# SURVEILLANCE STUDY OF PHOTOCONTACT DERMATITIS LEADING TO HOSPITALIZATION IN EUROPE WITH A SPECIAL FOCUS ON TOPICAL KETOPROFEN AND OTHER TOPICAL NSAIDs, INCLUDING EVALUATION OF SEVERE PHOTOSENSITIVITY REACTIONS

## PILOT STUDY

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## ABSTRACT


### Title

Surveillance Study of Photocontact Dermatitis Leading to Hospitalization in Europe with a Special Focus on Topical Ketoprofen and Other Topical NSAIDs, Including Evaluation of Severe Photosensitivity Reactions

**Version:** F.1 - 11 June 2012

**Coordinating investigator:** Dr. Luigi Naldi, MD (Centro Studi GISED - FROM)

### Rationale and background

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects. Topical ketoprofen is used in more than 70 countries worldwide. To date, however, there has been limited information on the association of severe photosensitivity reactions leading to hospitalization with topical ketoprofen use, and the incidence of such events in patients exposed to treatment is unknown.

As requested by EMA in 2010 (procedure No. EMEA/H/A-107/1259) and to better evaluate the risk and benefit profile of topical ketoprofen, an epidemiologic case-control study was proposed focusing on severe photosensitivity reactions leading to hospitalization and assessing risks linked to the use of topical ketoprofen and other topical NSAIDs. The study will be conducted within a network of dermatologic centers in Europe and requires that clear assumptions are made about exposure rates, criteria to adopt to define cases of severe photosensitivity, and incidence of severe photosensitivity reactions.

Thus to assess the feasibility of the case-control study and before embarking into a large scale Europe-wide case-control study, a pilot study will be conducted. It will address statistical consideration, in particular the incidence rate of severe photosensitivity reactions leading to hospitalization, the prevalence of exposure to topical ketoprofen among controls, and the size of the risk one would aim for. It will also address methodological issues granting validity to the study, including the ability to assess cases of photosensitivity in a standardized and reliable way, and the extent exposure among controls compares with the exposure in the underlying at risk population so that indirect methods to assess attributable risks could be applied.

Centers in three geographic areas, intended to represent the variety of Europe in terms of different rates of exposure to topical NSAIDs and of incidence of photosensitivity reactions, will participate (Lombardy region, Paris metropolitan area, Prague metropolitan area).

## Objectives

The pilot phase would pursue three main objectives:

- to assess the prevalence of exposure to topical NSAIDs in a sample of hospital controls selected according to the criteria adopted in case-control studies;
- to develop diagnostic criteria for severe photosensitivity with an expert panel of assessors to be adopted and used in the future planned case-control study;
- to obtain estimates of the incidence of severe photosensitivity leading to hospitalization in selected sampling areas. This study will involve the retrospective and prospective (six months) identification of all the hospital admissions due to severe photosensitivity. These estimates would improve the planning of the Europe-wide case-control study.

## Study design

To address the mentioned objectives, the pilot study will have three different components.

1. Assessment of the prevalence of exposure to topical NSAIDs and specifically topical ketoprofen among hospital controls.

   This study would involve the identification and interview of a sample of patients of both gender, aged between 18-74 years, consecutively admitted to hospitals in the geographic areas participating in the pilot phase and satisfying entry criteria for controls adopted in pharmacoepidemiologic case-control studies, namely, patients admitted for an acute condition or for an elective procedure not suspected of being related to medication use. Conditions will include: traumatic injuries, acute infections, abdominal emergencies, elective surgery such as hernia repair, ocular, nose and throat procedures. Patients with chronic disorders would be eligible if hospitalized for an unrelated acute disease but not if admitted for an acute exacerbation of their chronic disease. The eligible controls will be contacted and once informed consent has been obtained will be interviewed according to a standardized questionnaire exploring medication use during the last week and month preceding hospitalization. Using IMS sales data, we estimated that the 1-month prevalence of exposure to NSAIDs was not lower than 0.5%. Based on this estimate, using the exact (Clopper-Pearson) confidence interval method, we calculated that a total sample of about 900 people (300 subjects per centre) would enable to estimate exposure rates in a reliable way. Figures obtained in this sample will be used to refine statistical sample size estimates for the case-control study. Moreover, the figures from hospital controls in Lombardy will be compared with exposure data to topical NSAIDs obtained in a random sample of the general population recruited within the EDEN Fragrance Study in the same region (2000 subjects, aged 18-74 years). Exposure rates obtained within controls in Paris

and Prague will be also compared to available external exposure data within general population of these regions. The overall agreement between the figures obtained from hospital controls and from the general population will make the adoption of the indirect method proposed by McMahon and Cole feasible.

2. Development of diagnostic criteria for severe photosensitivity. This part of the pilot phase will involve the appointment of an expert panel (5 experts) and the review of selected cases (10 cases) with definition of tentative criteria. These criteria will then be applied to a separate sample of cases (another 10 cases) with independent assessment by each reviewer in duplicate and estimate of inter-rater and within-rater agreement. The process could be reiterated to optimize the reproducibility of adopted criteria. Imputability criteria for drug exposure will also be developed by considering the type of drug, alternative etiologic candidates, modality of exposure, timing of the reaction, and latency.

3. Incidence of severe photosensitivity leading to hospitalization in selected sampling areas. This study will involve the retrospective and prospective (six months) identification of all the hospital admissions (including emergency department one-day admission) due to severe photosensitivity. The charts of these cases will be reviewed by an expert panel to classify them into categories of possible, probable or definite case of photosensitivity reaction. Exposure data will be considered whenever possible. The number of cases will be then related to the underlying population of the hospital catchment area to obtain estimates of crude incidence rates. These estimates will be used to improve the case-control study planning in terms of study duration and geographic extension.

**Milestones**

Development of diagnostic criteria: June-September 2012

Data collection start for controls: September 2012

Cases collection start: October 2012

Progress report and preliminary results: December 2012

Pilot phase results: April 2013

**AMENDAMENTS AND UPDATES**

No amendment or update has been made to the study protocol.

## LIST OF ABBREVIATIONS

| | |
|---|---|
| **ADR** | Adverse Drug Reaction |
| **AE** | Adverse Event |
| **CI** | Confidence Interval |
| **EDC** | Electronic Data Capture |
| **EDEN** | European Dermato-Epidemiology Network |
| **EMA** | European Medicines Agency |
| **GCP** | Good Clinical Practice |
| **GISED** | Italian Group for Epidemiological Studies in Dermatology |
| **GUI** | Graphical User Interface |
| **ICD** | International Classification of Diseases |
| **ID** | Identification |
| **ISF** | Investigator's Site File |
| **MAHs** | Marketing Authorization Holders |
| **NSAID** | Non-Steroidal Anti-Inflammatory Drug |
| **OR** | Odds Ratio |
| **PAR** | Population Attributable Risk |
| **PHI** | Protected Health Information |
| **PSUR** | Periodic Safety Update Report |
| **RegiSCAR** | Registry of Severe Cutaneous Adverse Reactions |
| **RR** | Relative Risk |
| **SOP** | Standard Operative Procedure |
| **SSL** | Secure Sockets Layer |
| **WHO** | World Health Organization |

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## 1. RATIONALE AND BACKGROUND

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects.

It is available in several forms including oral, parenteral, and topical preparations. The topical form of ketoprofen usually consists in a 2.5% to 5% gel, but there are other formulations (e.g. liquid spray) with different concentrations.

Topical ketoprofen is used to treat the symptoms of pain and inflammation in conditions such as minor trauma (sprains, bruising), tendonitis, small-joint osteoarthritis, acute low-back pain and phlebitis.

Topical ketoprofen is used in more than 70 countries worldwide. Since its first market authorization in Europe in 1978, cases of photoallergic contact dermatitis related to ketoprofen have been described and characterized [1-4]. To date, however, there has been limited information on the association of severe photosensitivity reactions leading to hospitalization with topical ketoprofen use, and the incidence of such events in patients exposed to treatment is unknown. From spontaneous surveillance data, in France, originated in different areas and different time periods, it was estimated that the frequency of reporting of any cutaneous adverse events attributed to topical ketoprofen ranged from 0.8 to 2.8 per 100,000 inhabitants per year and that around 6% to 18% of these cutaneous side-effects were cases of photoallergy leading to hospitalization [4-6]. In an analysis of spontaneous reports in Italy, the observed reporting rate of photosensitivity reactions from any causes was 5.5 per 100,000 inhabitants per year and the rate of serious photosensitivity reactions was 0.09 per 100,000 inhabitants per year [7]. In another study conducted in Spain using clinical records of subjects with contact allergy and/or photoallergy due to topical NSAIDs, the rate of photoallergic reactions was 1.2 per 100,000 per year [8]. Photoallergy is considered within the International Classification of Diseases (ICD) with codes ICD-10 L57.8 and code ICD-9 692.79.

As requested by EMA in 2010 (procedure No. EMEA/H/A-107/1259) and to better evaluate the risk and benefit profile of topical ketoprofen, an epidemiologic study was proposed focusing on severe photosensitivity reactions leading to hospitalization and assessing risks linked to the use of topical ketoprofen and other topical NSAIDs (ibuprofen, niflumic acid, diclofenac, piroxicam). The design of the study to be conducted within a network of dermatologic centers in Europe requires that clear assumptions are made about exposure rates, criteria to adopt to define cases of severe photosensitivity, and incidence of severe photosensitivity reactions.

## 2. PILOT STUDY PROPOSAL

The feasibility of a case-control study to estimate the association between severe photosensitivity reactions leading to hospitalization and use of topical ketoprofen in Europe is under scrutiny. It depends, on statistical consideration, in particular the incidence rate of severe photosensitivity reactions leading to hospitalization, the prevalence of exposure to topical ketoprofen among controls, and on the size of the risk one would aim for. It also depends on methodological issues granting validity to the study, including the ability to assess cases of photosensitivity in a standardized and reliable way, and the extent exposure among controls compare with the exposure in the underlying at risk population so that indirect methods to assess attributable risks could be applied.

The pilot study we propose is aimed at addressing the above mentioned issues early in advance and before embarking into a large scale Europe-wide case-control study.

## 3. OBJECTIVES

The pilot study would pursue three main objectives:

- to assess the prevalence of exposure to topical NSAIDs in a sample of hospital controls selected according to the criteria adopted in case-control studies;
- to develop diagnostic criteria for severe photosensitivity with an expert panel of assessors to be adopted and used in the future planned case-control study;
- to obtain estimates of the incidence of severe photosensitivity leading to hospitalization in selected sampling areas. These estimates would improve the planning of the Europe-wide case-control study.

## 4. STUDY DESIGN

### 4.1. General rules and responsibility

#### 4.1.1 Coordination of the study

The coordinating center and coordinating investigator will be responsible for central data management and storage, for study setup, coordination and hospital network establishment and supervision. The coordinating centre will be also a reference for guidance and assistance of monitors and/or local network centers and investigators.

### 4.1.2 Local study center

The local study center and local investigator will be responsible for setting up, maintaining and updating the Investigator's Site File (ISF). The local study monitor and eventually the local investigator must be alerted upon notification of a new case. All local centers must refer to the coordinating center for any problem encountered during the study. They will also give regular update about study progress to the coordinating center.

### 4.1.3 Hospitals

Hospitals in selected catchments areas will be identified by each local study center. A unique identification number will be assigned to each participating hospital by the coordinating center. Policies and procedures of each hospital involved in the study will be observed and respected.

### 4.1.4 Local and central monitor

Each local center will have a qualified person responsible for interviewer trainings, checking of finished interview questionnaires for completeness and legibility and for maintaining contacts with the local network. Any circumstance which could alter the study's methodology must be promptly communicated to the local investigator.

The central monitor, at the coordinating center, will be responsible for harmonization of procedures and supervising of all involved centers and local networks. He/she will visit each participating centre at regular interval to review collected data and the related procedures.

### 4.1.5 Scientific steering committee

A scientific steering committee will be established before the study starts. The composition will consider expertise in epidemiological methods with special reference to pharmacoepidemiology and practical expertise in photo-allergy. The members are: Dr. Maja Mockenhaupt (Department of Dermatology, University of Friburg, Coordinator of the RegiSCAR network in Germany), Prof. Thomas Diepgen (Head of the Department of Social Medicine, Occupational and Environmental Dermatology, University of Heidelberg), Prof. Carlo La Vecchia (Head, Department of Epidemiology Istituto di Ricerche Farmacologiche "Mario Negri" in Milan), Prof. Magnus Bruze (Department of Occupational and Environmental Dermatology, Malmö University Hospital, Lund University), Prof. Olivier Chosidow (Head Department of Dermatology, Hôpital Henri-Mondor, Créteil, France), Prof. Jana Hercogova (Head Department of Dermatology, 2nd Medical School, Charles University, Prague) and Dr. Luigi Naldi (Centro Studi GISED - FROM, Ospedali Riuniti di Bergamo).

### 4.1.6 Joint scientific committee

A Joint Scientific Committee, chaired by Sanofi-Aventis Group, has been set up to coordinate actions among the industries supporting the study and holding marketing authorizations.

### 4.1.7 Safety reporting

Definition of Adverse Drug Reaction (ADR): a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

A case-control study is one of the rare designs where it is not feasible or appropriate to make an assessment of causality individually, at least at the time of data collection. In fact, this should indeed be avoided as this may introduce a bias in the ascertainment of cases (with an emphasis on those considered related to topical ketoprofen to the detriment of other types of exposure), whereas this adjudication should be done without knowledge of, or inference on, the exposure.

Photosensitivity ADR associated with topical ketoprofen use collected during this study should not be systematically reported individually in an expedited manner to regulatory authorities.

Individual ADR reporting (for any ADR to any medicinal product) should be done by the investigators, or any other healthcare professional taking care of the patient, on a spontaneous basis, as per local regulations.

### 4.1.8 Electronic Data Capture (EDC)

The questionnaire will be developed by the coordinating center using a web-based computerized system designed for the collection of clinical data in electronic format. It will consist of a graphical user interface (GUI) for data entry and management, a validation component to check user data input and a reporting tool for fast analysis of the collected data. It will comply with Good Clinical Practice (GCP) and regulatory guidelines (EMA GCP, Annex 11) by strict observation of differentiated user roles and privileges, password and user authentication security, electronic signatures, SSL encryption, de-identification of Protected Health Information (PHI), and comprehensive auditing to record and monitor access and data changes.

Data input in the EDC system will be made by the interviewers.

### 4.1.9 Quality control

Different mechanisms of quality control will be adopted. Copies of questionnaires, documents and any other collected data will be maintained and kept organized by each local study center. Collected data will be periodically reviewed by the local and central monitor for completeness and

compliance with source data. Data collected in the questionnaire will be automatically checked for consistency by the EDC system during input procedures. Daily and hourly backup will be implemented for the EDC database by using redundancy storage system. Copies of any electronic document inherent to the study as well as statistical programs used for computations will be regularly backed up by the coordinating center and by local study centers. All documents related to the study will be maintained and conserved by the coordinating center for at least 15 years.
Any change made to paper or electronic documents will be tracked and their previous copies will be backed up.

#### 4.1.10 Privacy and protection of human subjects

For data collections, enrollment of subjects and interview procedures, ethical policies and rules in force in each institutions will be followed. Protocol will be submitted to local Ethics Committees for approval before the study starts. A standard form, developed in accordance to European GCP guidelines, will be used as informed consent (see Annex 3). Each country should adapt the document to its ethical rules. Privacy will be guaranteed by anonymous data collection system. Interviewers will be trained in order to approach patients with appropriate procedures to preserve privacy. No interventional procedure will be performed. Subjects will be free to join the study and withdraw their consent at any time.

### 4.2. PART 1: Prevalence of exposure to topical ketoprofen and other NSAIDs

#### 4.2.1 Background

This part of the study will involve the identification and interview of a sample of patients consecutively admitted to hospitals in the geographic areas participating in the pilot phase. Figures obtained in the sample will be used to refine statistical sample size estimates for the case-control study. Moreover, the figures from Lombardy region in Italy will be compared with exposure data to topical NSAIDs obtained in a random sample of the general population recruited within the EDEN fragrance study [9] in the same region (2000 subjects, aged 18-74 years). Exposure rates obtained within controls in Paris and Prague will be also compared to the available exposure data from the general population of these regions. The overall agreement between the figures obtained from hospital controls and from the general population will make the adoption of the indirect method proposed by McMahon and Cole [10] feasible. In case there is no overall agreement we will opt for selecting controls taken from the general population in the same catchment areas where cases are observed.

### 4.2.2 Population recruitment

After approval by the local Ethic Committee, identification of controls will start by maintaining regular contacts with hospital departments where suitable controls could originate. This operation will be done by a trained interviewer who will be authorized to contact the hospital staff in charge of the departments.

All consecutive patients fulfilling inclusion/exclusion criteria will be contacted and asked to provide their informed consent to participate in the study. Before recruitment, in particular when a patient is admitted for disease of particular disability or severity, the interviewer may contact the appropriate hospital staff in order to ascertain the patient's current status. Once eligible controls sign off their informed consent, an appointment for the interview is fixed in agreement with the hospital staff. The interview will take place in hospital departments where identified subjects are admitted, according to each hospital department policy. It will also be possible to organize the interview after hospital discharge, provided arrangements with identified subjects are made before hospital discharge. In each case the interview must take place within 10 days from hospital admission in order to ensure a proper recall of events prior to hospital admission. A unique identification (ID) number will be assigned to each elected control by the interviewer, following a list with anonymous progressive number coding. The ID will be formed by a prefix indicating the hospital code and by a progressive number assigned to the patient.

#### *4.2.2.1 Inclusion criteria*

- age 18-74 years
- consecutive patients of both gender admitted for any of the following acute conditions or elective procedures:
  - acute infection or inflammation*
    - pneumonia
    - gastroenteritis
    - cellulitis
    - pancreatitis (first episode)
    - otitis media
    - peritonitis
    - epididymitis
    - abscess
    - meningitis
    - encephalitis
    - pelvic inflammatory disease
  - trauma (not related to alcohol or osteoporosis)
    - fractures

  - sprains/strains
  - dislocations
- acute abdominal emergencies*
  - appendicitis
  - strangulated hernia
  - rupture or torsion of an ovarian cyst
  - acute abdominal pain
  - ectopic pregnancy
- thrombophlebitis (males only, first episode)
- spontaneous pneumothorax
- alternative diagnoses (when the previous ones are not available)
  - hernias
  - hallux valgus
  - cosmetic surgery
  - deviated nasal septum

* Diagnosis in this group are not all-inclusive, but rather examples of appropriate conditions

- signed informed consent

#### *4.2.2.2 Exclusion criteria*

- patients whose conditions at hospitalization are not acute or whose elective procedures are not urgent (excluding the alternative diagnoses listed in inclusion criteria).
- patients admitted for conditions or elective procedures suspected of being related to medication use
- patients admitted for conditions or elective procedures occurring as a regular progression or complication of an underlying chronic disease (e.g. reacutization of chronic bronchitis).
- patients admitted for any skin problem, suspected to be related to photosensitivity
- patients admitted for:
  - stroke
  - head trauma resulting in concussion or loss of consciousness
  - all cancers related in any way to the present admission
  - abdominal emergencies related to peptic ulcers
- patients whose hospital stay had been more than 10 days or whose time frame between hospital admission and the agreed interview is more than 10 days

### 4.2.3 Sampling procedure

To obtain a representative sample of the population within each geographical area, a proportionate stratified sampling design without replacement will be used [11]. In the sampling plan, the

distribution of the population by age, gender, and geographic location will be accounted for. All consecutive individuals belonging to each stratum and fulfilling inclusion/exclusion criteria will be eligible for the study.

### 4.2.4 Interview

The interview will be done by using a standard questionnaire (see Annex 1). The interviewer will be trained regarding data collection and coding, as well as how to approach and speak to subjects and other ethical questions. For coding and data collection a codebook will be developed. The codebook will contain all basic and additional information regarding categorization of subject answers and hints to guide the interviewed to recognize the interviewed person present or past conditions and exposures. Each country will add a specific local list of brand names of drugs of interest.

The interview will be conducted as described below:

1. Ensure that the subject had signed the informed consent to conduct the interview, according to the rules and regulations in existence at each institution;
2. Enter the assigned subject code on each page of the interview form;
3. Start the interview unhurried and giving the impression that all interest rests on the person with whom the interviewer is speaking;
4. If necessary, during the interview, reassure subject that his/her information will be kept confidential;
5. Provide a time frame for the subject (from the date of the admission) and repeat it frequently in order to maintain the focus on events relevant to the questions being asked;
6. If necessary, connect events for subjects (e.g. when a subject mentions a condition that generally requires medication but there is no medication use forthcoming);
7. When investigating exposure measures, read to the subject a list of indications for potential treatment followed by a list of brand names of drugs of interest.
8. Conclude the interview making the subject to feel as though he/she has made a significant contribution to this study;
9. If there are any reasons to conclude the interview prematurely, the reason should be indicated at the top of the page being used at the time of termination.

During the interview it is also important to complete all the form in a neat and legible manner and to do not use abbreviations. Once the interview has been concluded no additional information should be added. The estimated time to questionnaire completion is about 25 minutes.

### 4.2.5 Coding system

A standard coding system will be developed in the codebook. In particular for diseases classification the last version of International Classification of Diseases system (ICD-10) will be used. History of drug exposure will be recorded by using WHO drug dictionary.

### 4.2.6 Questionnaire validation

The reliability of the questionnaire is a crucial point in order to ensure reproducibility and validity of the variables considered. In order to evaluate agreement upon consecutive measurements of the same variables by the same subjects, a random sample of at least 20 people per centre will be taken from controls. These subjects will be interviewed and re-interviewed after a period of 1 week by the same questionnaire and the same interviewer. Test re-test reproducibility will be assessed by calculating Cohen's kappa statistics and by intra-class correlation coefficients. Values greater than 0.60 will indicate an acceptable reliability of questionnaire variables. In case of poor agreement questionnaire formulation will be revised and the same variables will be tested again by subsequent reliability exercise.

### 4.2.7 Collected data

For each subject the following data will be recorded:

- General data;
- Demographics;
- Recent and general medical history;
- Exposure data with special focus on:
  - topical ketoprofen (e.g. start date, frequency of daily use, duration of use) and conditions of use (e.g. occlusive dressing);
  - other topical NSAIDs including ibuprofen, diclofenac, and piroxicam (e.g. start date, frequency of daily use);
  - other topical medications;
  - systemic drugs taken according to indications (e.g. drugs for pain, antihypertensives, anticonvulsivants, lipid and cholesterol lowering drugs);
- History of sun exposure (e.g. pattern of exposure, duration of exposure, use of sunscreens);
- Skin phenotype
- History of environment exposure (e.g. pesticides, photosensitizing plants)
- Past history of allergic reaction to ketoprofen and other topical NSAIDs;
- Diseases predisposing to photosensitivity (e.g. systemic lupus erythematosus, porphyrias)

### 4.2.8 Exposure

Exposure will be defined as the use of drugs or medications within one month prior to the index date. The index date will be the date of hospitalization after symptoms onset.

Exposure measurement will be made using a structured questionnaire day by day for the week preceding the index date and week by week for the preceding three weeks.

### 4.2.9 Outcomes

The main outcome of this study part will be the prevalence of exposure to topical ketoprofen in the general population.

According to the experience of the Slone Epidemiology Unit [12], drug exposure in the general population is expected to be reliably estimated from controls as selected in the present study. Similar comparisons have been made in the SCAR and EuroSCAR studies confirming that the figures obtained among hospital controls, selected in a way similar to the one proposed in our study, are comparable to those obtained from the general population [13-15].

To further confirm this hypothesis, data obtained in Lombardy area will be compared with population estimates taken from the same area in the frame of the EDEN Fragrance Study. Exposure rates obtained within controls in Paris and Prague will be also compared to available external exposure data within general population of these regions.

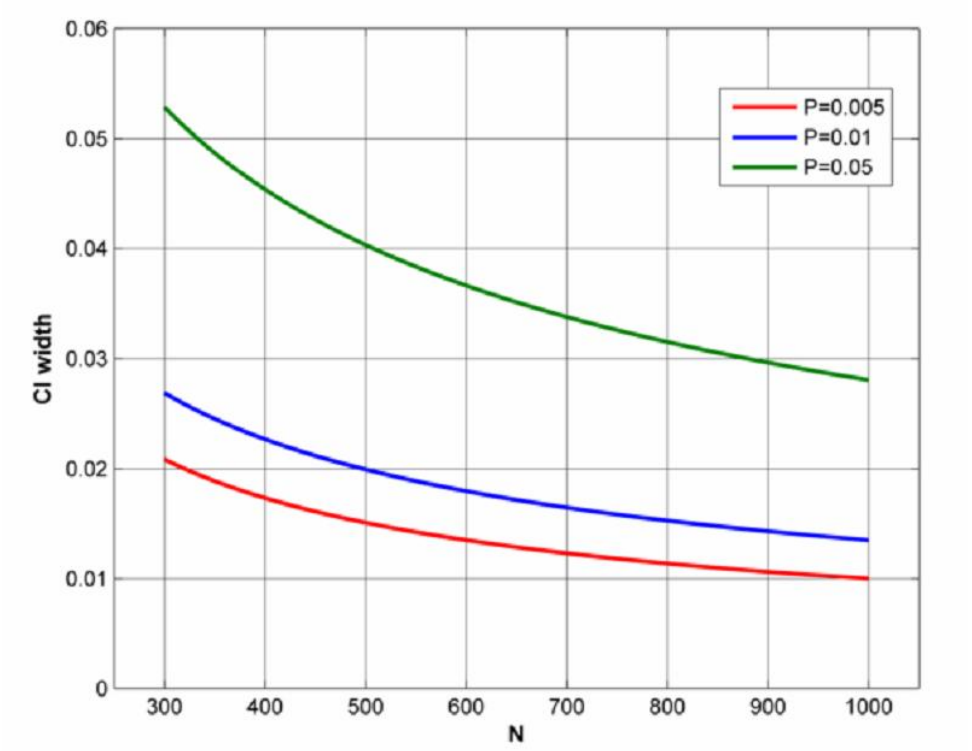
The prevalence of exposure to other topical NSAIDs will be estimated (secondary outcome) by using the same methodology.

### 4.2.10 Sample size

Using IMS sales data, we estimated that the 1-month prevalence of exposure to NSAIDs was not lower than 0.5%. Based on this estimate, we performed a power analysis (Figure 1). Using the exact (Clopper-Pearson) confidence interval method, we estimated that a total sample of about 900 controls (300 per centre) would enable to estimate exposure in a reliable way. This ensures a 95% Confidence Interval (CI) total width of about 1% for a prevalence of 0.5%.

Agreement of questionnaire variables will be calculated by using Cohen's kappa coefficient for categorical items and intra-class correlation coefficient (ICC) for quantitative data. Values from 0.41 to 0.60 will indicate moderate agreement, values from 0.61 to 0.80 substantial agreement, and values from 0.81 to 1.00 almost perfect agreement. It can be computed that a sample size of 60 subjects is adequate to see whether an agreement of 0.8 differs significantly from 0.4 or less (power 80%, significance level 5%, assumed "yes" frequency between 20-80%).

**Figure 1: The graph illustrates the width of the 95% confidence interval (CI), for estimation of a given proportion (P), based on different sample sizes (N)**




### 4.2.11 Data analysis

Numerical data will be presented as means with standard deviations or medians with ranges, while categorical data as numbers with percentages. Row prevalence rates together with their 95% confidence intervals (CI) will be calculated for NSAIDs expure as well as for other variables of interest. Weighted estimates of exposure prevalence will be also computed by taking the European Standard Population as a reference. Stratification by gender and country will be used for general descriptive statistics as well as for exposure rates. Differences among categories will be tested with Pearson's $\chi^2$ test or Fisher's exact test for nominal variables and by Mann-Whitney U test for continuous variables. To estimate possible selection biases in the collection of the sample, a comparison of general characteristics of individuals undergoing the interview and, in particular, their exposure rates to topical NSAIDs, with the expected distribution based on demographic and general sales data obtained from individual areas will be made. The assessment will be done by comparing 95% CI for the difference between proportions against fixed tolerance. Additionally, Westlake-Schuirmann test of equivalence between proportions will be performed.

## 4.3. PART 2: Development of diagnostic criteria for severe photosensitivity

### 4.3.1 Background

This part of the pilot phase will involve the appointment of an expert panel (5 experts) and the review of selected cases (10 cases), retrospectively collected before the beginning of the study, with definition of tentative criteria. These criteria will then be applied to a separate sample of cases (another 10 cases) with independent assessment by each reviewer in duplicate and estimate of inter-rater and within-rater agreement. The process could be reiterated to optimize the reproducibility of adopted criteria. Imputability criteria for drug exposure will also be developed by considering the type of drug, alternative etiologic candidates, modality of exposure, timing of the reaction, and latency.

### 4.3.2 Diagnostic criteria

Photosensitivity reaction will be defined as erythematous reaction associated with vesicles and/or bullae involving one or several body districts triggered by sun exposure and leading to hospitalization. Diagnosis will be based on clinical data, including patient's medical history, clinical features and picture of lesions and, if existing, results of photopatch tests. The adjudication will classify cases, in a way similar to the one adopted for severe cutaneous reaction within the RegiSCAR program, according to a likelihood scale (certain/definite, probable, possible, unlikely, excluded). Delphi method [16] will be used to improve the classification system. In case of disagreement, the issue will be judged by voting.

### 4.3.3 Outcomes

The main outcome of this study part will be development of diagnostic criteria for the identification of serious photosensitivity reaction. These criteria will be used in the subsequent identification of cases (Part 3) and in the final case-control study by defining a Standard Operative Procedure (SOP).

## 4.4. PART 3: Incidence of severe photosensitivity leading to hospitalization

### 4.4.1 Background

This part of the study will involve the retrospective and prospective identification of all the hospital admissions (including emergency department one-day admission) due to severe photosensitivity. The charts of these cases will be reviewed by an expert panel to classify them into categories of possible, probable or definite case of photosensitivity reaction. Moreover,

exposure data will be considered whenever possible. The number of cases will be then related to the underlying population of the hospital catchment area to obtain estimates of crude incidence rates. These estimates will be used to improve the case-control study planning in terms of study duration and geographic extension of the surveillance.

### 4.4.2 Cases identification

After approval by the local Ethic Committee, identification of cases will start from the review of medical records of patients admitted during the 6 months preceding an index date corresponding to the date of Ethic Committee approval. In addition, all the new cases occurring after the beginning of the study will be recorded. New cases should be reported to the local monitor who will be responsible for establishing and maintaining regular contacts with the hospital departments. Local monitor will be also responsible for data retrieval and collection. This will be done only after proper authorization has been obtained to access paper or electronic medical records of patients according to hospital policies and rules.

All patients fulfilling inclusion/exclusion criteria will be eligible as cases. Information regarding these subjects will be collected through medical records and whenever possible an interview to the patient.

#### *4.4.2.1 Inclusion criteria for cases*

- age 18-74 years
- patients of both gender, admitted for erythematous reactions associated with vesicles and/or bullae involving one or several body districts
- history of sun exposure in the last month and week before hospitalization
- diagnosis or history of photosensitivity in the medical charts
- signed informed consent

#### *4.4.2.2 Exclusion criteria for cases*

- reactions attributable to underlying diseases (e.g., systemic lupus erythematous)

### 4.4.3 Collected data

Patient’s information will be retrieved from hospital records, whenever it will be possible, using the same questionnaire as used for controls.

Additional data for collected cases will include (if available):

- clinical features of lesions;

- picture of lesions;
- results of pathologic examination
- results of photopatch test.

### 4.4.4 Exposure

Exposure for cases will be defined as for controls. The index date will be the date of hospitalization after symptoms onset.

Exposure assessment will be made, whenever it will be possible, using the same structured questionnaire form used for controls.

### 4.4.5 Outcomes

The main outcomes of this study part will be the incidence of photosensitivity reaction leading to hospitalization in selected European areas and, whenever it will be possible, the exposure to topical ketoprofen and other topical NSAIDs among cases.

### 4.4.6 Sample size and statistical analysis

According to the most recent estimates from Italy and Spain [4-7] the expected incidence of serious photosensitivity reactions leading to hospitalization is about 1 case per million inhabitants per year. Since the total catchment area of the study is about 25 million inhabitants, the estimated number of collected cases is 25 in one year of study. This time frame will cover a retrospective period of 6 months preceding the date of Ethic Committee approval and a prospective period of 6 months after the beginning of data collection.

In order to estimate the population attributable risk percentage (PAR%), since the fraction of subject exposed to topical ketoprofen in the general population will not be directly available, the indirect method proposed by McMahon and Cole, will be used:

$$PAR\% = P_e (RR - 1) / [1 + P_e (RR - 1)] \times 100$$

$P_e$ = proportion of controls exposed

RR = relative risk for exposed

Whenever general and/or exposure data will be available, statistics will be computed in the same way as for controls. Whenever it will be possible, as appropriate and in a case-control study, risk estimate for exposure will be derived from odds ratio calculation. Multiple logistic regressions will be used to adjust risk estimates for potential confounders: age, gender, occlusive dressing, treatment duration and frequency of topical ketoprofen use, past history of allergic reaction to ketoprofen, and

concomitant medications. Other potential confounders or effect modifiers will be detected by multiple logistic regressions with stepwise forward selection algorithm or by stratified analysis.

## 5. CONDUCT OF THE STUDY

The Study Center of the Italian Group for Epidemiological Studies in Dermatology (GISED) will be the promoter and coordinator of the study.

Three geographic areas will participate in the pilot phase of the study: the Lombardy region in Italy (9 million people), the Paris metropolitan area (10 million people), and the Prague metropolitan area (5 million people). The identification of the geographic areas was based on the following criteria:

1. total coverage of about 25 million people;
2. location in European countries where topical NSAIDs including topical ketoprofen are available on the market;
3. presence of a reference academic centre which could act as a local coordinator for the study.

### 5.1. Participating local study centers

For the Lombardy region: Department of Dermatology, Ospedali Riuniti di Bergamo.

For the Paris metropolitan area: Service de Dermatologie, Hôpital Henri Mondor Creteil (France)

For the Prague metropolitan area: Department of Dermatology, Charles University Prague (Czech Republic)

### 5.2. Participating hospitals

For the Lombardy region: Ospedali Riuniti di Bergamo, Spedali Civili di Brescia, Ospedale di Treviglio-Caravaggio, Ospedale Niguarda Ca' Granda - Milano.

For the Paris metropolitan area: Hôpital Henri Mondor - Creteil

For the Prague metropolitan area: Charles University Hospital - Pilsen

### 5.3. Sources of fundings

The study will be supported by a consortium of companies marketing topical ketoprofen in Europe (MAHs): Menarini Industrie Farmaceutiche Riunite S.r.l, Bayer S.p.A, Cyathus Exquirere Pharmaforschungs GmbH, Dompe' S.p.A, EG S.p.A, JSC Grindeks, Hisamitsu UK Ltd, Istituto Biochimico Italiano G. Lorenzini S.p.A, Italfarmaco S.p.A, Pierre Fabre Ibérica S.A, Sandoz International GmbH, Sanofi-Aventis Groupe.

### 5.4. Plans for communicating study results

For the purpose of the Periodic Safety Update Report (PSUR) preparation, periodical data exchange with the sponsors will be organized in terms of study update, timelines completion, and patient enrolment. In particular an interim progress report and preliminary data analysis will be provided by the coordinating center in the Q4 of 2012. The final report and data analysis of the pilot study will be available in Q2 of 2013.

## 6. MILESTONES

| | 2012 | | | | | | | 2013 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Activities** | Jun | Jul | Aug | Sep | Oct | Nov | Dec | Jan | Feb | Mar | Apr |
| Ethics committee approval | X | X | X | | | | | | | | |
| Development of EMR system | X | X | X | X | | | | | | | |
| Interview and data collection for control (P-1) | | | | X | X | X | X | X | X | X | |
| Reliability measures (P-1) | | | | | | X | X | | | | |
| Diagnostic criteria for cases (P-2) | X | X | X | X | | | | | | | |
| Prospective cases identification (P-3) | | | | | X | X | X | X | X | X | |
| Progress report and preliminary results | | | | | | | X | | | | |
| Database closure and data management | | | | | | | | | | | X |
| Pilot study results | | | | | | | | | | | X |

## 7. REFERENCES

### 7.1 Bibliography

1. Bagheri H, Lhiaubet V, Montastruc JL, Chouini-Lalanne N. Photosensitivity to ketoprofen: mechanisms and pharmacoepidemiological data. Drug Saf. 2000;22(5):339-49.
2. Cantisani C, Grieco T, Faina V, Mattozzi C, Bohnenberger H, Silvestri E, Calvieri S. Ketoprofen allergic reactions. Recent Pat Inflamm Allergy Drug Discov. 2010;4(1):58-64.
3. Matthieu L, Meuleman L, Van Hecke E, Blondeel A, Dezfoulian B, Constandt L, Goossens A. Contact and photocontact allergy to ketoprofen. The Belgian experience. Contact Dermatitis. 2004;50(4):238-41.

4. Noize P, Bénard-Laribière A, Aulois-Griot M, Moore N, Miremont-Salamé G, Haramburu F. Cutaneous adverse effects of ketoprofen for topical use: clinical patterns and costs. Am J Clin Dermatol. 2010;11(2):131-6.

5. Baudot S, Milpied B, Larousse C. Cutaneous side effects of ketoprofen gels: results of a study based on 337 cases [in French]. Thérapie, 1998; 53: 137-44

6. Veyrac G, Paulin M, Milpied B, Bourin M, Jolliet P. Results of a French nationwide survey of cutaneous side effects of ketoprofen gel reported between September 1996 and August 2000 [in French]. Therapie. 2002;57(1):55-64.

7. Naldi L, Conforti A, Venegoni M, Troncon MG, Caputi A, Ghiotto E, Cocci A, Moretti U, Velo G, Leone R. Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions. Br J Clin Pharmacol. 1999;48(6):839-46.

8. Diaz RL, Gardeazabal J, Manrique P, Ratón JA, Urrutia I, Rodríguez-Sasiain JM, Aguirre C. Greater allergenicity of topical ketoprofen in contact dermatitis confirmed by use. Contact Dermatitis. 2006;54(5):239-43.

9. Rossi M, Coenraads PJ, Diepgen T, Svensson Å, Elsner P, Gonçalo M, Bruze M, Naldi L. Design and feasibility of an international study assessing the prevalence of contact allergy to fragrances in the general population: the European Dermato-Epidemiology Network Fragrance Study. Dermatology. 2010;221(3):267-75.

10. Cole P, MacMahon B. Attributable risk percent in case-control studies. Br J Prev Soc Med. 1971 Nov;25(4):242-4.

11. Kalton G. Introduction to Survey Sampling. In: Sage University Paper series on Quantitative Applications in the Social Sciences, vol.35 pp 19-23. 1983 Beverly Hills: SAGE Publications.

12. Slone D, Shapiro S, Miettinen O. Case control surveillance of serious illnesses attributable to ambulatory use of drugs. In: Epidemiological evaluation of drugs. (Colombo F, Slone D, Shapiro S, Tognoni G, eds) 1977 Amsterdam: Elsevier North Holland Biomedical Press.

13. Kelly JP, Auquier A, Rzany B, Naldi L, Bastuji-Garin S, Correia O, Shapiro S, Kaufman DW. An international collaborative case-control study of severe cutaneous adverse reactions (SCAR). Design and methods. J Clin Epidemiol. 1995 Sep;48(9):1099-108.

14. Auquier-Dunant A, Mockenhaupt M, Naldi L, Correia O, Schröder W, Roujeau JC; SCAR Study Group. Severe Cutaneous Adverse Reactions. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal

necrolysis: results of an international prospective study. Arch Dermatol. 2002 Aug;138(8):1019-24.

15. Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN, Sidoroff A, Schneck J, Roujeau JC, Flahault A. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. J Invest Dermatol. 2008 Jan;128(1):35-44. Epub 2007 Sep 6.
16. de Villiers MR, de Villiers PJ, Kent AP. The Delphi technique in health sciences education research. Med Teach. 2005 Nov;27(7):639-43.

## 7.2 Annexes

1. Study questionnaire
2. ENCePP checklist
3. Informed consent