



Risk of Upper Gastrointestinal Complications in Users of Nonsteroidal Anti-inflammatory Drugs

Study Protocol—V2.0 (Final)

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ABBREVIATIONS

AIFA	Agenzia Italiana del Farmaco
AOUD Udine	Azienda Ospedaliero Universitaria di Udine
ARS	Agenzia Regionale di Sanità (Regional Health Agency)
ASS	Azienda per i Servizi Sanitari (local health district)
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COX-2	Cyclooxygenase-2
FVG	Friuli-Venezia Giulia, Italy
GI	Gastrointestinal
ICD-9	International Classification of Diseases, Ninth Revision
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
NSAID	Nonsteroidal anti-inflammatory drug
PPV	Positive predictive value
PSUR	Periodic Safety Update Report
RTI-HS	RTI Health Solutions
SSR	Servizio Sanitario Regionale (Regional Health Service)
UGIC	Upper gastrointestinal complication

1 STUDY SYNOPSIS

Title	Risk of Upper Gastrointestinal Complications in Users of Nonsteroidal Anti-inflammatory Drugs
Rationale	<p>The gastrointestinal (GI) safety of nonsteroidal anti-inflammatory drugs (NSAIDs) has been evaluated in many epidemiologic studies across numerous populations. Very few studies have examined the risk of upper GI complications (UGIC) associated with the use of nimesulide. Relative risk from these studies comparing current use of nimesulide with nonuse of NSAIDs ranged from 2.5 (95% confidence interval [CI] 1.2-5.3) to 4.4 (95% CI 1.2-13.8). None of the studies provided information on the effect of nimesulide by dose and duration of use or on the effect measure modification of risk factors for UGIC.</p> <p>To further evaluate the GI safety of nimesulide, we propose to conduct a retrospective cohort study with a nested case-control analysis to (1) estimate the risk of UGIC associated with the use of nimesulide in a large population of users, and (2) evaluate the effect of dose and duration of nimesulide use and the role of potential risk factors for UGIC. The study will also describe the characteristics of nimesulide users over time. The findings of this study will support the evaluation of the overall safety profile of nimesulide and other NSAIDs used in Italy.</p> <p>The study will be conducted in Italy, the country with the largest number of users of nimesulide, using information from the Friuli-Venezia Giulia automated health databases and hospital medical records accessible to researchers. Results from a feasibility study completed by epidemiologists at RTI Health Solutions (RTI-HS), the Institute of Hygiene and Epidemiology of the University of Udine and Azienda Ospedaliero Universitaria di Udine (AOUD Udine), and the Agenzia Regionale della Sanità (ARS, Regional Health Agency), showed that the databases from FVG are appropriate and potentially accessible for conducting a full epidemiologic study with validation of hospital medical charts on the risk of UGIC associated with the use of individual NSAIDs, including nimesulide.</p>
Key Roles and Responsibilities	<p>A core research team of epidemiologists from RTI-HS, AOUD Udine, and ARS has been established to implement the full epidemiological study on the use of NSAIDs and the risk of UGIC. The core research team is composed of the following organizations (with each organization's role) and members:</p> <p>Scientific Coordination—RTI-HS</p> <ul style="list-style-type: none"> ▪ Susana Perez-Gutthann, MD, PhD ▪ Jordi Castellsague, MD, MPH <p>Study Coordination Center—Udine University, AOUD Udine</p> <ul style="list-style-type: none"> ▪ Fabio Barbone, MD, DrPH ▪ Federica Pisa, MD, MStat <p>Database Coordination—ARS</p> <ul style="list-style-type: none"> ▪ Loris Zanier, MD ▪ Elena Clagnan, BSc <p>The financial sponsor of this study is Helsinn Healthcare, a privately owned pharmaceutical group with headquarters in Switzerland. Helsinn, the worldwide licensor of original nimesulide, is interested in evaluating the overall benefits and risks of nimesulide. The results of this epidemiological study could be shared with the European Medicines Agency in the context of regulatory activities. The agreement for the epidemiologic study will reflect Helsinn's commitment to maintain its role as financial sponsor, while giving the research partners scientific independence, including publication of manuscripts in accord with the requirements of the International Committee of Medical Journal Editors.</p>

Objectives	<ul style="list-style-type: none"> ▪ To estimate the incidence rates of UGIC in users of nimesulide and other individual NSAIDs. ▪ To compare the risk of UGIC in users of nimesulide and other individual NSAIDs with the risk in nonusers of NSAIDs. ▪ To estimate the effect of dose and duration of nimesulide use and the potential effect modification of risk factors for UGIC. ▪ To describe the characteristics of nimesulide users and the nimesulide utilization patterns over time.
Source Population and Databases	<p>The study will be conducted in the region of FVG in northeastern Italy, which has a total population of 1.2 million. All residents in the region are registered in the Regional Health Service, which provides health care to all enrollees. FVG maintains a regional system of databases with computerized information on the individual use of health care resources. Individual records from the different databases can be linked by a unique personal identifier, the Fiscal Identification Number. The main databases in the FVG system include the Patient Identification Database, the Outpatient Prescription Database, and the Hospital Service Database.</p>
Study Design	<p>Retrospective cohort and nested case-control study of users of NSAIDs. Study cohort: All residents in the FVG region with at least 1 year of permanent residence who were prescribed nimesulide or any other NSAID between January 1, 2001, and December 31, 2008.</p>
Exclusion Criteria	<p>No exclusion criteria will be applied. This will allow us to estimate population-based incidence rates of UGIC in users of NSAIDs.</p>
Follow-up	<p>Each member of the study cohort will be followed from the first date the patient is prescribed an NSAID (start date) to the earliest of the following dates: (1) hospital admission for UGIC, (2) emigration or disenrollment from database, (3) end of study period, or (4) death.</p>
Case Definition	<p>A case of UGIC is defined as any patient with a hospital admission for hemorrhage or perforation located in the stomach and/or duodenum, or a bleeding or perforated peptic ulcer, confirmed by clinical evidence of hematemesis and/or melena, endoscopy, radiology, surgery, or autopsy. The date of hospital admission will be considered the index date.</p>
Case Identification	<p>Potential cases of UGIC will be identified through hospital discharge ICD-9 codes compatible with UGIC. Both site- and lesion-specific ICD-9 codes and nonspecific ICD-9 codes will be used to identify potential cases. Site- and lesion-specific ICD-9 codes will include acute or chronic ulcer with hemorrhage and/or perforation for gastric ulcer (ICD-9 531), duodenal ulcer (ICD-9 531), peptic ulcer site unspecified (ICD-9 533), and gastrojejunal ulcer (ICD-9 534). Nonspecific ICD-9 codes will include diagnosis potentially reflecting upper GI bleeding: hematemesis (578.0), melena (578.1), and unspecified bleeding of intestinal tract (578.9).</p>
Case Validation	<p>Once potential cases are identified, the case definition criteria for UGIC will be confirmed in a validation process that will include (1) review of computerized information and (2) review of hospital medical charts. Prior validation of hospital discharge ICD-9 codes for UGIC in the FVG database showed a high positive predictive value (PPV) for the site-specific ICD-9 codes 531 (gastric ulcer) and 532 (duodenal ulcer). However, the PPVs for the rest of ICD-9 codes were lower, between 54% and 84%. Thus, to confirm the diagnosis of UGIC, we will review the hospital medical records for the following groups:</p> <ul style="list-style-type: none"> ▪ A random sample of 100 potential cases identified with primary discharge ICD-9 codes 531 and 532. ▪ All potential cases identified with primary discharge ICD-9 codes 533, 534, and 578.

	<ul style="list-style-type: none"> All potential cases identified with secondary discharge ICD-9 codes 531, 532, 533, 534, and 578. <p>The medical data of interest will be abstracted from medical records by trained personnel using a standardized abstraction form. Final confirmation of cases will be conducted independently by two clinicians who will be blinded to exposure to NSAIDs.</p>
Nested Case-Control Study. Selection of Controls	<p>A case-control study nested in the study cohort of users of NSAIDs will be conducted to adjust simultaneously for the effect of potential confounders. All the confirmed cases identified in the study cohort will be included in the case-control analysis. Density-based sampling will be used to select controls from the whole study cohort. Controls will be randomly selected from the unique set of members of the study cohort who are at risk at the index date of each case (risk set). This procedure ensures that the probability of being selected as a control is proportional to the amount of person-time at risk of each member of the study cohort. A total of 20,000 controls will be selected using this procedure.</p>
Exposure Assessment	<p>For each person, exposure to each NSAID will be ascertained using the days of supply of each individual prescription. Days of supply will be estimated according to defined daily dose, number of boxes prescribed, number of units, and strength of the medication. This will be supplemented with results from analyses of the time between consecutive prescriptions.</p> <p>Exposure to each individual NSAID in both the cohort and the nested case-control study will be aggregated in four mutually exclusive categories: current use, recent use, past use, and nonuse. The current use of multiple NSAIDs and switching among NSAIDs will be also assessed.</p>
Assessment of Dose and Duration	<p>The daily dose for each NSAID will be derived from the analyses of the time between consecutive prescriptions and prescribing information (strength, number of units, and number of boxes). The estimated daily dose of each NSAID will be categorized as low-medium or high according to predetermined cutoff values.</p> <p>Duration of current use of each individual NSAID is defined as the cumulative person-time of consecutive current use, allowing for a maximum 30-day gap between the end of the previous prescription and start of the current prescription.</p>
Confounding	<p>Potential confounding factors are those potentially related to the risk of UGIC and the prescription of NSAIDs. The main risk factors for UGIC are increasing age, male gender, prior peptic ulcer disease, and prior peptic ulcer complications. Severe comorbidity and life-threatening conditions and concurrent use of other medications are also potential confounding factors. The presence of these potential confounding factors will be ascertained at cohort entry and at the index date, and their effect will be examined in the analysis.</p> <p>Concurrent use of any prescription medication will be also considered in the analysis. Relevant medications include aspirin, platelet aggregation inhibitors, anticoagulants, antacids, H₂-receptor antagonists, proton pump inhibitors, oral corticosteroids, antirheumatic drugs, bisphosphonates, nitrovasodilators, and selective serotonin reuptake inhibitors.</p>
Study Size	<p>Results from the feasibility study show that nimesulide is the NSAID most frequently used in FVG, with an average of about 79,000 users per year from 2001 through 2008. According to the use of nimesulide, this study should be able to detect, with a statistical power of at least 80%, a true relative risk of 1.5 for the comparison of nimesulide with nonuse of NSAIDs.</p>
Statistical Analysis	<p>Cohort Analysis</p> <p><i>Cohort Description</i></p> <p>Standard descriptive analyses will describe the baseline and follow-up</p>

	<p>characteristics of patients exposed to each individual NSAID, and any changes over the study period.</p> <p><i>Estimation of Incidence Rates</i></p> <p>Crude age- and sex-specific and age- and sex-adjusted incidence rates and 95% confidence intervals (CIs) of UGIC will be estimated for each period of exposure to each individual NSAID and for the period of nonuse of any NSAID.</p> <p><i>Estimation of Incidence Rate Ratios</i></p> <p>Poisson regression analysis will be used to estimate age- and sex-adjusted rate ratios comparing the rates for each period of exposure to each individual NSAID with the rates for the period of nonuse of any NSAID.</p> <p>Nested Case-Control Analysis</p> <p>Unconditional multiple logistic regression will be used to estimate crude and adjusted odds ratios comparing the risk of UGIC during the periods of exposure to each individual NSAID with the risk during the period of nonuse of NSAIDs. Stratified analysis will be conducted according to categories of relevant risk factors.</p> <p><i>Analysis of New Users of NSAIDs</i></p> <p>A secondary analysis will be conducted restricting the study cohort to new users of NSAIDs, defined as those members of the study cohort who at the time of cohort entry had not received any NSAID in the prior 12 months. The analysis of inception cohorts of new users avoids potential biases associated with the inclusion of prevalent users, mainly potential underascertainment of events occurring at the start of therapy, and inability to control for risk factors that may be modified by the study drugs.</p>
Ethical and Scientific Review Procedures	<p>Institutional review board (IRB) approval and/or any other required reviews by specific committees will be obtained in accord with applicable national and local regulations.</p> <p>The study will be conducted under Good Pharmacoepidemiology Practices (International Society for Pharmacoepidemiology [ISPE]), Ethical Guidelines for Epidemiological Studies (Council for International Organizations of Medical Sciences [CIOMS]), and International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS).</p> <p>The study will comply with the definition of the noninterventional (observational) study provided in Article 2(c) of Directive 2001/20/EC and its refinement provided in Chapter I.7 Section 1 of Volume 9A of the Rules governing Medicinal Products in the European Union.</p> <p>Informed consent to retrieve original medical records will be administered as needed according to applicable local regulations.</p>
Regulatory Communication Plan	<p>Protocol, study status, and report(s) could be included in regulatory communications in line with the risk management plan, Periodic Safety Update Report (PSUR), and other regulatory milestones and requirements.</p>
Publication and Communication Plan	<p>Study results will be published following the International Committee of Medical Journal Editors (ICMJE) guidelines, and communication in appropriate scientific venues, e.g., ISPE, will be considered.</p>

2 BACKGROUND

The gastrointestinal (GI) safety of nonsteroidal anti-inflammatory drugs (NSAIDs) has been evaluated in many epidemiologic studies across numerous populations. However, very few studies have investigated the risk of upper GI complications (UGIC) associated with nimesulide as used in clinical practice (Appendix A). The largest of these studies was a

matched case-control study conducted in Finland between 2000 and 2004 with 9,191 cases and 41,780 controls. A total of 259 cases were exposed to nimesulide (Helin-Salmivaara et al., 2007). Cases were ascertained according to hospital discharge ICD-9 (International Classification of Diseases, 9th Revision) codes without validation of the recorded diagnoses. Another large matched case-control study conducted in Italy and Spain provided data on nimesulide. The study included 2,813 cases and 7,193 controls; 48 cases were exposed to nimesulide (Laporte et al., 2004). Three other smaller studies, all conducted in Italy, estimated the risk of UGIC associated with the use of nimesulide (García Rodríguez et al., 1998; Menniti-Ippolito et al., 1998; Pilotto et al., 2003). The relative risk for UGIC comparing current use of nimesulide with nonuse of NSAIDs estimated in these five studies ranged from 2.5 (95% CI, 1.2-5.3) to 4.4 (95% CI, 1.2-13.8). In general, information for nimesulide from these studies was scarce; none of the studies examined the effect of nimesulide according to dose and duration of use, or the potential effect measure modification of risk factors for UGIC.

With the goal to further evaluate the GI safety of nimesulide, we propose to conduct a retrospective cohort study with a nested case-control analysis to estimate the risk of UGIC associated with the use of nimesulide and other individual NSAIDs in a large population of users, and to evaluate the effect of dose and duration of use of individual NSAIDs and the role of potential risk factors for UGIC. The study will also describe the characteristics of nimesulide users over time. Overall, the findings of this study will support the evaluation of the overall safety profile of nimesulide and other NSAIDs used in Italy, as well as describe the potential changes in drug prescription patterns over the last years.

The study will be conducted in Italy, the country with the largest number of nimesulide users, using information from the health databases of the Friuli-Venezia Giulia (FVG) region in northeastern Italy. A feasibility study recently completed by epidemiologists at RTI Health Solutions (RTI-HS), the Institute of Hygiene and Epidemiology of the University of Udine and Azienda Ospedaliero Universitaria di Udine (AOUD Udine), and the Agenzia Regionale della Sanità (ARS, Regional Health Agency) showed that the databases from FVG are appropriate and potentially accessible for conducting a full epidemiological study, with validation of hospital medical charts, on the risk of UGIC associated with the use of individual NSAIDs, including nimesulide (Castellsague et al., 2009).

3 KEY ROLES AND RESPONSIBILITIES

A core research team of epidemiologists from RTI-HS, AOUD Udine, and ARS has been established to implement the full epidemiological study on the use of NSAIDs and the risk of UGIC. The core research team is composed of the following organizations (with each organization's role) and members:

Scientific Coordination—RTI-HS

- Susana Perez-Gutthann, MD, PhD
- Jordi Castellsague, MD, MPH

Study Coordination Center—Udine University, AOUD Udine

- Fabio Barbone, MD, DrPH
- Federica Pisa, MD, MStat

Databases Coordination—ARS

- Loris Zanier, MD
- Elena Clagnan, BSc

The core research team is responsible for designing, implementing, and communicating results of the study. Members of the core research team will also provide training and coaching to personnel involved in the project on methods for case studies and use of automated health databases for the conduct of safety epidemiology studies.

The core research team will work in close collaboration with experts in the Servizio Sanitario Regionale (SSR, Regional Health Service), including Dr. Francesca Tosolini, who leads the Department of Pharmaceutical Services (Servizio Assistenza Farmaceutica) in the Region.

3.1.1 Financial Sponsorship

The financial sponsor of this study is Helsinn Healthcare S.A. (Helsinn), a privately owned pharmaceutical group with headquarters in Switzerland. Helsinn, the worldwide licensor of original nimesulide, is interested in evaluating the overall benefits and risks of nimesulide, including the potential risk of gastrointestinal complications associated with the use of the product. The results of this epidemiological study could be shared with the European Medicines Agency in the context of regulatory activities. The agreement for the epidemiological study reflects Helsinn's commitment to maintain its role as financial sponsor, while giving the research partners—RTI-HS, Udine University, AOUD Udine, and ARS—scientific independence, including publication of manuscripts consistent with the requirements of the International Committee of Medical Journal Editors (<http://www.icmje.org/>).

4 OBJECTIVES

The objectives of this retrospective cohort study are the following:

- To estimate the incidence rates of UGIC in users of nimesulide and other individual NSAIDs.

- To compare the risk of UGIC in users of nimesulide and other individual NSAIDs with the risk in nonusers of NSAIDs.
- To estimate the effect of dose and duration of use of nimesulide and the potential effect modification of risk factors for UGIC.
- To describe the characteristics of users and the utilization patterns of nimesulide over time.

5 SOURCE POPULATION

The study will be conducted in the region of FVG in northeastern Italy with a total population of 1.2 million. All residents in the region are registered in the Regional Health Service, which provides health care to all enrollees. Health care services are provided practically free of charge. FVG maintains a regional system of databases with computerized information on the individual use of health care resources. Individual records from the different databases can be linked by a unique personal identifier, the Fiscal Identification Number. The main databases in the FVG system include the Patient Identification Database, the Outpatient Prescription Database, and the Hospital Service Database. A brief description of each database follows.

5.1 Patient Identification Database

The Patient Identification Database contains demographic and vital information of all residents in the region since 1970. The following variables are recorded for each person: first name, last name, sex, date of birth, municipality or township (“comune”) of birth, country of birth, individual regional health care code, fiscal code, citizenship, municipality or township (“comune”) of current residence, address of current residence, vital status, date of death, local health district (azienda per i servizi sanitari [ASS], and general practitioner or pediatrician. Continuous and complete data for the whole FVG region have been recorded since 1970.

5.2 Outpatient Prescription Database

The Outpatient Prescription Database includes data from prescription medications dispensed in the pharmacies of the region since 1991. Information recorded for each prescription includes the date of prescription, drug name, formulation, strength, number of units, and number of refills.

Only reimbursed medications are registered in the prescription database. Reimbursed medications are those included in the Italian National Prescription Formulary that are prescribed for approved indications and are written by prescribing physicians on the official prescription pad. Regarding NSAIDs, the AIFA Note number 66 issued in 1994 restricts the full reimbursement of nonselective NSAIDs and of cyclooxygenase-2 (COX-2)-selective inhibitor NSAIDs to patients affected by the following conditions:

- Arthropathy for connective tissue diseases
- Osteoarthritis pain or inflammation
- Neoplastic pain
- Acute gout arthritis

Based on sales data from pharmacy wholesale systems, it is estimated that about 50% of NSAID prescriptions are not captured in the prescription database. This impacts primarily the use of NSAIDs outside of reimbursed indications and the use for acute conditions.

5.3 Hospital Service Database

The Hospital Service Database contains hospital discharge diagnoses and medical procedures from all public and private hospitals. There are 24 hospitals in FVG, 18 public and 6 private. Twenty hospitals are general hospitals and four are specialty hospitals (one pediatric, two rehabilitation, and one oncology hospital). The largest hospitals in terms of annual number of discharges are the hospitals of Udine, Trieste, and Pordenone, accounting for 48% of all hospital discharges in FVG in 2008.

Recorded data in the Hospital Service Database includes one principal discharge diagnosis and up to five secondary discharge diagnoses and six procedures. The principal discharge diagnosis is the disease or condition primarily responsible for the need for care, intervention, or diagnostic procedures. If more than one disease or condition is listed as the principal diagnosis, the principal diagnosis is the one consuming more resources. Secondary diagnoses refer to diseases or conditions present at admission or developing during the in-hospital stay if they influence the treatment or length of stay. Diagnoses and procedures are recorded using the Internal Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM).

The quality of the data recorded in FVG databases is good, particularly beginning in 2001 when new quality control measures were implemented.

6 STUDY COHORT

The study will be implemented in a cohort of users of systemic NSAIDs identified in the source population. The study cohort will include all residents in the FVG region with at least 1 year of permanent residence who are prescribed nimesulide or any other NSAID between January 1, 2001, and December 31, 2008. The individual NSAIDs available in FVG during the period 2001-2008 are presented in Table 1.

Table 1. Individual NSAIDs available in FVG, 2001-2008

Aceclofenac	Ibuprofen
Acetametacin	Indomethacin
Mefenamic acid	Ketoprofen
Tiaprofenic acid	Lornoxicam
Amtolmetin	Meloxicam
Celecoxib	Nabumetone
Cinnoxycam	Naproxen
Dexibuprofen	Nimesulide
Diclofenac	Oxaprozin
Diclofenac + misoprostol	Piroxicam
Etoricoxib	Proglumetacin
Fentiazac	Sulindac
Flurbiprofen	Tenoxicam
Furaprofen	

Users of NSAIDs will be identified in the Outpatient Prescription Database, in which information for each reimbursed prescription is recorded. According to the reimbursement conditions for NSAIDs in Italy, the study cohort will be composed of patients prescribed NSAIDs for approved conditions—arthropathy for connective tissue diseases, osteoarthritis pain or inflammation, neoplastic pain, and acute gout arthritis.

6.1 Exclusion Criteria

No exclusion criteria will be applied. This will allow us to estimate population-based incidence rates of UGIC in users of NSAIDs.

Severe comorbidity may be associated with the risk of UGIC and the prescription and use of NSAIDs and may introduce confounding in the effect estimates. Although confounding can be controlled by restricting the study population to patients without specific comorbidities, we will examine the effect of comorbidity through stratified and multivariate analysis. The main comorbidities that will be considered in the analysis are specified in Section 10 on confounding.

6.2 Follow-up

Each member of the study cohort will be followed from the first date the patient is prescribed an NSAID (start date) to the earliest of the following dates: (1) hospital admission for UGIC, (2) emigration or disenrollment from database, (3) end of study period, or (4) death.

7 CASE ASCERTAINMENT

7.1 Case Definition

A case of UGIC is defined as any patient with a hospital admission for hemorrhage or perforation located in the stomach and/or duodenum, or a bleeding or perforated peptic ulcer, confirmed by clinical evidence of hematemesis and/or melena, endoscopy, radiology, surgery, or autopsy. The date of hospital admission will be considered to be the index date.

7.2 Case Identification

Potential cases of UGIC will be identified through primary and secondary hospital discharge diagnoses for UGIC. Both site- and lesion-specific ICD-9 codes and nonspecific ICD-9 codes will be used to identify potential cases (Table 2).

The pilot validation of cases of UGIC conducted as part of the feasibility study showed that about 29% of cases identified through secondary diagnoses were confirmed cases of UGIC (Castellsague et al., 2009). Thus, inclusion of secondary diagnoses can result in a more complete detection of cases of UGIC.

Table 2. ICD-9 Diagnosis Codes for Upper Gastrointestinal Complications

ICD-9 Code	Code Description
Site-specific codes	
531.0	Gastric ulcer acute with hemorrhage
531.1	Gastric ulcer acute with perforation
531.2	Gastric ulcer acute with hemorrhage and perforation
531.4	Gastric ulcer chronic or unspecified with hemorrhage
531.5	Gastric ulcer chronic or unspecified with perforation
531.6	Gastric ulcer chronic or unspecified with hemorrhage and perforation
532.0	Duodenal ulcer acute with hemorrhage
532.1	Duodenal ulcer acute with perforation
532.2	Duodenal ulcer acute with hemorrhage and perforation
532.4	Duodenal ulcer chronic or unspecified with hemorrhage
532.5	Duodenal ulcer chronic or unspecified with perforation
532.6	Duodenal ulcer chronic or unspecified with hemorrhage and perforation
534.0	Gastrojejunal ulcer acute with hemorrhage
534.1	Gastrojejunal ulcer acute with perforation
534.2	Gastrojejunal ulcer acute with hemorrhage and perforation
534.4	Gastrojejunal ulcer chronic or unspecified with hemorrhage
534.5	Gastrojejunal ulcer chronic or unspecified with perforation
534.6	Gastrojejunal ulcer chronic or unspecified with hemorrhage and perforation

ICD-9 Code	Code Description
Lesion-specific codes	
533.0	Peptic ulcer acute with hemorrhage
533.1	Peptic ulcer acute with perforation
533.2	Peptic ulcer acute with hemorrhage and perforation
533.4	Peptic ulcer chronic or unspecified with hemorrhage
533.5	Peptic ulcer chronic or unspecified with perforation
533.6	Peptic ulcer chronic or unspecified with hemorrhage and perforation
Nonspecific codes	
578.0	Hematemesis
578.1	Blood in stool
578.9	Hemorrhage of gastrointestinal tract, unspecified

7.3 Case Validation

Once potential cases are identified, the case definition criteria for UGIC will be confirmed in a validation process that will include (1) the review of computerized information and (2) the review of hospital medical charts. Potential cases not meeting the case definition criteria after the validation process will not be considered as final cases. Reasons for final case exclusion may include, among others, wrong ICD-9 code, lack of diagnostic procedures, or evidence of bleeding or perforation from sites other than the stomach or the duodenum (e.g., rectorrhagia from hemorrhoids, bleeding from esophageal varices). The two steps of the case validation process are described below.

7.3.1 *Review of Computerized Information*

The computerized longitudinal health information of potential cases will be reviewed to ascertain hospital discharge diagnoses and ICD-9 codes. The review will be conducted with the investigator blind to exposure to NSAIDs.

7.3.2 *Review of Hospital Medical Charts*

Prior validation of primary hospital discharge ICD-9 codes for UGIC in the FVG database showed a high positive predictive value (PPV) for the site-specific ICD-9 codes 531 (PPV 100%) and 532 (PPV 93%) (Table 3). However, the PPVs for the rest of the ICD-9 codes were lower; PPVs ranged from 84% for ICD-9 code 534 to 54% for code 578.9 (Cattaruzzi et al., 1999; García Rodríguez et al., 1998).

To confirm the diagnosis of UGIC, we plan to review the hospital medical records for the following sets of cases (see Table 2 for specific four-digit codes):

- A random sample of 100 potential cases identified with primary discharge ICD-9 codes 531 and 532.
- All potential cases identified with primary discharge ICD-9 codes 533, 534, and 578.
- All potential cases identified with secondary discharge ICD-9 codes 531, 532, 533, 534, and 578.

The medical data of interest will be abstracted from medical records by trained personnel using a computerized standardized abstraction form. Information to be abstracted will include admission and discharge diagnosis and dates, clinical findings, summary of results from diagnostic and therapeutic procedures (radiology, endoscopy, surgery, and autopsy), in-hospital death, laboratory test results, blood transfusions, and use of medications before admission.

Final confirmation of cases according to the study case definition will be conducted independently by two clinicians. Validation will be conducted with investigators blinded to NSAID exposure. Discrepancies will be solved by discussion and consensus between the two investigators.

Table 3. ICD-9 Diagnosis Codes and Positive Predictive Value for Upper Gastrointestinal Complications

ICD-9 Code	ICD-9 Description	PPV
Site-specific codes		
531 ^a	Gastric ulcer	100%
532 ^a	Duodenal ulcer	93%
534 ^a	Gastrojejunal ulcer	84%
Lesion-specific codes		
533 ^a	Peptic ulcer	80%
Nonspecific codes		
578.0	Hematemesis	67%
578.1	Blood in stool	65%
578.9	Hemorrhage of gastrointestinal tract, unspecified	54%

ICD-9 = International Classification of Diseases, Ninth Revision; PPV = positive predictive value.

^a Includes 53X.0, acute with hemorrhage; 53X.1, acute with perforation; 53X.2, acute with hemorrhage or perforation; 53X.4, chronic or unspecified with hemorrhage; 53X.5, chronic or unspecified with perforation; 53X.6, chronic or unspecified with hemorrhage or perforation

Source: Cattaruzzi et al., 1999; García Rodríguez et al., 1998.

7.3.3 Classification of Confirmed Cases

Confirmed cases will be classified according to the following characteristics:

- Site of lesion: gastric, duodenal, gastrojejunal (anastomotic), multiple, unknown (evidence of hematemesis and/or melena only)

- Type of complication: bleeding, perforation, bleeding and perforation.
- Type of lesion: peptic ulcer, erosion, gastritis, duodenitis, other.
- Diagnosis: endoscopy, radiology, surgery, autopsy, clinical (hematemesis and/or melena).

8 NESTED CASE-CONTROL STUDY: SELECTION OF CONTROLS

A case-control study nested in the study cohort of NSAID users will be conducted to estimate the risk of UGIC associated with the use of NSAIDs, adjusting simultaneously for the effect of potential confounders. All the confirmed cases identified in the study cohort will be included in the case-control analysis. Density-based sampling will be used to select controls from the whole study cohort. In density-based sampling, the probability of each member of the study cohort being selected as control is proportional to his or her person-time at risk. Density-based sampling in case-control studies provides valid estimates of the incidence rate ratio in the population studied when the sampling is conducted independently of exposure (Rothman, 2002).

To implement density-based sampling, controls will be randomly selected from the unique set of members of the study cohort who are at risk at the index date of each case (risk set).

Overall, this procedure ensures that the probability of being selected as a control is proportional to the amount of person-time at risk of each member of the study cohort. A total of 20,000 controls will be selected using this procedure. All selected controls will be eligible to become cases if they experience UGIC. Similarly, all selected controls remaining in the study cohort after selection will remain eligible to be selected as controls one or more times.

9 EXPOSURE ASSESSMENT

For each person, exposure to each NSAID will be ascertained using the days of supply of each individual prescription. Days of supply will be estimated according to defined daily dose and dispensing information including number of boxes, number of units, and strength of the medication. This will be supplemented with results from descriptive analyses of the time between consecutive prescriptions. The ascertainment of exposure is described below for the cohort study and the nested case-control study.

9.1 Cohort Study

The person-time of exposure to each individual NSAID will be aggregated in four mutually exclusive categories: current use, recent use, past use, and nonuse, defined as follows:

- **Current use:** person-time from the date of prescription of an NSAID to the end of days of supply plus 7 days. The extended time window of 7 days is intended to account for potential delays in the diagnosis of UGIC or the initiation of treatment.
- **Recent use:** person-time from the end of current use to 60 days after.
- **Past use:** person-time from the end of recent use to 90 days after.
- **Nonuse:** person-time after the end of past use.

9.2 Nested Case-Control Study

The same mutually exclusive exposure categories as those in the cohort study will be assessed in the nested case-control study. Exposure status will be ascertained for each individual NSAID according to the most recent dispensing before the index date. The index date for cases is the date of occurrence of the study endpoint: hospitalization for UGIC. The index date for each set of controls is the index date of the corresponding case (see Section 6 for details). Exposure categories in the nested case-control study are defined as follows:

- **Current use:** when the supply of the most recent dispensing for a specific NSAID overlapped the index date or ended within 7 days before the index date.
- **Recent use:** when the supply of the most recent dispensing ended from 8 days through 67 days before the index date.
- **Past use:** when the supply of the most recent dispensing ended from 68 through 157 days before the index date.
- **Nonuse:** when the supply of the most recent dispensing ended 158 days or more before the index date.

In addition, current use of each individual NSAID will be classified according to the following mutually exclusive categories:

- **Current single use:** current use of only one individual NSAID without recent use of a different NSAID.
- **Current switching use:** current use of only one individual NSAID with recent use of a different NSAID.
- **Current multiple use:** current use of more than one NSAID with or without recent use of other NSAIDs.

9.3 Assessment of Dose and Duration

The effect of daily dose will be estimated for current single users of each NSAID. The daily dose for each NSAID will be derived from the analyses of the time between consecutive prescriptions and prescribing information (strength, number of units, and number of boxes). For single, nonconsecutive prescriptions, the daily dose will be estimated from prescribing

information and defined daily dose. The estimated daily dose of each NSAID will be categorized as low-medium or high according to pre-determined cutoff values.

Duration of current use of each individual NSAID is defined as the cumulative person-time of consecutive current use, allowing for a maximum 30-day gap between the end of previous prescription and start of current prescription.

10 CONFOUNDING

Potential confounding factors are those potentially related to the risk of UGIC and the prescription of NSAIDs. A meta-analysis of observational studies showed that the main risk factors for UGIC are increasing age, male gender, prior peptic ulcer disease, and prior peptic ulcer complications (Hernández-Díaz and García Rodríguez, 2000). Severe comorbidity and life-threatening conditions, and concurrent use of other medications, are also potential confounding factors. The presence of these potential confounding factors will be ascertained at cohort entry and at the index date, and their effect will be examined in the analysis. Information for severe comorbidity and life-threatening conditions will be derived from prior hospitalizations recorded in the Hospital Database, and prior and concurrent use of specific medications will be identified in the Outpatient Prescription Database.

Assessment of severe comorbidity will include the following main conditions: alcohol-related diseases, liver disease, coagulopathies, malignancies, rheumatic disease, cardiovascular disease, cerebrovascular disease, asthma, chronic obstructive pulmonary disease, renal insufficiency, HIV infection, and organ transplant. In addition, hospitalizations for any cause prior to the index date will be examined.

Concurrent use of any prescription medication will be considered in the analysis. Medications will be categorized according to the Anatomical Therapeutic Chemical classification (<http://www.whocc.no/atcddd/>). Relevant medications include aspirin, platelet aggregation inhibitors, anticoagulants, antacids, H₂-receptor antagonists, proton pump inhibitors, oral corticosteroids, antirheumatic drugs (gold preparations, penicillamine, and methotrexate), bisphosphonates, nitrovasodilators (glyceryl trinitrate, isosorbide dinitrate, isosorbide mononitrate, transdermal nitroglycerin, other organic nitrates), and selective serotonin reuptake inhibitors. The effect of the use of other medications will be also evaluated.

11 STUDY SIZE

Sample size and power calculations are presented in Figure 1. Estimations are based on risks and risk ratios as approximations of rates and rate ratios. Calculations were conducted according to the following parameters:

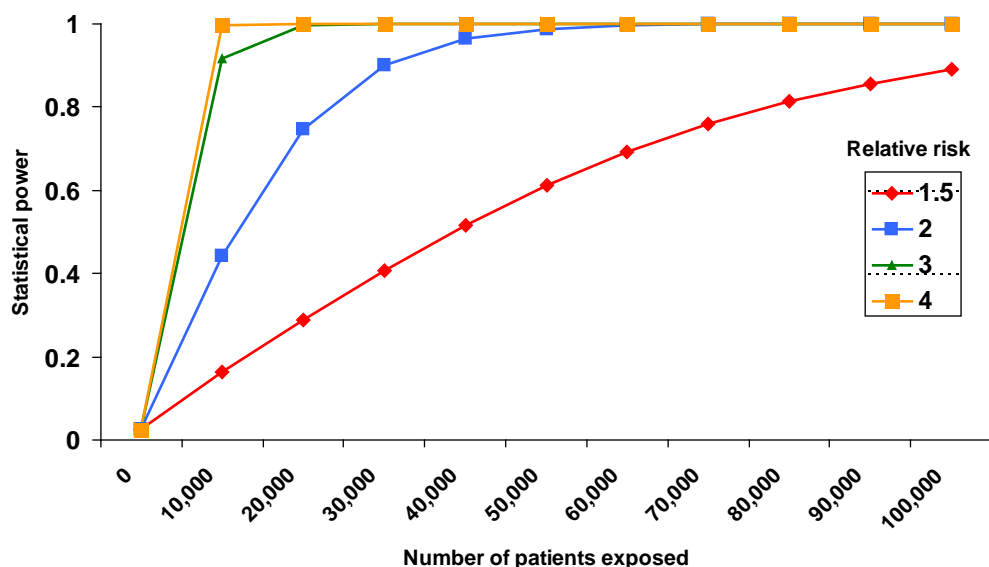
- Incidence of UGIC in unexposed subjects (nonusers of NSAIDs) of 1 case per 1,000 persons per year (Hernández-Díaz and García Rodríguez, 2001)

- Ratio of the number of unexposed subjects to the number of exposed subjects of 1:1.
- True risk ratios of 1.5, 2.0, 3.0, and 4.0.
- Z value of 1.96, corresponding to a two-sided significance level alpha of 0.05.

Calculations were conducted with Episheet developed by Kenneth Rothman (Rothman and Boice, 1979). Assuming a ratio of the number of unexposed to exposed subjects of 1:1, a total of 80,000 patients exposed to an individual medication would be required to detect a significant risk ratio given that the true risk ratio is 1.5 with a probability of 0.80. The sample size decreases to 22,500 patients to detect a significant risk ratio given the true risk ratio is 2.0 with a probability of 0.80.

Results from the feasibility study regarding the number of users in FVG for the period 2001-2008 are presented in Appendix B. Nimesulide is the NSAID most frequently used in FVG, with an average of about 79,000 users per year between 2001 through 2008. Diclofenac and celecoxib are the two next most used NSAIDs, with about 35,000 and 21,000 users per year, respectively. Given the use of nimesulide, this study should be able to detect, with a statistical power of at least 80%, a true relative risk of 1.5 for the comparison of nimesulide with nonuse of NSAIDs.

Figure 1. Statistical Power According to the Number of Patients Exposed and the Relative Risk to be Detected



12 STATISTICAL ANALYSIS

Analyses will be conducted separately in the cohort study and in the nested case-control study. Analysis in the cohort study will include the description of the study cohort and the estimation of incidence rates and crude and age- and sex-adjusted incidence rate ratios. The nested case-control analysis will include the estimation of relative risks adjusted for potential confounders. A description of these analyses follows.

12.1 Cohort Analysis

12.1.1 Cohort Description

Standard descriptive analysis tables will be produced to describe the baseline and follow-up characteristics of patients exposed to nimesulide and to each individual NSAID, and any changes over the study period in relation to labeling variations.

12.1.2 Estimation of Incidence Rates

Person-time of exposure to each individual NSAID will be aggregated across all subjects in the study cohort according to the different periods of exposure: current use, recent use, past use, and nonuse.

Crude and age- and sex-specific incidence rates and 95% confidence intervals (CI) of UGIC will be estimated for each period of exposure to each individual NSAID, and for the period of nonuse of any NSAID. Incidence rates will be calculated as the ratio between the number of cases of UGIC in each period of exposure and the corresponding person-time.

Age- and sex-adjusted incidence rates and 95% CIs of UGIC will be computed for each period of exposure to each NSAID and for the period of nonuse of NSAIDS.

12.1.3 Estimation of Incidence Rate Ratios

Poisson regression analysis will be used to estimate age- and sex-adjusted rate ratios comparing the rates for each period of exposure to each individual NSAID with the rates for the period of nonuse of any NSAID. Results will be presented as incidence rate ratios relative to periods of nonuse of any NSAID, with 95% CIs.

12.2 Nested Case-Control Analysis

We will conduct a nested case-control analysis to adjust relative risk estimates for the additional confounders described in Section 10. Unconditional multiple logistic regression will be used to estimate crude and adjusted odds ratios comparing the risk of UGIC during

the periods of exposure to each individual NSAID with the risk during the period of nonuse of NSAIDs. The odds ratios obtained in case-control studies are a valid estimate of the incidence rate ratio in the study population, particularly when evaluating uncommon events.

In addition, multiple logistic regression will be used to estimate the effect of dose and duration of NSAID use on the risk of UGIC. Also, stratified analyses will be conducted according to categories of relevant risk factors.

12.2.1 Analysis of New Users of NSAIDs

A secondary analysis will be conducted restricting the study cohort to new users of NSAIDs (inception cohort). New users are defined as those members of the study cohort who at the time of cohort entry (date of first prescription for an NSAID during the study period) had not received any NSAID in the prior 12 months. Analysis of the inception cohort (new users) avoids potential biases associated with the inclusion of prevalent users. Inclusion of prevalent users may result in underascertainment of events that occur at the start of therapy and in the inability to control for risk factors that may be modified by the study drugs (Ray, 2003). Prevalent users might be survivors of the earlier period of treatment, which may introduce bias in the study results if the risk varies with time. There is some evidence that the risk of UGIC in users of NSAIDs may be higher at the beginning of therapy, although some studies have found a similar risk of UGIC in prevalent and new users of NSAIDs (Hernández-Díaz and García Rodríguez, 2001). Potential biases secondary to modification of risk factors by the study drugs can be avoided by measuring these factors at the beginning of therapy, i.e., in new users, when they are not influenced by the treatment.

13 ETHICAL AND SCIENTIFIC REVIEW PROCEDURES

Institutional review board (IRB) approval and/or any other required reviews by specific committees will be obtained according to applicable national and local regulations.

The study will be conducted under Good Pharmacoepidemiology Practices (International Society for Pharmacoepidemiology [ISPE];

https://www.pharmacoepi.org/resources/guidelines_08027.cfm), Ethical Guidelines for Epidemiological Studies (Council for International Organizations of Medical Sciences [CIOMS]; http://www.cioms.ch/frame_ethical_guidelines_2009.htm), and International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS; http://www.cioms.ch/frame_guidelines_nov_2002.htm).

The study will comply with the definition of the noninterventional (observational) study provided in Article 2(c) of Directive 2001/20/EC and its refinement provided in Chapter I.7 Section 1 of Volume 9A of the Rules governing Medicinal Products in the European Union (http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2005/12-05/draft_of_volume_9a_12_2005.pdf).

14 REGULATORY COMMUNICATION PLAN

Protocol, study status, and report(s) could be included in regulatory communications in line with the risk management plan, Periodic Safety Update Report (PSUR), and other regulatory milestones and requirements.

15 PUBLICATION AND COMMUNICATION PLAN

Study results will be published following the International Committee of Medical Journal Editors (ICMJE) guidelines, and communication in appropriate scientific venues, e.g., ISPE, will be considered.

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Appendix A: Epidemiologic Studies

Table A-1. Epidemiologic Studies on the Risk of Upper Gastrointestinal Complications Associated With the Use of Nimesulide

Reference Country	Setting	Study Period	Study Design	Age	Case Definition	Number of Cases	Number of Cases/Controls Exposed to Nimesulide	Relative Risk (95% CI) for Nimesulide
Helin-Salmivaara et al. 2007 Finland	National Hospital Discharge and Prescription Registries	2000-2004	Case-control	All	Hospitalization for upper GI bleeding, perforation, ulceration. No case validation.	9,191	259/325	4.0 (3.23-4.96)
Laporte et al. 2004 Spain and Italy	Hospital network	1998-2001	Multicenter case-control	>18 years	Upper GI bleeding confirmed by endoscopy	4,309	48/46	3.2 (1.9-5.6)
Pilotto et al. 2003 Italy	Geriatric department	1997-2000	Case-control	>65 years	Upper GI bleeding confirmed by endoscopy	199	3/10	4.1 (1.2-13.8)
Menniti-Ippolito et al. 1998 Italy	Umbria residents	1993-1994	Cohort and nested case-control	35-84 years	Hospitalization for upper GI bleeding, perforation. Case validation performed.	326	14 cases (8,047 person-years of exposure)	2.5 (1.2-5.3)
García Rodríguez et al. 1998 Italy	Udine residents	1991-1995	Nested case-control	25-89 years	Hospitalization for upper GI bleeding, perforation. Case validation performed.	1,505	15/90	4.4 (2.5-7.7)

GI = gastrointestinal; NSAIDs = nonsteroidal anti-inflammatory drugs.

Appendix B:

Use of NSAIDs in Friuli-Venezia Giulia

Table B-1. Number of Patients Prescribed Oral NSAIDs in FVG, 2001-2008

NSAID	Year								Annual mean 2001-2008
	2001 <i>n</i>	2002 <i>n</i>	2003 <i>n</i>	2004 <i>n</i>	2005 <i>n</i>	2006 <i>n</i>	2007 <i>n</i>	2008 <i>n</i>	
Nimesulide	90,225	86,368	81,237	84,683	78,096	78,045	69,523	68,952	79,641
Diclofenac	33,932	35,683	32,304	33,396	33,999	34,591	36,540	39,074	34,940
Celecoxib	43,305	35,356	34,863	25,239	8,023	6,493	8,388	9,884	21,444
Ketoprofen	10,553	12,888	12,814	14,036	14,862	16,295	20,671	27,053	16,147
Piroxicam	21,618	20,921	17,363	16,375	16,002	14,136	12,216	9,187	15,977
Etoricoxib	0	0	0	25,745	14,114	18,043	25,002	24,006	13,364
Ibuprofen	4,629	4,572	5,014	6,108	9,060	12,147	26,477	30,965	12,372
Aceclofenac	0	633	10,040	12,425	13,654	15,439	15,095	15,853	10,392
Meloxicam	9,269	8,258	7,003	8,336	10,428	9,498	8,779	7,517	8,636
Diclofenac+ misoprostol	5,871	5,882	4,914	4,599	4,587	4,229	4,215	3,314	4,701
Indomethacin	3,270	3,662	3,769	4,193	4,366	4,375	4,331	4,523	4,061
Naproxen	3,265	3,093	3,025	2,572	2,391	2,139	2,064	2,201	2,594
Ketorolac	32	31	17	22	18	16	11	5	19
Other	13,788	13,100	11,176	11,783	13,087	16,606	18,713	23,494	15,218

Appendix C:

Protocol Deviations and Specifications

July 1, 2011

Several analyses, initially planned in the study protocol, were not conducted:

1. Replicate analysis of dose, duration, and effect measure modification for new users due to small impact of new user restriction in the overall current single use analyses.
2. Estimation of incidence rate ratios and incidence rates by individual NSAID due to timelines and more efficient control of confounding in the case-control analysis.

We conducted a preliminary analysis, not initially planned in the study protocol, of cases with discharge codes of high positive predictive value and their controls to provide interim findings in a regulatory referral report in September 2010.

Decisions and specifications

1. Decision to not conduct full validation of codes in the secondary position due to timelines of the regulatory referral and administrative issues in the region.
2. Number of days of supply to define current use of NSAIDs was specified following the sensitivity analysis.