or prior treatment defined as follows:
'Current' when the most recent exposure (calculated duration of the most recent prescription + 28 days) overlaps the 'index' date.
'Recent' when the most recent exposure (calculated duration of the most recent prescription + 28 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 + 28 days) ended on a date 61 to 180 days prior to the 'index' date (does not overlap index date).

[†] Including aceclofenac, acemetacin, azapropazone, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, feprazone, flurbiprofen, ketoprofen, lornoxicam, mefenamic acid, nabumetone, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, tolfenamic acid, or tolmetin

[‡] In the 6 months prior to the diagnosis date for cases and the same calendar date for his/her matched controls

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 using all databases combined.

10.4.2.4.2 Secondary Results

Combined CPRD+THIN and Germany IMS

The results of the secondary analysis (in all patients with or without a history of hypertension in the 6 months before entry into the AS cohort; exposure to a given medication defined as the calculated duration of the prescription +14 days of the prescription) performed with two-level modelling using data from the UK CPRD+THIN and Germany IMS databases are shown in **Table 39**. Baseline hypertension RS and the quartile of etoricoxib prescribing for the general practice were both adjusted. The adjusted OR for 'current' exposure to etoricoxib was 1.50 (95% CI 0.88, 2.49), compared with the referent group of no exposure. No association with hypertension was shown for 'recent' (adjusted OR 1.54; 95% CI 0.88, 2.68) or 'prior' (adjusted OR 0.94; 95% CI 0.56, 1.58) exposure to etoricoxib. Elevated associations with the 'current' exposures to some COX-2's and non-selective NSAIDs were also observed compared with the referent group of no exposure, but all but one of the CI's included 1. Some estimates for specific drugs could not be computed due to the lack of data. Due to the imprecision of the data, comparison of the risk estimates for hypertension with etoricoxib exposure to that of the other study drugs of interest is not reliable. The baseline hypertension RS is positively associated with hypertension in this analysis (OR 1.57; 95% CI 1.48, 1.66), whereas the quartile of etoricoxib prescribing for the practice is not associated with the outcome (OR 0.97; 95% CI 0.93, 1.01).

In sensitivity analysis that defined exposure to etoricoxib as equal to the duration of the prescription+28 days (**Table 40**), the results remained largely unchanged for 'current' (adjusted OR 1.67; 95% CI 1.00, 2.79), 'recent' (adjusted OR 1.38; 95% CI 0.79, 2.41), or 'prior' (adjusted OR 0.91; 95% CI 0.54, 1.57) exposure to etoricoxib. No association with hypertension was observed for 'current', 'recent' or 'prior' exposure to etoricoxib in all the sensitivity analyses that included a 12-month baseline period. In some of the above sensitivity analyses (**Tables 40, 41** and **42**), associations were observed between some of the exposures to diclofenac, meloxicam, ibuprofen, and other non-selective NSAIDs compared with the referent group of no exposure.

The above results specific to results for UK CPRD + THIN and Germany IMS databases separately are found in the **Annexes** specific to each under separate cover (**Tables 39a-42a** for UK CPRD + THIN, **Tables 39c-42c** for Germany IMS).

Table 39 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model
for New Hypertension Diagnosis by Exposure Category
(With/Without History, 6 Month baseline, 14 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Non-exposure*	.	.	.
Etoricoxib			
Current	1.479	0.878	2.492
Recent	1.537	0.880	2.682
Prior	0.941	0.563	1.575
Rofecoxib			
Current	1.502	0.677	3.331
Recent	1.348	0.648	2.800
Prior	0.741	0.365	1.503
Celecoxib			
Current	0.952	0.522	1.735
Recent	1.554	0.850	2.839
Prior	0.929	0.534	1.619
Valdecoxib			
Current	.	.	.
Recent	.	.	.
Prior	2.884	0.522	15.944
Lumiracoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Meloxicam			
Current	1.698	0.964	2.990
Recent	1.040	0.552	1.962
Prior	0.952	0.549	1.653
Etodolac			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Diclofenac			

Table 39 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model for New Hypertension Diagnosis by Exposure Category (With/Without History, 6 Month baseline, 14 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Current	1.038	0.811	1.330
Recent	1.527	1.221	1.909
Prior	1.035	0.840	1.276
Ibuprofen			
Current	1.295	0.945	1.774
Recent	1.241	0.931	1.655
Prior	0.952	0.727	1.245
Naproxen			
Current	1.633	0.940	2.837
Recent	1.046	0.601	1.820
Prior	1.078	0.652	1.784
Indomethacin			
Current	1.259	0.777	2.039
Recent	1.307	0.810	2.110
Prior	1.051	0.645	1.715
Other Non-Selective NSAIDs[†]			
Current	1.554	0.973	2.481
Recent	1.234	0.786	1.937
Prior	1.136	0.739	1.747
Multiple COX-2 / NSAIDs			
Current	0.526	0.089	3.104
Recent	1.103	0.381	3.197
Prior	0.762	0.312	1.864
Hypertension Disease Risk Score[‡]	1.567	1.480	1.658
COX-2 / NSAID[‡]	.	.	.
Quartile of etoricoxib prescribing for practice#	0.967	0.929	1.008

* No current, recent or prior treatment defined 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).

[†] Including aceclofenac, acemetacin, azapropazone, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, feprazone, flurbiprofen, ketoprofen, lornoxicam, mefenamic acid, nabumetone, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, tolfenamic acid, or tolmetin

[‡] In the 6 months prior to the diagnosis date for cases and the same calendar date for his/her matched controls

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 using all databases combined.

Table 40 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model
for New Hypertension Diagnosis by Exposure Category
(With/Without History, 6 Month baseline, 28 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Non-exposure*	.	.	.
Etoricoxib			
Current	1.667	0.997	2.787
Recent	1.384	0.794	2.412
Prior	0.917	0.537	1.566
Rofecoxib			
Current	1.463	0.681	3.143
Recent	1.299	0.609	2.768
Prior	0.772	0.385	1.545
Celecoxib			
Current	1.200	0.681	2.116
Recent	1.096	0.586	2.050
Prior	1.090	0.631	1.883
Valdecoxib			
Current	.	.	.
Recent	.	.	.
Prior	3.428	0.541	21.705
Lumiracoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Meloxicam			
Current	1.758	1.001	3.088
Recent	0.948	0.496	1.810
Prior	0.931	0.533	1.627
Etodolac			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Diclofenac			

Table 40 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model for New Hypertension Diagnosis by Exposure Category (With/Without History, 6 Month baseline, 28 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Current	1.281	1.022	1.605
Recent	1.412	1.124	1.774
Prior	0.952	0.768	1.180
Ibuprofen			
Current	1.316	0.987	1.755
Recent	1.288	0.965	1.719
Prior	0.902	0.684	1.188
Naproxen			
Current	1.466	0.847	2.540
Recent	1.142	0.658	1.982
Prior	0.998	0.595	1.676
Indomethacin			
Current	1.627	1.013	2.611
Recent	1.070	0.652	1.758
Prior	0.994	0.602	1.641
Other Non-Selective NSAIDs[†]			
Current	1.653	1.056	2.588
Recent	1.184	0.753	1.860
Prior	1.066	0.683	1.665
Multiple COX-2 / NSAIDs			
Current	0.728	0.149	3.550
Recent	1.028	0.343	3.074
Prior	0.804	0.328	1.972
Hypertension Disease Risk Score[‡]	1.567	1.481	1.659
COX-2 / NSAID[‡]	.	.	.
Quartile of etoricoxib prescribing for practice#	0.966	0.928	1.007

* No current, recent or prior treatment defined as follows:
'Current' when the most recent exposure (calculated duration of the most recent prescription + 28 days) overlaps the 'index' date.
'Recent' when the most recent exposure (calculated duration of the most recent prescription + 28 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 + 28 days) ended on a date 61 to 180 days prior to the 'index' date (does not overlap index date).

[†] Including aceclofenac, acemetacin, azapropazone, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, feprazone, flurbiprofen, ketoprofen, lornoxicam, mefenamic acid, nabumetone, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, tolfenamic acid, or tolmetin

[‡] In the 6 months prior to the diagnosis date for cases and the same calendar date for his/her matched controls

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 using all databases combined.

Table 41 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model
for New Hypertension Diagnosis by Exposure Category
(With/Without History, 12 Month baseline, 14 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Non-exposure*	.	.	.
Etoricoxib			
Current	1.475	0.850	2.558
Recent	1.487	0.822	2.691
Prior	0.964	0.559	1.663
Rofecoxib			
Current	1.638	0.705	3.805
Recent	1.282	0.596	2.759
Prior	0.753	0.358	1.583
Celecoxib			
Current	0.951	0.498	1.815
Recent	1.635	0.835	3.203
Prior	0.907	0.497	1.656
Valdecoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Lumiracoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Meloxicam			
Current	1.946	1.064	3.561
Recent	1.027	0.516	2.044
Prior	0.852	0.460	1.580
Etodolac			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Diclofenac			

Table 41 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model for New Hypertension Diagnosis by Exposure Category (With/Without History, 12 Month baseline, 14 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Current	1.040	0.796	1.357
Recent	1.495	1.178	1.897
Prior	1.020	0.813	1.279
Ibuprofen			
Current	1.434	1.032	1.991
Recent	1.174	0.868	1.588
Prior	0.915	0.689	1.215
Naproxen			
Current	1.561	0.876	2.781
Recent	1.173	0.651	2.113
Prior	1.082	0.626	1.871
Indomethacin			
Current	1.237	0.722	2.119
Recent	1.484	0.887	2.481
Prior	1.051	0.620	1.780
Other Non-Selective NSAIDs†			
Current	1.336	0.789	2.261
Recent	1.425	0.865	2.349
Prior	1.159	0.723	1.860
Multiple COX-2 / NSAIDs			
Current	0.488	0.081	2.928
Recent	1.231	0.405	3.740
Prior	0.983	0.366	2.642
Hypertension Disease Risk Score‡	1.538	1.457	1.623
COX-2 / NSAID‡	.	.	.
Quartile of etoricoxib prescribing for practice#	0.978	0.937	1.021

* No current, recent or prior treatment defined 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).

† Including aceclofenac, acemetacin, azapropazone, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, feprazone, flurbiprofen, ketoprofen, lornoxicam, mefenamic acid, nabumetone, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, tolfenamic acid, or tolmetin

‡ In the 6 months prior to the diagnosis date for cases and the same calendar date for his/her matched controls

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 using all databases combined.

Table 42 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model
for New Hypertension Diagnosis by Exposure Category
(With/Without History, 12 Month baseline, 28 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Non-exposure*	.	.	.
Etoricoxib			
Current	1.528	0.890	2.625
Recent	1.475	0.813	2.674
Prior	0.911	0.518	1.603
Rofecoxib			
Current	1.439	0.645	3.208
Recent	1.335	0.602	2.961
Prior	0.850	0.413	1.752
Celecoxib			
Current	1.228	0.670	2.251
Recent	1.072	0.542	2.120
Prior	1.113	0.622	1.991
Valdecoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Lumiracoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Meloxicam			
Current	1.994	1.099	3.617
Recent	1.011	0.496	2.063
Prior	0.794	0.424	1.488
Etodolac			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Diclofenac			

Table 42 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model for New Hypertension Diagnosis by Exposure Category (With/Without History, 12 Month baseline, 28 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Current	1.255	0.985	1.600
Recent	1.450	1.137	1.850
Prior	0.917	0.725	1.159
Ibuprofen			
Current	1.395	1.032	1.886
Recent	1.278	0.942	1.734
Prior	0.833	0.621	1.117
Naproxen			
Current	1.356	0.757	2.430
Recent	1.311	0.722	2.383
Prior	1.039	0.583	1.851
Indomethacin			
Current	1.546	0.916	2.610
Recent	1.223	0.715	2.093
Prior	1.016	0.592	1.742
Other Non-Selective NSAIDs[†]			
Current	1.462	0.879	2.432
Recent	1.282	0.778	2.113
Prior	1.146	0.702	1.871
Multiple COX-2 / NSAIDs			
Current	0.686	0.139	3.394
Recent	1.098	0.350	3.449
Prior	1.033	0.384	2.782
Hypertension Disease Risk Score[‡]	1.537	1.456	1.622
COX-2 / NSAID[‡]	.	.	.
Quartile of etoricoxib prescribing for practice#	0.977	0.936	1.020

* No current, recent or prior treatment defined as follows:
'Current' when the most recent exposure (calculated duration of the most recent prescription + 28 days) overlaps the 'index' date.
'Recent' when the most recent exposure (calculated duration of the most recent prescription + 28 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 + 28 days) ended on a date 61 to 180 days prior to the 'index' date (does not overlap index date).

[†] Including aceclofenac, acemetacin, azapropazone, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, feprazone, flurbiprofen, ketoprofen, lornoxicam, mefenamic acid, nabumetone, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, tolfenamic acid, or tolmetin

[‡] In the 6 months prior to the diagnosis date for cases and the same calendar date for his/her matched controls

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 using all databases combined.

10.4.3 All Vascular Events + Sudden Death

Overall, in the primary analysis population (the subset of the cohort without a history of vascular events in the 6 months before entry into the AS cohort) there were a total of 2,288 vascular events/sudden death cases and 10,612 controls from all the databases combined. Four hundred forty-eight (19.6%) of the cases and 1,974 (18.6%) of the controls were currently exposed to an NSAID or COX-2 inhibitor at the time of diagnosis. There were 813 cases from UK CPRD+THIN, 197 from UK IMS, 1189 from Germany IMS, and 89 from France IMS. There were 3,745 controls from UK CPRD+THIN, 709 from UK IMS, 5,825 from Germany IMS, and 333 from France IMS.

10.4.3.1 Baseline Characteristics of Vascular Event / Sudden Death Cases and Controls

Baseline characteristics (assessed during the 6 months prior to entry into the AS cohort) for the primary analysis cases and controls are shown for patients in the CPRD+THIN databases, the UK IMS database, the Germany IMS database, and the France IMS database in **Tables 43a**, **43b**, **43c**, and **43d**, respectively. As mentioned previously, the prevalence of baseline medical history diagnoses and baseline medication use may be lower than expected given the relatively short baseline assessment period (the 6 months prior to entry into the AS cohort).

For the patients from the UK CPRD+THIN databases, the cases were statistically significantly ($p<0.05$) more likely to have renal disease than the controls; while controls were statistically significantly more likely to be a non-smoker, to have a history of dyslipidemia, to have used proton pump inhibitors, and to have used cardiovascular medications than cases (**Table 43a**).

For the patients from the UK IMS database, cases were statistically significantly ($p<0.05$) more likely to be female and to take narcotic pain medications than the controls. (**Table 43b**).

For the patients from the Germany IMS database, cases were statistically significantly ($p<0.05$) more likely to have a baseline history of atherosclerotic cardiovascular disease, IBD, PAD, and diabetes than controls. Cases also had more prior health care encounters than controls. (**Table 43c**).

For the patients from the France IMS database, cases were statistically significantly ($p<0.05$) more likely have entered the cohort before the Urgent Safety Restriction (**Table 43d**).

Table 43a (THIN/CPRD UK)
Baseline Characteristics for Vascular Cases and Controls
(Assessed During the Six Months Prior to Cohort Entry Without History)

Baseline Characteristics	Cases N=813	Control N=3,745	p-value
Age (years)			
Mean (sd)	61.18 (13.53)	61.79 (12.20)	0.2384
Gender: n (%)			
Male	539 (66.30)	2,560 (68.36)	0.2537
Female	274 (33.70)	1,185 (31.64)	
Smoking status (most recent): n (%) **			
Non-Smoker	301 (37.02)	1,534 (40.96)	0.0012
Current Smoker	200 (24.60)	789 (21.07)	
Ex-Smoker	157 (19.31)	850 (22.70)	
Missing	155 (19.07)	572 (15.27)	
Alcohol status (most recent): n (%) **			
Non-Alcohol Use	117 (14.39)	619 (16.53)	0.4140
Current Alcohol Use	466 (57.32)	2,135 (57.01)	
Ex-Alcohol Use	17 (2.09)	80 (2.14)	
Missing	213 (26.20)	911 (24.33)	
Body mass index (kg/m2) (most recent) **			
Mean (sd)	27.41 (5.32)	27.09 (4.68)	0.1703
Cohort entry before cox-2 Urgent Safety Restriction (17Feb05): n (%)			
Yes	624 (76.75)	2,823 (75.38)	0.4088
No	189 (23.25)	922 (24.62)	
Total number of prior health care encounters*			
Mean (sd)	7.15 (6.15)	7.40 (5.87)	0.2791
Referral to Rheumatologist: n (%) **			
Yes	105 (12.92)	477 (12.74)	0.8903
No	708 (87.08)	3,268 (87.26)	
X-ray of the sacrum or spine: n (%) **			
Yes	32 (3.94)	150 (4.01)	0.9271
No	781 (96.06)	3,595 (95.99)	
Both Referral to Rheumatologist and X-ray of the sacrum or spine: n (%) **			
Yes	6 (0.74)	9 (0.24)	0.0247
No	807 (99.26)	3,736 (99.76)	
Blood pressure (most recent) (mmHg)			
Mean (sd) Systolic	139.80 (20.71)	138.88 (20.10)	0.2824
Mean (sd) Diastolic	80.29 (10.93)	79.42 (10.51)	0.0543
Medical History[†]: n (%)			
Osteoarthritis	82 (10.09)	383 (10.23)	0.9043

Table 43a (THIN/CPRD UK)
Baseline Characteristics for Vascular Cases and Controls
(Assessed During the Six Months Prior to Cohort Entry Without History)

Baseline Characteristics	Cases N=813	Control N=3,745	p-value
Rheumatoid Arthritis	2 (0.25)	4 (0.11)	0.2916
Gout	3 (0.37)	21 (0.56)	0.4935
Arthritis NOS	23 (2.83)	84 (2.24)	0.3171
GI PUB	9 (1.11)	25 (0.67)	0.1868
Acute or Subacute CHD (excluding MI or UAP)	30 (3.69)	109 (2.91)	0.2413
Atherosclerotic Cardiovascular Disease	1 (0.12)	1 (0.03)	0.3250
Renal Disease	3 (0.37)	2 (0.05)	0.0426
Acute Renal Failure	1 (0.12)	15 (0.40)	0.2252
Hypertension (diagnosis only)	44 (5.41)	235 (6.28)	0.3521
CHF	6 (0.74)	32 (0.85)	0.7406
IBD	8 (0.98)	43 (1.15)	0.6866
PAD		2 (0.05)	1.0000
Dyslipidemia	8 (0.98)	79 (2.11)	0.0335
DM (diagnosis or medication)	58 (7.13)	342 (9.13)	0.0680
Medications: n (%)			
Anti-inflammatory Drugs	374 (46.00)	1,637 (43.71)	0.2331
Non-selective NSAID	333 (40.96)	1,419 (37.89)	0.1030
COX-2 selective inhibitor	41 (5.04)	218 (5.82)	0.3851
Narcotic Pain Medications	410 (50.43)	1,829 (48.84)	0.4105
Rheumatic Disease Treatments	77 (9.47)	370 (9.88)	0.7224
Disease Modifying Anti-Rheumatic Drugs	38 (4.67)	203 (5.42)	0.3886
Oral Corticosteroids	49 (6.03)	207 (5.53)	0.5748
Gastrointestinal Drugs	241 (29.64)	1,293 (34.53)	0.0076
Histamine 2-Receptor Antagonists	87 (10.70)	407 (10.87)	0.8898
Prostaglandin Analogues (incl. misoprostol + NSAID)	33 (4.06)	160 (4.27)	0.7842
Proton Pump Inhibitors	137 (16.85)	846 (22.59)	0.0003
Other Ulcer-healing Drugs	3 (0.37)	7 (0.19)	0.3978
Cardiovascular / Lipid-Modifying Medications	381 (46.86)	2,051 (54.77)	<.0001
Cardiac Glycosides	17 (2.09)	91 (2.43)	0.5647
Diuretics	134 (16.48)	656 (17.52)	0.4800
Beta-Blockers	133 (16.36)	752 (20.08)	0.0150
Angiotensin-Converting Enzyme Inhibitors	96 (11.81)	653 (17.44)	<.0001
Angiotensin-II Receptor Antagonists	37 (4.55)	147 (3.93)	0.4112
Nitrates	77 (9.47)	471 (12.58)	0.0136
Calcium-Channel Blockers	118 (14.51)	550 (14.69)	0.8999
Oral Anticoagulants	18 (2.21)	206 (5.50)	<.0001

Table 43a (THIN/CPRD UK)
Baseline Characteristics for Vascular Cases and Controls
(Assessed During the Six Months Prior to Cohort Entry Without History)

Baseline Characteristics	Cases N=813	Control N=3,745	p-value
Oral Antiplatelet Drugs (Including Low Dose Aspirin)	167 (20.54)	1,004 (26.81)	0.0002
Ezetimibe	6 (0.74)	18 (0.48)	0.3580
Fibrates	7 (0.86)	36 (0.96)	0.7886
Statins	116 (14.27)	876 (23.39)	<.0001
Oral Contraceptives	6 (0.74)	16 (0.43)	0.2465
Estrogen Replacement Therapy	19 (2.34)	99 (2.64)	0.6179
Prescription Aspirin (≥300 mg/day)	20 (2.46)	97 (2.59)	0.8316
Vascular Disease Risk Score			
Mean (sd)	3.90 (0.88)	3.88 (0.78)	0.4159

* Total number of visits to GP and referrals to specialists in the 6 months prior to cohort entry

† NOS = Not Otherwise Specified; PUB = Perforation, Ulcer, Bleeding; MI = Myocardial Infarction; UAP = Unstable Angina Pectoris; CHD = Coronary Heart Disease; CVD = Cerebrovascular Disease; TIA = Transient Ischemic Attack; DVT = Deep Venous Thrombosis; PE = Pulmonary Embolism; CHF = Congestive Heart Failure or Left Ventricular Dysfunction; IBD = Inflammatory Bowel Disease; PAD = Peripheral Arterial Disease; DM = Diabetes Mellitus;

Table 43b (IMS-UK)
Baseline Characteristics for Vascular Cases and Controls
(Assessed During the Six Months Prior to Cohort Entry Without History)

Baseline Characteristics	Cases N=197	Control N=709	p-value
Age (years)			
Mean (sd)	55.23 (15.18)	54.96 (12.89)	0.8195
Gender: n (%)			
Male	150 (76.14)	595 (83.92)	0.0115
Female	47 (23.86)	114 (16.08)	
Body mass index (kg/m2) (most recent) **			
Mean (sd)	27.20 (5.83)	27.55 (5.61)	0.4951
Cohort entry before cox-2 Urgent Safety Restriction (17Feb05): n (%)			
Yes	175 (88.83)	621 (87.59)	0.6362
No	22 (11.17)	88 (12.41)	
Total number of prior health care encounters*			
Mean (sd)	6.16 (8.46)	5.33 (6.62)	0.2013
Medical History[†]: n (%)			
Osteoarthritis	3 (1.52)	9 (1.27)	0.7301
Rheumatoid Arthritis	6 (3.05)	12 (1.69)	0.2286
Gout	3 (1.52)	5 (0.71)	0.3815
Arthritis NOS	10 (5.08)	43 (6.06)	0.6009
GI PUB	4 (2.03)	10 (1.41)	0.5183
Acute or Subacute CHD (excluding MI or UAP)	4 (2.03)	10 (1.41)	0.5183
Atherosclerotic Cardiovascular Disease	2 (1.02)	1 (0.14)	0.1210
Edema	2 (1.02)	7 (0.99)	1.0000
Renal Disease	5 (2.54)	6 (0.85)	0.0680
Hypertension (diagnosis only)	25 (12.69)	94 (13.26)	0.8347
CHF	2 (1.02)		0.0471
IBD	4 (2.03)	5 (0.71)	0.1094
Dyslipidemia	5 (2.54)	18 (2.54)	0.9995
DM (diagnosis or medication)	14 (7.11)	28 (3.95)	0.0622
Medications: n (%)			
Anti-inflammatory Drugs	78 (39.59)	314 (44.29)	0.2395
Non-selective NSAID	68 (34.52)	282 (39.77)	0.1801
COX-2 selective inhibitor	10 (5.08)	32 (4.51)	0.7397
Narcotic Pain Medications	9 (4.57)	12 (1.69)	0.0176
Rheumatic Disease Treatments	21 (10.66)	71 (10.01)	0.7907
Disease Modifying Anti-Rheumatic Drugs	11 (5.58)	22 (3.10)	0.1001
Oral Corticosteroids	14 (7.11)	56 (7.90)	0.7127
Gastrointestinal Drugs	37 (18.78)	156 (22.00)	0.3287

Table 43b (IMS-UK)
Baseline Characteristics for Vascular Cases and Controls
(Assessed During the Six Months Prior to Cohort Entry Without History)

Baseline Characteristics	Cases N=197	Control N=709	p-value
Histamine 2-Receptor Antagonists	12 (6.09)	75 (10.58)	0.0586
Prostaglandin Analogues (incl. misoprostol + NSAID)	6 (3.05)	34 (4.80)	0.2902
Proton Pump Inhibitors	24 (12.18)	75 (10.58)	0.5231
Cardiovascular / Lipid-Modifying Medications	45 (22.84)	198 (27.93)	0.1542
Cardiac Glycosides	7 (3.55)	12 (1.69)	0.1069
Diuretics	16 (8.12)	77 (10.86)	0.2626
Beta-Blockers	2 (1.02)	2 (0.28)	0.2078
Angiotensin-Converting Enzyme Inhibitors	1 (0.51)	8 (1.13)	0.6925
Angiotensin-II Receptor Antagonists	20 (10.15)	63 (8.89)	0.5857
Calcium-Channel Blockers	7 (3.55)	35 (4.94)	0.4140
Oral Anticoagulants	5 (2.54)	7 (0.99)	0.1483
Oral Antiplatelet Drugs (Including Low Dose Aspirin)	16 (8.12)	98 (13.82)	0.0328
Ezetimibe		6 (0.85)	0.3494
Fibrates		4 (0.56)	0.5822
Statins	13 (6.60)	59 (8.32)	0.4291
Oral Contraceptives	1 (0.51)		0.2174
Vascular Disease Risk Score			
Mean (sd)	3.57 (1.02)	3.52 (0.86)	0.5424

* Total number of visits to GP and referrals to specialists in the 6 months prior to cohort entry

† NOS = Not Otherwise Specified; PUB = Perforation, Ulcer, Bleeding; MI = Myocardial Infarction; UAP = Unstable Angina Pectoris; CHD = Coronary Heart Disease; CVD = Cerebrovascular Disease; TIA = Transient Ischemic Attack; DVT = Deep Venous Thrombosis; PE = Pulmonary Embolism; CHF = Congestive Heart Failure or Left Ventricular Dysfunction; IBD = Inflammatory Bowel Disease; PAD = Peripheral Arterial Disease; DM = Diabetes Mellitus;

Table 43c (IMS-Germany)
Baseline Characteristics for Vascular Cases and Controls
(Assessed During the Six Months Prior to Cohort Entry Without History)

Baseline Characteristics	Cases N=1,189	Control N=5,825	p-value
Age (years)			
Mean (sd)	57.54 (14.44)	57.93 (13.62)	0.3887
Gender: n (%)			
Male	740 (62.24)	3,637 (62.44)	0.8965
Female	449 (37.76)	2,188 (37.56)	
Smoking status (most recent): n (%) **			
Non-Smoker	129 (10.85)	681 (11.69)	0.6550
Current Smoker	73 (6.14)	344 (5.91)	
Ex-Smoker	34 (2.86)	196 (3.36)	
Missing	953 (80.15)	4,604 (79.04)	
Body mass index (kg/m2) (most recent) **			
Mean (sd)	28.47 (5.21)	28.38 (4.81)	0.7164
Cohort entry before cox-2 Urgent Safety Restriction (17Feb05): n (%)			
Yes	591 (49.71)	2,806 (48.17)	0.3348
No	598 (50.29)	3,019 (51.83)	
Total number of prior health care encounters*			
Mean (sd)	4.87 (3.79)	4.60 (3.73)	0.0223
Medical History[†]: n (%)			
Osteoarthritis	68 (5.72)	309 (5.30)	0.5637
Rheumatoid Arthritis	64 (5.38)	328 (5.63)	0.7342
Gout	26 (2.19)	106 (1.82)	0.3961
Arthritis NOS	174 (14.63)	867 (14.88)	0.8251
GI PUB	25 (2.10)	98 (1.68)	0.3144
Acute or Subacute CHD (excluding MI or UAP)	126 (10.60)	524 (9.00)	0.0827
Atherosclerotic Cardiovascular Disease	19 (1.60)	41 (0.70)	0.0023
Edema	14 (1.18)	51 (0.88)	0.3221
Renal Disease	55 (4.63)	256 (4.39)	0.7245
Acute Renal Failure	15 (1.26)	64 (1.10)	0.6277
Hypertension (diagnosis only)	365 (30.70)	1,913 (32.84)	0.1504
CHF	53 (4.46)	227 (3.90)	0.3683
IBD	34 (2.86)	96 (1.65)	0.0048
PAD	32 (2.69)	102 (1.75)	0.0309
Dyslipidemia	193 (16.23)	955 (16.39)	0.8901
DM (diagnosis or medication)	175 (14.72)	699 (12.00)	0.0097
Medications: n (%)			
Anti-inflammatory Drugs	460 (38.69)	2,161 (37.10)	0.3019

Table 43c (IMS-Germany)
Baseline Characteristics for Vascular Cases and Controls
(Assessed During the Six Months Prior to Cohort Entry Without History)

Baseline Characteristics	Cases N=1,189	Control N=5,825	p-value
Non-selective NSAID	394 (33.14)	1,898 (32.58)	0.7108
COX-2 selective inhibitor	66 (5.55)	263 (4.52)	0.1237
Narcotic Pain Medications	119 (10.01)	620 (10.64)	0.5155
Rheumatic Disease Treatments	102 (8.58)	470 (8.07)	0.5582
Disease Modifying Anti-Rheumatic Drugs	40 (3.36)	192 (3.30)	0.9048
Oral Corticosteroids	75 (6.31)	348 (5.97)	0.6597
Gastrointestinal Drugs	233 (19.60)	1,018 (17.48)	0.0818
Histamine 2-Receptor Antagonists	30 (2.52)	149 (2.56)	0.9447
Prostaglandin Analogues (incl. misoprostol + NSAID)	8 (0.67)	32 (0.55)	0.6064
Proton Pump Inhibitors	201 (16.90)	856 (14.70)	0.0523
Other Ulcer-healing Drugs	6 (0.50)	29 (0.50)	0.9759
Cardiovascular / Lipid-Modifying Medications	477 (40.12)	2,344 (40.24)	0.9374
Cardiac Glycosides	36 (3.03)	137 (2.35)	0.1709
Diuretics	153 (12.87)	820 (14.08)	0.2716
Beta-Blockers	79 (6.64)	393 (6.75)	0.8977
Angiotensin-Converting Enzyme Inhibitors	107 (9.00)	481 (8.26)	0.4004
Angiotensin-II Receptor Antagonists	189 (15.90)	1,093 (18.76)	0.0197
Nitrates	18 (1.51)	57 (0.98)	0.1019
Calcium-Channel Blockers	72 (6.06)	347 (5.96)	0.8962
Oral Anticoagulants	11 (0.93)	33 (0.57)	0.1535
Oral Antiplatelet Drugs (Including Low Dose Aspirin)	87 (7.32)	399 (6.85)	0.5631
Anion-Exchange Resins		2 (0.03)	1.0000
Ezetimibe	4 (0.34)	21 (0.36)	0.8989
Fibrates	27 (2.27)	66 (1.13)	0.0018
Statins	111 (9.34)	590 (10.13)	0.4060
Nicotinic Acid	17 (1.43)	69 (1.18)	0.4838
Oral Contraceptives	9 (0.76)	28 (0.48)	0.2308
Estrogen Replacement Therapy	1 (0.08)	1 (0.02)	0.3103
Prescription Aspirin (≥300 mg/day)	2 (0.17)	9 (0.15)	1.0000
Vascular Disease Risk Score			
Mean (sd)	2.37 (0.71)	2.36 (0.66)	0.7138

* Total number of visits to GP and referrals to specialists in the 6 months prior to cohort entry

† NOS = Not Otherwise Specified; PUB = Perforation, Ulcer, Bleeding; MI = Myocardial Infarction; UAP = Unstable Angina Pectoris; CHD = Coronary Heart Disease; CVD = Cerebrovascular Disease; TIA = Transient Ischemic Attack; DVT = Deep Venous Thrombosis; PE = Pulmonary Embolism; CHF = Congestive Heart Failure or Left Ventricular Dysfunction; IBD = Inflammatory Bowel Disease; PAD = Peripheral Arterial Disease; DM = Diabetes Mellitus;

Table 43d (IMS-France)
Baseline Characteristics for Vascular Cases and Controls
(Assessed During the Six Months Prior to Cohort Entry Without History)

Baseline Characteristics	Cases N=89	Control N=333	p-value
Age (years)			
Mean (sd)	53.51 (14.00)	55.14 (12.04)	0.3158
Gender: n (%)			
Male	47 (52.81)	178 (53.45)	0.9138
Female	42 (47.19)	155 (46.55)	
Body mass index (kg/m2) (most recent) **			
Mean (sd)			
Cohort entry before cox-2 Urgent Safety Restriction (17Feb05): n (%)			
Yes	36 (40.45)	92 (27.63)	0.0194
No	53 (59.55)	241 (72.37)	
Total number of prior health care encounters*			
Mean (sd)	3.85 (2.77)	3.70 (2.10)	0.6328
Medical History[†]: n (%)			
Osteoarthritis	3 (3.37)	2 (0.60)	0.0655
Rheumatoid Arthritis	2 (2.25)	8 (2.40)	1.0000
Arthritis NOS	14 (15.73)	43 (12.91)	0.4897
GI PUB		1 (0.30)	1.0000
Acute or Subacute CHD (excluding MI or UAP)	2 (2.25)	5 (1.50)	0.6419
Renal Disease		4 (1.20)	0.5833
Hypertension (diagnosis only)	23 (25.84)	74 (22.22)	0.4708
CHF	1 (1.12)	1 (0.30)	0.3777
IBD	3 (3.37)	18 (5.41)	0.4330
PAD		1 (0.30)	1.0000
Dyslipidemia	8 (8.99)	19 (5.71)	0.2609
DM (diagnosis or medication)	6 (6.74)	22 (6.61)	0.9638
Medications: n (%)			
Anti-inflammatory Drugs	2 (2.25)	9 (2.70)	1.0000
Non-selective NSAID	2 (2.25)	9 (2.70)	1.0000
Rheumatic Disease Treatments	18 (20.22)	42 (12.61)	0.0678
Disease Modifying Anti-Rheumatic Drugs	2 (2.25)	4 (1.20)	0.6107
Oral Corticosteroids	17 (19.10)	40 (12.01)	0.0822
Gastrointestinal Drugs	47 (52.81)	185 (55.56)	0.6436
Histamine 2-Receptor Antagonists		2 (0.60)	1.0000
Prostaglandin Analogues (incl. misoprostol + NSAID)		2 (0.60)	1.0000
Proton Pump Inhibitors	46 (51.69)	179 (53.75)	0.7283
Other Ulcer-healing Drugs	1 (1.12)	2 (0.60)	0.5096

Table 43d (IMS-France)
Baseline Characteristics for Vascular Cases and Controls
(Assessed During the Six Months Prior to Cohort Entry Without History)

Baseline Characteristics	Cases N=89	Control N=333	p-value
Cardiovascular / Lipid-Modifying Medications	28 (31.46)	137 (41.14)	0.0964
Cardiac Glycosides	2 (2.25)	5 (1.50)	0.6419
Diuretics	7 (7.87)	44 (13.21)	0.1691
Beta-Blockers	3 (3.37)	10 (3.00)	0.7416
Angiotensin-Converting Enzyme Inhibitors	3 (3.37)	4 (1.20)	0.1657
Angiotensin-II Receptor Antagonists	13 (14.61)	57 (17.12)	0.5717
Calcium-Channel Blockers	4 (4.49)	13 (3.90)	0.8013
Oral Anticoagulants	1 (1.12)	1 (0.30)	0.3777
Oral Antiplatelet Drugs (Including Low Dose Aspirin)	11 (12.36)	59 (17.72)	0.2274
Fibrates	4 (4.49)	6 (1.80)	0.2293
Statins	2 (2.25)	6 (1.80)	0.6775
Oral Contraceptives	4 (4.49)	9 (2.70)	0.4863
Estrogen Replacement Therapy	1 (1.12)	2 (0.60)	0.5096
Vascular Disease Risk Score			
Mean (sd)	1.79 (0.92)	1.83 (0.97)	0.8185

* Total number of visits to GP and referrals to specialists in the 6 months prior to cohort entry

† NOS = Not Otherwise Specified; PUB = Perforation, Ulcer, Bleeding; MI = Myocardial Infarction; UAP = Unstable Angina Pectoris; CHD = Coronary Heart Disease; CVD = Cerebrovascular Disease; TIA = Transient Ischemic Attack; DVT = Deep Venous Thrombosis; PE = Pulmonary Embolism; CHF = Congestive Heart Failure or Left Ventricular Dysfunction; IBD = Inflammatory Bowel Disease; PAD = Peripheral Arterial Disease; DM = Diabetes Mellitus;

10.4.3.2 Incidence of All Vascular Events + Sudden Death According to Current Exposure

The numbers of patients with vascular event / sudden death diagnoses and the incidence rates (95% CI) of these events among patients without a baseline medical history of vascular events, according to "current' exposure status, are shown in **Tables 44a, 44b, 44c,** and **44d** for the UK CPRD+THIN, UK IMS, Germany IMS, and France IMS databases, respectively.

The incidence rate / 1000py of follow-up (95% CI) of vascular event / sudden death in patients without non-steroidal anti-inflammatory exposure during follow-up was 13.2 (11.4, 15.1), 7.9 (5.7, 10.7), 12.4 (11.3, 13.7), and 4.6 (3.7, 5.8) in the UK CPRD+THIN, UK IMS, Germany IMS and France IMS databases, respectively.

The incidence rate of vascular event or sudden death / 1000 person-year (95% CI) with 'current' exposure to etoricoxib was 7.4 (4.3, 12.1), 12.0 (4.4, 26.0) and 26.2 (14.0, 44.8) in the UK CPRD+THIN, UK IMS, and Germany IMS, respectively. There were no cases with current etoricoxib exposure in France. Due to the small numbers of exposed cases and the limited person-time of exposure in the UK IMS and Germany IMS databases, the above rates are highly imprecise.

Table 44a (THIN/CPRD)
Vascular Incidence Rates by Current Treatment
(Without History)

Treatment	n/N	P-Y of Exposure	Rate/ 1000 P-Y	95% CI
None*	200/7823	15183.5233	13.17	(11.41, 15.13)
Etoricoxib	16/1356	2150.6329	7.44	(4.25, 12.08)
Rofecoxib	6/686	580.4301	10.34	(3.79, 22.50)
Celecoxib	13/1160	1417.6274	9.17	(4.88, 15.68)
Valdecoxib	0/46	17.2658	0.00	(0.00, 213.65)
Lumiracoxib	0/11	3.4959	0.00	(0.00, 1055.20)
Meloxicam	16/1109	1734.1699	9.23	(5.27, 14.98)
Etodolac	3/462	600.7068	4.99	(1.03, 14.59)
Diclofenac	69/4291	6012.8000	11.48	(8.93, 14.52)
Ibuprofen	19/2287	1640.5041	11.58	(6.97, 18.09)
Naproxen	17/2878	2968.5479	5.73	(3.34, 9.17)
Indometacin	17/990	2426.6027	7.01	(4.08, 11.22)
Other Non-Selective NSAIDs†	25/1550	2008.8658	12.44	(8.05, 18.37)
Multiple COX-2 / NSAIDs	3/411	95.7890	31.32	(6.46, 91.53)

* No current COX-2 or NSAID

† Including Aceclofenac, Acemetacin, Azapropazone, Dexibuprofen, Dexfetoprofen, Fenbufen, Fenoprofen, Feprazone, Flurbiprofen, Ketoprofen, Lornoxicam, Mefenamic Acid, Nabumetone, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac, Tenoxicam, Tiaprofenic Acid, Tolfenamic Acid or Tolmetin

Table 44b (IMS-UK)
Vascular Incidence Rates by Current Treatment
(Without History)

Treatment	n/N	P-Y of Exposure	Rate/ 1000 P-Y	95% CI
None*	41/1309	5205.2164	7.88	(5.65, 10.69)
Etoricoxib	6/210	501.6630	11.96	(4.39, 26.03)
Rofecoxib	3/165	161.0603	18.63	(3.84, 54.43)
Celecoxib	7/213	649.3425	10.78	(4.33, 22.21)
Valdecoxib	0/6	4.0575	0.00	(0.00, 909.14)
Lumiracoxib	0/1	0.3014	0.00	(0.00, 12240.37)
Meloxicam	2/260	971.1753	2.06	(0.25, 7.44)
Etodolac	0/86	153.0356	0.00	(0.00, 24.10)
Diclofenac	19/981	2133.4110	8.91	(5.36, 13.91)
Ibuprofen	1/440	405.0685	2.47	(0.06, 13.75)
Naproxen	9/592	1404.5068	6.41	(2.93, 12.16)
Indometacin	7/305	1964.7370	3.56	(1.43, 7.34)
Other Non-Selective NSAIDs†	6/328	904.8712	6.63	(2.43, 14.43)
Multiple COX-2 / NSAIDs	0/87	14.1945	0.00	(0.00, 259.88)

* No current COX-2 or NSAID

† Including Aceclofenac, Acemetacin, Azapropazone, Dexibuprofen, Dexfetoprofen, Fenbufen, Fenoprofen, Feprazone, Flurbiprofen, Ketoprofen, Lornoxicam, Mefenamic Acid, Nabumetone, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac, Tenoxicam, Tiaprofenic Acid, Tolfenamic Acid or Tolmetin

Table 44c (IMS-Germany)
Vascular Incidence Rates by Current Treatment
(Without History)

Treatment	n/N	P-Y of Exposure	Rate/ 1000 P-Y	95% CI
None*	430/8950	34620.1151	12.42	(11.27, 13.65)
Etoricoxib	13/962	495.8712	26.22	(13.96, 44.83)
Rofecoxib	2/241	84.3781	23.70	(2.87, 85.62)
Celecoxib	7/630	399.4767	17.52	(7.05, 36.10)
Valdecoxib	1/75	10.2630	97.44	(2.47, 542.89)
Lumiracoxib	0/18	1.0384	0.00	(0.00, 3552.61)
Meloxicam	11/469	293.2384	37.51	(18.73, 67.12)
Etodolac	.		.	.
Diclofenac	74/3842	2567.6493	28.82	(22.63, 36.18)
Ibuprofen	45/3251	1335.9233	33.68	(24.57, 45.07)
Naproxen	3/260	103.7890	28.90	(5.96, 84.47)
Indometacin	18/654	884.9699	20.34	(12.05, 32.15)
Other Non-Selective NSAIDs†	7/706	397.9151	17.59	(7.07, 36.25)
Multiple COX-2 / NSAIDs	1/253	34.4877	29.00	(0.73, 161.55)

* No current COX-2 or NSAID

† Including Aceclofenac, Acemetacin, Azapropazone, Dexibuprofen, Dexfetoprofen, Fenbufen, Fenoprofen, Feprazone, Flurbiprofen, Ketoprofen, Lornoxicam, Mefenamic Acid, Nabumetone, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac, Tenoxicam, Tiaprofenic Acid, Tolfenamic Acid or Tolmetin

Table 44d (IMS-France)
Vascular Incidence Rates by Current Treatment
(Without History)

Treatment	n/N	P-Y of Exposure	Rate/ 1000 P-Y	95% CI
None*	81/2984	17493.0658	4.63	(3.68, 5.76)
Etoricoxib	0/5	2.9836	0.00	(0.00, 1236.40)
Rofecoxib	0/2	0.1370	0.00	(0.00, 26928.82)
Celecoxib	0/27	18.5123	0.00	(0.00, 199.27)
Valdecoxib	.		.	.
Lumiracoxib	.		.	.
Meloxicam	1/67	16.6137	60.19	(1.52, 335.36)
Etodolac	0/5	0.3890	0.00	(0.00, 9481.98)
Diclofenac	0/145	41.2466	0.00	(0.00, 89.43)
Ibuprofen	.		.	.
Naproxen	.		.	.
Indometacin	.		.	.
Other Non-Selective NSAIDs†	1/168	57.6110	17.36	(0.44, 96.71)
Multiple COX-2 / NSAIDs	0/1	0.0384	0.00	(0.00, 96174.36)

* No current COX-2 or NSAID

† Including Aceclofenac, Acemetacin, Azapropazone, Dexibuprofen, Dexfetoprofen, Fenbufen, Fenoprofen, Feprazone, Flurbiprofen, Ketoprofen, Lornoxicam, Mefenamic Acid, Nabumetone, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac, Tenoxicam, Tiaprofenic Acid, Tolfenamic Acid or Tolmetin

10.4.3.3 Association of NSAID / COX-2 Exposure with Vascular Events + Sudden Death

There were a total of 35 vascular event / sudden death cases with current exposure to etoricoxib overall (16, 6, 13, and 0 in the CPRD+THIN, UK IMS, Germany IMS, and France IMS databases, respectively). The number (%) of vascular event / sudden death cases and controls with current exposure by database are shown in **Table 45**. In the CPRD+THIN databases the proportion of cases and controls with current exposure to etoricoxib on the index date were 2.0% and 1.6% respectively. In the UK IMS database these proportions were 3.1% and 2.1% respectively, while in the Germany IMS database they were 1.1% and 1.0 respectively.

Table 45
Number (%) of Vascular Cases and Controls with Current Exposure by Database and Current Treatment
Patients without a Baseline Medical History of Vascular

	CPRD + THIN				UK IMS				Germany IMS				France IMS			
	Cases N=813		Controls N=3745		Cases N=197		Controls N=709		Cases N=1189		Controls N=5825		Cases N=89		Controls N=333	
Treatment	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
None*	609	74.91	2852	76.15	137	69.54	492	69.39	1007	84.69	4963	85.20	87	97.75	331	99.40
Etoricoxib	16	1.97	60	1.60	6	3.05	15	2.12	13	1.09	60	1.03	0	0.00	0	0.00
Rofecoxib	6	0.74	26	0.69	3	1.52	4	0.56	2	0.17	16	0.27	0	0.00	0	0.00
Celecoxib	13	1.60	65	1.74	7	3.55	14	1.97	7	0.59	48	0.82	0	0.00	0	0.00
Valdecoxib	0	0.00	1	0.03	0	0.00	0	0.00	1	0.08	3	0.05	0	0.00	0	0.00
Lumiracoxib	0	0.00	2	0.05	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Meloxicam	16	1.97	48	1.28	2	1.02	6	0.85	11	0.93	46	0.79	1	1.12	0	0.00
Etodolac	3	0.37	30	0.80	0	0.00	5	0.71	0	0.00	0	0.00	0	0.00	0	0.00
Diclofenac	69	8.49	256	6.84	19	9.64	52	7.33	74	6.22	326	5.60	0	0.00	1	0.30
Ibuprofen	19	2.34	113	3.02	1	0.51	14	1.97	45	3.78	192	3.30	0	0.00	0	0.00
Naproxen	17	2.09	115	3.07	9	4.57	27	3.81	3	0.25	9	0.15	0	0.00	0	0.00
Indomethacin	17	2.09	85	2.27	7	3.55	38	5.36	18	1.51	101	1.73	0	0.00	0	0.00
Other Non-Selective NSAIDs†	25	3.08	88	2.35	6	3.05	42	5.92	7	0.59	51	0.88	1	1.12	1	0.30
Multiple COX-2 / NSAIDs	3	0.37	4	0.11	0	0.00	0	0.00	1	0.08	10	0.17	0	0.00	0	0.00

* No current COX-2 or NSAID

† Including Aceclofenac, Acemetacin, Azapropazone, Dexibuprofen, Dexfetoprofen, Fenbufen, Fenoprofen, Feprazone, Flurbiprofen, Ketoprofen, Lornoxicam, Mefenamic Acid, Nabumetone, Oxyphenbutazone, Phenylbutazone, Piroxicam, Sulindac, Tenoxicam, Tiaprofenic Acid, Tolfenamic Acid or Tolmetin

10.4.3.4 Vascular Event / Sudden Death Case-control Analysis Results

The protocol specified that the case-control analysis would be conducted separately in each country / database for each outcome. However, because of insufficient data in the UK IMS and France IMS databases, the analyses were not possible. In addition, the protocol specified that two-level modelling would be used to fit the data from different countries / databases to get a combined summary odds ratio. This was done for the estimates of effect for etoricoxib and the other study drugs of interest using the CPRD+THIN databases and the Germany IMS database.

10.4.3.4.1 Primary Results

Combined CPRD+THIN and Germany IMS

The results of the protocol-specified primary case-control analysis (in patients without a history of vascular disease in the 6 months before entry into the AS cohort; exposure to a given medication defined as the calculated duration of the prescription + 14 days), performed with two-level modelling using data from the UK CPRD+THIN and Germany IMS databases are shown in **Table 46**. After adjustment of baseline vascular event RS and the quartile of etoricoxib prescribing for the general practice, the results showed no association between 'current' (adjusted OR 0.95; 95% CI 0.40, 2.27), 'recent' (adjusted OR 1.67; 95% CI 0.76, 3.70) or 'prior' (adjusted OR 0.67; 95% CI 0.30, 1.52) exposure to etoricoxib and vascular events / sudden death, compared with the referent group of no exposure. In the primary analysis, no associations were seen with 'current', 'recent', or 'prior' exposure to any of the other non-steroidal anti-inflammatory drugs of interest and vascular events / sudden death, compared with the referent group of no exposure. In general, the confidence intervals are wide for all of the OR estimates, reflecting generally sparse data. Some estimates could not be computed due to the lack of data. Due to the imprecision of the estimates, comparison of the risk estimates for etoricoxib exposure to the other study drugs of interest is not reliable. The baseline vascular disease RS is positively associated with the outcome in this analysis (adjusted OR 1.16; 95% CI 1.03, 1.30), whereas the quartile of etoricoxib prescribing for the practice is not associated with the outcome (OR 0.96; 95% CI 0.91, 1.02).

The same conclusions apply to the results for etoricoxib from the sensitivity analyses that varied the baseline period and the exposure definition (**Tables 47**, **48** and **49**). In general the same conclusions also apply to the results for the other study drugs from the sensitivity analyses as well, except that for some exposures of some of the study drugs, the estimates of effect are elevated, albeit with wide 95% CI.

The results of the above analyses for the separate countries / databases are found in the Annexes specific to each under separate cover (Tables 46a – 49a for UK CPRD + THIN and Tables 46c – 49c for Germany IMS). The results of those analyses should be interpreted cautiously due to small numbers of patients with outcomes of interest in each database, small numbers of patients with current exposure to the medications of interest, variation in patient characteristics across the different databases, variation in medical care across the different countries, etc.

Table 46 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model
for New Vascular Diagnosis by Exposure Category
(Without History, 6 Month baseline, 14 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Non-exposure*	.	.	.
Etoricoxib			
Current	0.954	0.401	2.272
Recent	1.672	0.755	3.701
Prior	0.671	0.295	1.522
Rofecoxib			
Current	1.028	0.214	4.948
Recent	0.824	0.187	3.637
Prior	0.908	0.323	2.548
Celecoxib			
Current	0.828	0.306	2.240
Recent	0.703	0.246	2.014
Prior	1.319	0.607	2.870
Valdecoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Lumiracoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Meloxicam			
Current	1.282	0.558	2.944
Recent	1.188	0.506	2.791
Prior	1.036	0.491	2.189
Etodolac			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Diclofenac			

Table 46 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model for New Vascular Diagnosis by Exposure Category (Without History, 6 Month baseline, 14 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Current	1.158	0.818	1.638
Recent	1.160	0.830	1.621
Prior	0.913	0.682	1.222
Ibuprofen			
Current	0.946	0.600	1.489
Recent	1.355	0.901	2.039
Prior	0.965	0.673	1.384
Naproxen			
Current	0.850	0.314	2.303
Recent	1.103	0.398	3.055
Prior	0.865	0.367	2.040
Indomethacin			
Current	0.614	0.279	1.349
Recent	1.067	0.474	2.400
Prior	1.517	0.739	3.114
Other Non-Selective NSAIDs[†]			
Current	0.699	0.320	1.528
Recent	1.457	0.735	2.885
Prior	1.111	0.598	2.066
Multiple COX-2 / NSAIDs			
Current	1.575	0.148	16.762
Recent	0.430	0.009	21.585
Prior	1.200	0.314	4.587
Vascular Disease Risk Score[‡]	1.156	1.025	1.304
COX-2 / NSAID[‡]	.	.	.
Quartile of etoricoxib prescribing for practice#	0.964	0.908	1.023

* No current, recent or prior treatment defined 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).

[†] Including aceclofenac, acemetacin, azapropazone, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, feprazone, flurbiprofen, ketoprofen, lornoxicam, mefenamic acid, nabumetone, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, tolfenamic acid, or tolmetin

[‡] In the 6 months prior to the diagnosis date for cases and the same calendar date for his/her matched controls

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 using all databases combined.

Table 47 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model
for New Vascular Diagnosis by Exposure Category
(Without History, 6 Month baseline, 28 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Non-exposure*	.	.	.
Etoricoxib			
Current	1.510	0.698	3.267
Recent	0.865	0.366	2.048
Prior	0.820	0.380	1.768
Rofecoxib			
Current	0.645	0.141	2.950
Recent	1.829	0.492	6.797
Prior	0.672	0.224	2.019
Celecoxib			
Current	0.793	0.290	2.166
Recent	0.689	0.232	2.040
Prior	1.416	0.653	3.071
Valdecoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Lumiracoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Meloxicam			
Current	1.010	0.434	2.351
Recent	1.350	0.594	3.065
Prior	1.103	0.528	2.306
Etodolac			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Diclofenac			

Table 47 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model
for New Vascular Diagnosis by Exposure Category
(Without History, 6 Month baseline, 28 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Current	1.152	0.823	1.612
Recent	1.135	0.809	1.592
Prior	0.903	0.673	1.213
Ibuprofen			
Current	1.024	0.667	1.571
Recent	1.454	0.965	2.190
Prior	0.831	0.571	1.209
Naproxen			
Current	0.960	0.358	2.578
Recent	0.846	0.306	2.337
Prior	0.948	0.409	2.197
Indomethacin			
Current	0.666	0.302	1.471
Recent	1.019	0.431	2.412
Prior	1.527	0.722	3.233
Other Non-Selective NSAIDs[†]			
Current	0.831	0.387	1.784
Recent	1.210	0.606	2.416
Prior	1.316	0.720	2.407
Multiple COX-2 / NSAIDs			
Current	1.601	0.153	16.770
Recent	0.432	0.009	21.436
Prior	1.187	0.310	4.550
Vascular Disease Risk Score[‡]	1.154	1.024	1.301
COX-2 / NSAID[‡]	.	.	.
Quartile of etoricoxib prescribing for practice#	0.963	0.908	1.022

* No current, recent or prior treatment defined as follows:
'Current' when the most recent exposure (calculated duration of the most recent prescription + 28 days) overlaps the 'index' date.
'Recent' when the most recent exposure (calculated duration of the most recent prescription + 28 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 + 28 days) ended on a date 61 to 180 days prior to the 'index' date (does not overlap index date).

† Including aceclofenac, acemetacin, azapropazone, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, feprazone, flurbiprofen, ketoprofen, lornoxicam, mefenamic acid, nabumetone, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, tolfenamic acid, or tolmetin

‡ In the 6 months prior to the diagnosis date for cases and the same calendar date for his/her matched controls

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 using all databases combined.

Table 48 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model
for New Vascular Diagnosis by Exposure Category
(Without History, 12 Month baseline, 14 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Non-exposure*	.	.	.
Etoricoxib			
Current	1.323	0.510	3.428
Recent	1.271	0.514	3.143
Prior	0.679	0.262	1.758
Rofecoxib			
Current	1.273	0.189	8.575
Recent	1.347	0.279	6.499
Prior	0.779	0.204	2.970
Celecoxib			
Current	0.751	0.260	2.170
Recent	0.778	0.259	2.332
Prior	1.590	0.646	3.917
Valdecoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Lumiracoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Meloxicam			
Current	1.592	0.629	4.027
Recent	1.446	0.529	3.958
Prior	0.925	0.379	2.254
Etodolac			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Diclofenac			

Table 48 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model for New Vascular Diagnosis by Exposure Category (Without History, 12 Month baseline, 14 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Current	1.350	0.898	2.029
Recent	1.174	0.794	1.736
Prior	0.788	0.556	1.117
Ibuprofen			
Current	0.932	0.562	1.544
Recent	1.582	1.011	2.478
Prior	1.045	0.705	1.549
Naproxen			
Current	0.603	0.196	1.852
Recent	1.119	0.360	3.482
Prior	1.009	0.409	2.491
Indomethacin			
Current	1.117	0.420	2.968
Recent	1.180	0.403	3.459
Prior	0.981	0.376	2.560
Other Non-Selective NSAIDs[†]			
Current	1.077	0.419	2.765
Recent	0.963	0.394	2.354
Prior	1.475	0.681	3.198
Multiple COX-2 / NSAIDs			
Current	0.974	0.065	14.577
Recent	.	.	.
Prior	1.905	0.408	8.891
Vascular Disease Risk Score[‡]	1.097	0.957	1.256
COX-2 / NSAID[‡]	.	.	.
Quartile of etoricoxib prescribing for practice#	0.957	0.896	1.023

* No current, recent or prior treatment defined 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).

[†] Including aceclofenac, acemetacin, azapropazone, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, feprazone, flurbiprofen, ketoprofen, lornoxicam, mefenamic acid, nabumetone, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, tolfenamic acid, or tolmetin

[‡] In the 6 months prior to the diagnosis date for cases and the same calendar date for his/her matched controls

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 using all databases combined.

Table 49 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model
for New Vascular Diagnosis by Exposure Category
(Without History, 12 Month baseline, 28 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Non-exposure*	.	.	.
Etoricoxib			
Current	1.599	0.698	3.665
Recent	0.860	0.322	2.299
Prior	0.806	0.327	1.986
Rofecoxib			
Current	0.684	0.116	4.045
Recent	3.078	0.719	13.186
Prior	0.514	0.121	2.196
Celecoxib			
Current	0.696	0.237	2.042
Recent	0.894	0.283	2.824
Prior	1.548	0.642	3.736
Valdecoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Lumiracoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Meloxicam			
Current	1.215	0.469	3.148
Recent	1.345	0.517	3.502
Prior	1.238	0.521	2.942
Etodolac			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Diclofenac			

Table 49 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model for New Vascular Diagnosis by Exposure Category (Without History, 12 Month baseline, 28 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Current	1.307	0.882	1.937
Recent	1.185	0.801	1.752
Prior	0.773	0.545	1.098
Ibuprofen			
Current	0.973	0.602	1.571
Recent	1.714	1.091	2.694
Prior	0.934	0.623	1.399
Naproxen			
Current	0.767	0.255	2.303
Recent	0.873	0.282	2.701
Prior	0.980	0.393	2.442
Indomethacin			
Current	1.475	0.562	3.865
Recent	0.788	0.249	2.494
Prior	1.118	0.420	2.974
Other Non-Selective NSAIDs[†]			
Current	1.104	0.435	2.805
Recent	0.900	0.359	2.254
Prior	1.631	0.769	3.461
Multiple COX-2 / NSAIDs			
Current	0.938	0.063	13.892
Recent	.	.	.
Prior	1.613	0.353	7.381
Vascular Disease Risk Score[‡]	1.095	0.955	1.254
COX-2 / NSAID[‡]	.	.	.
Quartile of etoricoxib prescribing for practice#	0.958	0.896	1.024

* No current, recent or prior treatment defined as follows:
'Current' when the most recent exposure (calculated duration of the most recent prescription + 28 days) overlaps the 'index' date.
'Recent' when the most recent exposure (calculated duration of the most recent prescription + 28 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 + 28 days) ended on a date 61 to 180 days prior to the 'index' date (does not overlap index date).

[†] Including aceclofenac, acemetacin, azapropazone, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, feprazone, flurbiprofen, ketoprofen, lornoxicam, mefenamic acid, nabumetone, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, tolfenamic acid, or tolmetin

[‡] In the 6 months prior to the diagnosis date for cases and the same calendar date for his/her matched controls

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 using all databases combined.

10.4.3.4.2 Secondary Results

Combined CPRD+THIN and Germany IMS

The results of the case-control analysis in all patients (with and without a history of vascular event in the 6 months before entry into the AS cohort; exposure to a given medication defined as the calculated duration of the prescription + 14 days), performed with two-level modelling using data from the UK CPRD+THIN and Germany IMS databases are shown in **Table 50**. The results, adjusted for baseline vascular event RS and the quartile of etoricoxib prescribing for the general practice, showed no association between 'current' (adjusted OR 1.04; 95% CI 0.46, 2.33), 'recent' (adjusted OR 1.49; 95% CI 0.69, 3.24) or 'prior' (adjusted OR 0.75; 95% CI 0.36, 1.58) exposure to etoricoxib and vascular events/sudden death, compared with the referent group of no exposure. No significant associations between 'current', 'recent', and 'prior' exposure to other NSAIDs were observed compared with the referent group of no exposure and in general, the confidence intervals are wide for all of the OR estimates, reflecting generally sparse data. Some estimates for specific drugs could not be computed due to the lack of data. Due to the imprecision of the data, comparison of the risk estimates for vascular event / sudden death with etoricoxib exposure to that of the other study drugs of interest is not reliable. The baseline vascular disease RS is positively associated with vascular events / sudden death in this analysis (OR 1.19; 95% CI 1.07, 1.31), whereas the quartile of etoricoxib prescribing for the practice is not associated with the outcome (OR 0.97; 95% CI 0.92, 1.03).

The same conclusions apply to the results for etoricoxib (in all patients) from the sensitivity analyses that varied the baseline period and the exposure definition (**Tables 51, 52** and **53**). In some analyses the point estimates for the association of etoricoxib is elevated, however the 95% CI for the estimates are very wide. In these same analyses, associations between some of the exposures to other study drugs of interest were also observed compared with the referent group of no exposure; however for most, the 95% CI around those estimates were wide.

The results of the above analyses for the separate countries / databases are found in the **Annexes** specific to each under separate cover (**Tables 50a – 53a** for UK CPRD + THIN and **Tables 50c – 53c** for Germany IMS). The results of those analyses should be interpreted cautiously due to small numbers of patients with outcomes of interest in each database, small numbers of patients with current exposure to the medications of interest, variation in patient characteristics across the different databases, variation in medical care across the different countries, etc.

Table 50 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model
for New Vascular Diagnosis by Exposure Category
(With/Without History, 6 Month baseline, 14 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Non-exposure*	.	.	.
Etoricoxib			
Current	1.041	0.464	2.333
Recent	1.493	0.688	3.240
Prior	0.751	0.356	1.582
Rofecoxib			
Current	1.186	0.307	4.583
Recent	0.939	0.247	3.566
Prior	1.085	0.424	2.780
Celecoxib			
Current	0.896	0.349	2.299
Recent	0.706	0.265	1.883
Prior	1.359	0.638	2.894
Valdecoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Lumiracoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Meloxicam			
Current	1.345	0.610	2.965
Recent	1.204	0.529	2.741
Prior	1.053	0.509	2.180
Etodolac			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Diclofenac			

Table 50 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model for New Vascular Diagnosis by Exposure Category (With/Without History, 6 Month baseline, 14 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Current	1.221	0.878	1.697
Recent	1.168	0.851	1.604
Prior	0.945	0.714	1.251
Ibuprofen			
Current	0.994	0.646	1.528
Recent	1.412	0.957	2.083
Prior	0.924	0.652	1.308
Naproxen			
Current	0.910	0.346	2.393
Recent	1.154	0.425	3.133
Prior	0.866	0.372	2.020
Indomethacin			
Current	0.707	0.342	1.462
Recent	0.988	0.460	2.120
Prior	1.536	0.778	3.032
Other Non-Selective NSAIDs[†]			
Current	0.823	0.399	1.697
Recent	1.475	0.760	2.865
Prior	1.041	0.565	1.920
Multiple COX-2 / NSAIDs			
Current	1.519	0.142	16.239
Recent	0.441	0.009	21.891
Prior	1.581	0.472	5.294
Vascular Disease Risk Score[‡]	1.186	1.074	1.309
COX-2 / NSAID[‡]	.	.	.
Quartile of etoricoxib prescribing for practice#	0.969	0.916	1.025

* No current, recent or prior treatment defined 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).

[†] Including aceclofenac, acemetacin, azapropazone, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, feprazone, flurbiprofen, ketoprofen, lornoxicam, mefenamic acid, nabumetone, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, tolfenamic acid, or tolmetin

[‡] In the 6 months prior to the diagnosis date for cases and the same calendar date for his/her matched controls

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 using all databases combined.

Table 51 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model
for New Vascular Diagnosis by Exposure Category
(With/Without History, 6 Month baseline, 28 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Non-exposure*	.	.	.
Etoricoxib			
Current	1.588	0.765	3.294
Recent	0.796	0.345	1.839
Prior	0.904	0.447	1.829
Rofecoxib			
Current	0.816	0.220	3.029
Recent	1.781	0.530	5.986
Prior	0.868	0.324	2.323
Celecoxib			
Current	0.853	0.329	2.208
Recent	0.697	0.254	1.913
Prior	1.445	0.679	3.074
Valdecoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Lumiracoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Meloxicam			
Current	1.118	0.501	2.497
Recent	1.374	0.623	3.028
Prior	1.048	0.507	2.164
Etodolac			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Diclofenac			

Table 51 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model for New Vascular Diagnosis by Exposure Category (With/Without History, 6 Month baseline, 28 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Current	1.269	0.926	1.739
Recent	1.112	0.804	1.539
Prior	0.924	0.696	1.227
Ibuprofen			
Current	1.112	0.744	1.662
Recent	1.451	0.978	2.152
Prior	0.805	0.560	1.156
Naproxen			
Current	1.034	0.398	2.686
Recent	0.877	0.324	2.369
Prior	0.953	0.417	2.181
Indomethacin			
Current	0.854	0.415	1.757
Recent	0.904	0.407	2.007
Prior	1.473	0.721	3.008
Other Non-Selective NSAIDs[†]			
Current	0.930	0.457	1.892
Recent	1.237	0.633	2.418
Prior	1.227	0.677	2.224
Multiple COX-2 / NSAIDs			
Current	1.533	0.145	16.161
Recent	0.449	0.009	22.058
Prior	1.603	0.476	5.397
Vascular Disease Risk Score[‡]	1.184	1.073	1.306
COX-2 / NSAID[‡]	.	.	.
Quartile of etoricoxib prescribing for practice#	0.969	0.916	1.025

* No current, recent or prior treatment defined as follows:
'Current' when the most recent exposure (calculated duration of the most recent prescription + 28 days) overlaps the 'index' date.
'Recent' when the most recent exposure (calculated duration of the most recent prescription + 28 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 + 28 days) ended on a date 61 to 180 days prior to the 'index' date (does not overlap index date).

[†] Including aceclofenac, acemetacin, azapropazone, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, feprazone, flurbiprofen, ketoprofen, lornoxicam, mefenamic acid, nabumetone, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, tolfenamic acid, or tolmetin

[‡] In the 6 months prior to the diagnosis date for cases and the same calendar date for his/her matched controls

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 using all databases combined.

Table 52 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model
for New Vascular Diagnosis by Exposure Category
(With/Without History, 12 Month baseline, 14 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Non-exposure*	.	.	.
Etoricoxib			
Current	1.435	0.612	3.367
Recent	1.138	0.481	2.691
Prior	0.745	0.325	1.712
Rofecoxib			
Current	1.508	0.312	7.282
Recent	1.289	0.309	5.383
Prior	1.053	0.334	3.321
Celecoxib			
Current	0.904	0.352	2.321
Recent	0.693	0.261	1.843
Prior	1.502	0.652	3.464
Valdecoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Lumiracoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Meloxicam			
Current	1.414	0.605	3.307
Recent	1.627	0.649	4.080
Prior	0.949	0.407	2.213
Etodolac			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Diclofenac			

Table 52 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model
for New Vascular Diagnosis by Exposure Category
(With/Without History, 12 Month baseline, 14 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Current	1.424	0.984	2.060
Recent	1.120	0.784	1.600
Prior	0.844	0.613	1.162
Ibuprofen			
Current	1.052	0.670	1.651
Recent	1.546	1.032	2.316
Prior	0.983	0.683	1.414
Naproxen			
Current	0.680	0.235	1.972
Recent	1.187	0.396	3.557
Prior	1.000	0.411	2.432
Indomethacin			
Current	1.178	0.498	2.788
Recent	1.006	0.389	2.605
Prior	1.138	0.499	2.599
Other Non-Selective NSAIDs[†]			
Current	1.249	0.544	2.867
Recent	1.012	0.450	2.278
Prior	1.299	0.630	2.682
Multiple COX-2 / NSAIDs			
Current	0.924	0.062	13.722
Recent	.	.	.
Prior	2.020	0.533	7.654
Vascular Disease Risk Score[‡]	1.179	1.069	1.299
COX-2 / NSAID[‡]	.	.	.
Quartile of etoricoxib prescribing for practice#	0.969	0.913	1.030

* No current, recent or prior treatment defined 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).

† Including aceclofenac, acemetacin, azapropazone, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, feprazone, flurbiprofen, ketoprofen, lornoxicam, mefenamic acid, nabumetone, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, tolfenamic acid, or tolmetin

‡ In the 6 months prior to the diagnosis date for cases and the same calendar date for his/her matched controls

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 using all databases combined.

Table 53 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model
for New Vascular Diagnosis by Exposure Category
(With/Without History, 12 Month baseline, 28 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Non-exposure*	.	.	.
Etoricoxib			
Current	1.640	0.764	3.521
Recent	0.805	0.323	2.004
Prior	0.874	0.394	1.941
Rofecoxib			
Current	0.819	0.187	3.586
Recent	2.656	0.710	9.932
Prior	0.814	0.242	2.734
Celecoxib			
Current	0.829	0.320	2.151
Recent	0.777	0.286	2.110
Prior	1.486	0.653	3.385
Valdecoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Lumiracoxib			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Meloxicam			
Current	1.131	0.473	2.706
Recent	1.582	0.654	3.827
Prior	1.126	0.488	2.595
Etodolac			
Current	.	.	.
Recent	.	.	.
Prior	.	.	.
Diclofenac			

Table 53 (CPRD/THIN/IMS Germany)
Results of Conditional Logistic Regression Model
for New Vascular Diagnosis by Exposure Category
(With/Without History, 12 Month baseline, 28 Day Rx, Baseline Risk Score)

Parameter	Adjusted OR	95% CI	
		Lower	Upper
Current	1.474	1.037	2.095
Recent	1.071	0.746	1.538
Prior	0.817	0.592	1.128
Ibuprofen			
Current	1.137	0.744	1.737
Recent	1.573	1.047	2.361
Prior	0.885	0.609	1.287
Naproxen			
Current	0.854	0.301	2.423
Recent	0.945	0.319	2.800
Prior	0.969	0.395	2.375
Indomethacin			
Current	1.704	0.733	3.961
Recent	0.667	0.245	1.812
Prior	1.185	0.502	2.798
Other Non-Selective NSAIDs†			
Current	1.296	0.576	2.914
Recent	0.851	0.366	1.980
Prior	1.476	0.725	3.006
Multiple COX-2 / NSAIDs			
Current	0.884	0.060	12.917
Recent	0.778	0.007	81.096
Prior	1.815	0.485	6.796
Vascular Disease Risk Score‡	1.176	1.067	1.296
COX-2 / NSAID‡	.	.	.
Quartile of etoricoxib prescribing for practice#	0.971	0.914	1.031

* No current, recent or prior treatment defined as follows:
'Current' when the most recent exposure (calculated duration of the most recent prescription + 28 days) overlaps the 'index' date.
'Recent' when the most recent exposure (calculated duration of the most recent prescription + 28 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 + 28 days) ended on a date 61 to 180 days prior to the 'index' date (does not overlap index date).

† Including aceclofenac, acemetacin, azapropazone, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, feprazone, flurbiprofen, ketoprofen, lornoxicam, mefenamic acid, nabumetone, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, tolfenamic acid, or tolmetin

‡ In the 6 months prior to the diagnosis date for cases and the same calendar date for his/her matched controls

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 using all databases combined.

10.5 Other analyses

Not applicable

10.6 Adverse events/adverse reactions

No reporting to regulatory agencies of individual Serious Adverse Events (SAE) was planned as part of this retrospective observational database study. This was 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). Aaggregated data on health outcomes of interest have been included in the interim and final reports.

11. DISCUSSION

11.1 Key results

This document describes the results of the 2015 updated analysis for a post-marketing commitment to the Committee for Medicinal Products for Human Use (CHMP) of the EMA. The updated protocol for this analysis, entitled 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 is submitted with this report. This analysis was conducted using data from the combined Clinical Practice Research Datalink and The Health Improvement Network Databases (CPRD + THIN) in the UK, and the separate IMS Disease Analyser Databases in the UK, France and Germany.

For this analysis 27,381 patients with AS met the inclusion criteria for the study. A patient entered the cohort on the date on which he or she first met entry criteria. The exposure period ended 30Jun2013 and the study period ended on 30Jun2014. The large increase in patients since the 2014 report is due to the observation 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. This was particularly an issue with the Germany IMS data where the number of patients more than doubled. This resulted in an increase in the absolute numbers of patients in many tables, but did not have a substantial effect on rates of various outcomes.

The baseline characteristics of the cohort are consistent with the known epidemiology of AS. About 41.5% of the patients entered the cohort prior to the COX-2 inhibitor Urgent Safety Restriction of 17Feb2005. The database contains a significant amount of information for the cohort, with a mean (SD) and median duration of follow-up for the cohort during the study period of 7.9 (5.5), and 6.6 years, respectively.

The baseline comorbid disease burden for the cohort was generally low. This may be due to the age of the study population (mean age 48.2 years), but it may also be partly due to the length of the baseline period during which the medical history was assessed (6 months prior to cohort entry). However, among patients with at least one year of medical records data at baseline, the baseline comorbid disease burden was also generally low. The patients who received etoricoxib as their first non-steroidal anti-inflammatory therapy following entry into the cohort had a relatively low burden of baseline comorbidity, including GI and vascular diseases, except 9.1% had a medical history of unspecified arthritis diagnosis, 8.8 % hypertension, 3.6% dyslipidemia, and 4.4% diabetes.

About a fifth **(18.3%)** of the cohort used narcotic pain medication at least once during the baseline period of 6 months while about 6-7% used rheumatic disease treatments (DMARDS and/or oral corticosteroids). Among patients who received etoricoxib as their first non-steroidal anti-inflammatory therapy following entry into the cohort 26.9% used narcotic pain medications, 18.4% rheumatic disease treatments (11.9% DMARDs, 11.5% oral corticosteroids); 26.4% gastroprotective medications, and 19.3% cardiovascular medications at least once during the 6 months prior to entry into the cohort.

Relatively few patients in the cohort received etoricoxib and the amount of exposure to the treatment is limited in this analysis. Five hundred fifty-four patients (2.0%) had a history of etoricoxib prescription during the 6-month baseline period prior to entry into the cohort. One thousand eighty (3.9%) received etoricoxib as their first non-steroidal anti-inflammatory therapy following entry into the cohort (but not necessarily their first ever etoricoxib prescription). Two thousand six-hundred forty (9.6%) received etoricoxib at any time during the study period. Among the 1,080 patients whose first non-steroidal anti-inflammatory treatment following entry in the AS cohort was etoricoxib, 459 (42.5%) had used etoricoxib during the baseline period. The doses of etoricoxib prescribed to patients in this cohort are generally consistent with the labelling for the AS indication. Among the 554 patients who had used etoricoxib during the baseline period, the mean (SD) and median dose of etoricoxib was 87.0 (21.0) and 90 mg, respectively; the maximum was 180mg. The mean (SD) and median duration of the first course of etoricoxib therapy after entry into the cohort was 104.5 (170.8) and 59 days, respectively. The mean (SD) and median total cumulative duration of etoricoxib therapy (all courses combined) during the study was 391.5 (631.2) and 105 days, respectively.

The incidences of most of the prespecified clinical outcomes of interest for this study were uncommon. The most commonly occurring clinical event, overall and among those currently exposed to etoricoxib, was hypertension. As expected, the rates of the prespecified clinical outcomes were higher for those with prior histories of these events, although there were relatively small numbers of such patients. It should be noted that interpretation of a clinical outcome rate in patients with a medical history of the same event is hampered by uncertainty as to whether the diagnosis in the medical record of a patient during follow-up is actually a new diagnosis or simply the re-recording of the prior diagnosis addressed during a follow-up clinical encounter. Overall there were 177 clinical outcome events of interest in 152 patients (104 events in 92 men and 73 events in 60 women), while 'currently' exposed to etoricoxib.

The number of incident hypertension events and the number of incident events for the composite outcome of all vascular events + sudden death in this analysis exceeded the protocol specified minimum number (700) required to conduct a case-control analysis for the association of that outcome with exposure to etoricoxib and the other non-steroidal anti-inflammatory therapies.

The primary case-control analysis was done in patients without a history of the event of interest during the baseline period. A secondary analysis was done in all patients (with and without a history of the event of interest). Interpretation of the secondary analysis results is 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 re-recording of a prior diagnosis addressed during a follow-up clinical encounter. Sensitivity analyses were done as described in the protocol and the body of this report.

Although a total of 3,066 hypertension cases and 2,288 vascular event / sudden death cases occurred during follow-up (in patients without a history of hypertension / vascular events in the 6 months before entry into the AS cohort), the prevalence of exposure to etoricoxib and the other non-steroidal anti-inflammatory drugs of interest was limited, resulting is too little data to conduct the protocol-specified separate case-control analysis in IMS UK and IMS France databases, as described in the body of the report. Therefore, the case-control analyses were conducted with the UK CPRD+THIN databases, and with the Germany IMS database, for both outcomes. As specified in the protocol two-level modelling was used to fit the data from these countries / databases to get a combined summary odds ratio.

The protocol-specified primary hypertension case-control analysis (in patients without a history of hypertension in the 6 months before entry into the AS cohort; exposure to a given medication defined as the calculated duration of the prescription + 14 days) using data from the UK CPRD+THIN and Germany IMS databases (combined) showed no association between 'current' (adjusted OR 1.35; 95% CI 0.68, 2.69), 'recent' (adjusted OR 1.23; 95% CI 0.61, 2.50) or 'prior' (adjusted OR 1.0; 95% CI 0.54, 1.86) exposure to etoricoxib and hypertension, compared with the referent group of no exposure. Although the OR estimate for 'current' etoricoxib exposure was elevated, the 95% confidence interval was very wide. Comparison of these results to those of other non-steroidal anti-inflammatory treatments

using the common non-exposed comparator was not possible due to the sparseness of the data. The results for sensitivity analyses with varying baseline periods and exposure definitions were generally similar. The secondary analyses in patients with and without a prior history of hypertension were also generally similar. As pointed out previously, interpretation of the results is 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 re-recording of a prior diagnosis addressed during a follow-up clinical encounter.

The protocol-specified primary vascular event / sudden death case-control analysis (in patients without a history of vascular events) in the 6 months before entry into the AS cohort exposure to a given medication defined as the calculated duration of the prescription + 14 days) using data from the UK CPRD+THIN and Germany IMS databases (combined) showed no association between 'current' (adjusted OR 0.95; 95% CI 0.40, 2.27), 'recent' (adjusted OR 1.67; 95% CI 0.76, 3.70) or 'prior' (adjusted OR 0.67; 95% CI 0.30, 1.52) exposure to etoricoxib and vascular events / sudden death, compared with the referent group of no exposure. Comparison of these results to those of other non-steroidal anti-inflammatory treatments using the common non-exposed comparator was not possible due to the sparseness of the data. The results of sensitivity analyses and secondary analyses were similar with respect to the findings for the etoricoxib; in none of the analyses was there definitive evidence that 'current', 'recent' or 'prior' exposure to etoricoxib is associated with an increased risk of vascular event / sudden death.

Overall, the results of this study do not change the previously established favourable benefit-risk profile for etoricoxib.

11.2. Limitations

As described in the protocol, this study has a number of limitations that potentially affect the validity of findings or the interpretation of the results. Some of the limitations are discussed briefly here; see the protocol for a detailed discussion of the limitations.
First, the data for this study are from General Practitioners (GPs). In the UK, patients are required to register with a GP and 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. 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 effects of any delays in such information being recorded by the GPs on the study results are unknown. In Germany and France, patients are not required to register with a GP as in the UK, and they may receive medical care from more than one physician for the same condition; therefore the data on medical treatments and clinical outcomes may be less complete in Germany and France compared with the UK.

Second, it is likely that the true onset of AS is earlier than recorded in medical records for most AS patients. Thus 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. It is not clear if such patients would be preferentially channelled to certain NSAIDs. In addition, mild cases of AS may go undetected. It is not clear if these issues will bias the results of the analysis.

Third, exposures to drugs in this study 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. In addition, the databases do not capture prescriptions issued by hospital-based specialists (e.g., consultant rheumatologists), nor during hospital admission. Thus there may be some degree of misclassification of exposure in this study and potential for bias as a result.

Fourth, the clinical outcomes under study are based on GP recorded diagnoses based on clinical care standards. It is expected that there is 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.

Fifth, 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 channelling bias in this study because it is feasible that patients prescribed certain non-steroidal anti-inflammatory treatments 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 a COX-2 inhibitor over non-selective NSAIDs.

11.3 Interpretation

In summary, 27,381 patients from the UK, Germany and France with AS met the inclusion criteria for this analysis. The characteristics of the cohort are 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 relatively short baseline period of 6 months 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 is limited in this analysis. The doses of etoricoxib prescribed to patients in this cohort are consistent with the EU labelling for the AS indication. The incidences of most of the prespecified clinical outcomes of interest for this study were uncommon among patients without a prior history of a given event. A total of 177 clinical outcome events of interest occurred in 152 patients (104 events in 92 men and 73 events in 60 women), while 'currently' exposed to etoricoxib. Case-control analyses of the association of etoricoxib and other NSAID exposure to hypertension and to the composite outcome of all vascular events plus sudden death showed that current, recent, or prior exposure generally did not increase the risk of these events relative to no exposure. None of the results demonstrated a significant association for etoricoxib, and the results for the other NSAIDs were generally similar. This study has a number of limitations as discussed in the Limitations section of this document.

The results of this study are consistent with the findings from the first report of the other AS safety study conducted by the MAH: Safety Data on Etoricoxib from Swedish Registries of Spondyloarthropathy / Ankylosing Spondylitis Patients which did not demonstrate a significantly increased risk of clinical outcomes for AS and SpA patients taking etoricoxib compared to those taking other Coxibs, non-selective NSAIDs or those not taking any NSAIDs. Despite the limited exposure to etoricoxib in the cohorts in the current study, and the small numbers of patients with clinical outcome events of interest while exposed to etoricoxib, the safety profile of etoricoxib in the treatment of AS appears to be consistent with the safety profile of the product as labelled and as previously demonstrated during clinical development and through post-marketing pharmacovigilance.

The MAH is submitting the 2015 report as the final report for this study.

11.4. Generalisability

This study includes 27,381 patients with AS from the UK, Germany and France. Given that there is no reason to believe that these patients with AS are not typical and the consistency of the results of this study and the study of Swedish AS patients, the results should be generalizable to patients with AS treated with etoricoxib, particularly those seen in general practice settings.

12. Other information

Not applicable

13. Conclusion

Overall, the results of this analysis suggest, given the characteristics of the patient population, the safety profile of etoricoxib in the treatment of AS is consistent with the safety profile of the product as labelled and as previously demonstrated during clinical development and through post-marketing pharmacovigilance.

14. References

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