PASS Information

Title	Cilostazol drug utilisation study
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Date of last version of protocol	5 November 2015
EU PAS register number	ENCEPP/SDPP/3596 http://www.encepp.eu/encepp/viewResource.htm?id=10426 Accessed 5 November 2015
Active substance	Cilostazol, ATC code B01AC23, Platelet aggregation inhibitors excluding heparin
Medicinal product	Pletal, Ekistol
Product reference	UK/H/0291/001 and 002
Procedure number	EMEA/H/A-31/1306
Marketing authorisation holder(s) (MAH)	Otsuka Pharmaceutical Europe Ltd. Lacer S.A.
Joint PASS	No
Research question and objectives	This study protocol was developed in the context of the European Medicines Agency (EMA) referral (article 31 of Council Directive 2001/83/EC) on the risks and benefits of the use of cilostazol. The study objectives are to characterise patients using cilostazol according to demographics, comorbidity, comedications, and duration of treatment. In addition, the study will describe the dosing of cilostazol, the prescribing physician specialties, and the potential off-label prescribing.
Country(-ies) of study	Spain, United Kingdom, Germany, Sweden
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Approval Page

Project Title: Cilostazol drug utilisation study

Otsuka Protocol ID Number: 21-13-101

Effective Date: 5 November 2015

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Version:	2.3
Version Date:	5 November 2015

The following people have reviewed the protocol and give their approval:

RTI Health Solutions

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2 List of Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (classification system)
BUN	blood urea nitrogen
CMBD-AH	Catalan Health Services database of hospital admissions (Conjunto Mínimo Básico de Datos de Altas Hospitalarias)
CYP	cytochrome P-450
DDD	defined daily dose

DUS	drug utilisation study
EBM	codes used for treatments and diagnostic procedures (Einheitlicher Bewertungsmaßstab), GePaRD
EBS	ambulatory operation or procedure codes, GePaRD
EMA	European Medicines Agency
HCP	health care provider
GePaRD	German Pharmacoepidemiological Research Database
GGT	gamma-glutamyl transpeptidase
GP	general practitioner
GVP	Guideline on Good Pharmacovigilance Practice
IACS	Aragón Health Sciences Institute (Instituto Aragonés de Ciencias de la Salud)
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
ICD-10-CM	International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification
ICD-10-GM	International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification
ICD-9	International Classification of Diseases, 9th Revision
ICPC	International Classification of Primary Care (codes)
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology
OPED	Odense University Pharmacoepidemiology Database
OPS	hospital operation and procedures codes (Operationen- und Prozedurenschlüssel); (GePaRD)
PASS	postauthorisation safety study
PSUR	Periodic Safety Update Report
RMP	risk management plan
SD	standard deviation
SHI	statutory health insurance agencies
SIDIAP	Information System for the Advancement of Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària), database in Catalonia, Spain
SmPC	summary of product characteristics
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
THIN	The Health Improvement Network, United Kingdom
UK	United Kingdom

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Collaborating Institutions	**Study Sites**
EpiChron Research Group on Chronic Diseases,[a] the Aragón Health Sciences Institute (IACS),[b] Spain	IACS, Spain
The Health Improvement Network (THIN), United Kingdom (UK)	THIN database, UK
Research Institute in Primary Care (IDIAP) Jordi Gol (IDIAP),[c] Spain	The Information System for the Advancement of Research in Primary Care (SIDIAP) [d] database, Spain
Department of Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology – BIPS GmbH, Bremen, Germany	The German Pharmacoepidemiological Research Database (GePaRD), Germany[e]
Karolinska Institutet, Sweden	National Registers, Sweden

[a] Grupo EpiChron de Investigación en Enfermedades Crónicas.

[b] Instituto Aragonés de Ciencias de la Salud.

[c] Institute d'Investigació en Atenció Primària.

[d] Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària.

[e] Pending approval by the statutory health insurance providers (SHIs).

4 Abstract

Title: Cilostazol drug utilisation study

Rationale and background: This is a drug utilisation study (DUS) on the use of cilostazol in several European populations in the context of the cilostazol referral under Article 31 of Council Directive 2001/83/EC. The DUS is planned to be conducted using database sources to understand the characteristics of users of cilostazol, duration and patterns of cilostazol use, and prevalence of concomitant use of cilostazol and other drugs with which it may interact. The DUS is planned to be conducted in two phases. DUS1 will evaluate cilostazol as currently used in several European countries during the period from launch through 2011. DUS2 will be conducted after the implementation of changes to the summary of product characteristics (SmPC) and the follow-up communication activities with health care professionals (HCPs) and will evaluate the impact of these measures during the year 2014 in the same countries. DUS2 will be conducted using the same protocol as used in DUS1. Both DUS1 and DUS2 will include all the marketed products containing cilostazol in the countries, irrespective of brand.

Research question and objectives: The primary objectives of the DUS are the following:

- To describe the characteristics of new users of cilostazol according to (1) demographics, (2) baseline comorbidity including conditions listed in the SmPC and the risk management plan (RMP) as potential or identified safety concerns, (3) baseline and concurrent use of medications potentially interacting with cilostazol, and (3) specific comorbidity
- To describe the duration of the use of cilostazol and discontinuation patterns
- Secondary objectives of the DUS are to (1) quantify and describe off-label prescribing, (2) describe dosage patterns of the use of cilostazol, (3) to assess the proportion of patients who are hospitalised for any cause while treated with cilostazol, and (4) identify the medical specialties of physicians prescribing cilostazol.

Study design: Cohort study of new users of cilostazol identified in five proposed European population-based automated health databases from Spain (two databases), Germany, the United Kingdom, and Sweden (see Data Sources). New users of cilostazol will be characterised in terms of demographics, comorbidity, and comedications at the date of receiving the first prescription for cilostazol (start date). Diseases and conditions that will be used to evaluate the risk minimisation measures will be assessed for the 6 months before the start date. Concurrent use of potentially interacting medications will be assessed for the 3 months before the start date and during follow-up. Duration of use of cilostazol will be assessed during follow-up.

Population: The source population includes all individuals registered in the study databases since the date of cilostazol availability in each country. The study period is defined as the time between the date of cilostazol availability and the latest date of data availability in each database. The study cohort includes all individuals from the source population who have a first recorded prescription of cilostazol (new users) during the study period and have been continuously enrolled in the database for at least 6 months.

Each member of the study cohort will be followed from the start date until the earliest of date of death or end of study period.

Variables:

Use of cilostazol and patterns of use: The number of new users of cilostazol and the number of prescriptions, packages, and defined daily dose (DDD) will be ascertained overall and by strength, quantity, and year. Current use of cilostazol will be ascertained according to the days of supply of each prescription for cilostazol.

- *Duration of use of cilostazol*: Total duration of use of cilostazol will be ascertained by the total number of days of supply of consecutive prescriptions.
- *Daily dose of cilostazol*: Daily dose of cilostazol will be calculated using the recorded information on strength and quantity prescribed and the days of supply of each prescription.

Characterisation of users at the start date: New users of cilostazol will be characterised at the start date according to demographic, family history, comorbidity, and comedications.

Concurrent use of medications that may interact with cilostazol: Use of medications potentially interacting with cilostazol, including potent inhibitors of CYP3A4 and CYP2C19, will be ascertained at the start date, in the 3 months before the start date, and in the follow-up during current use of cilostazol.

Concurrent use of selected antithrombotic agents: The concurrent use of cilostazol with platelet aggregation inhibitors and antithrombotic agents will be ascertained at the start date and during follow-up. Use of each antithrombotic agent will be defined according to the days of supply of each prescription. The number of patients simultaneously contributing time to current use of cilostazol and current use of antithrombotic agents at the start date and during follow-up will be ascertained.

Use of platelet aggregation inhibitors: New users of cilostazol concurrently treated with platelet aggregation inhibitors at the start date will be followed to assess the proportion of patients discontinuing the use of platelet aggregation inhibitors.

Characterisation of users for the assessment of risk minimisation measures (SmPC changes): Users of cilostazol will be characterised to evaluate the impact of the risk minimisation measures that Otsuka submitted to the EMA in October 2012. For this evaluation, DUS2 is planned to be initiated 6 months after the implementation of the SmPC changes, and results will be compared with those obtained in DUS1. Evaluation of the impact of the risk minimisation measures will be conducted through the following variables according to the sections of the SmPC:

- Indications: Smoking status at the start date; number of patients with a visit to the general practitioner and/or to a specialist between 3 months and 4 months after the start date; number of patients discontinuing cilostazol between 3 months and 4 months after the start date
- New contraindications: Number of patients with a recorded diagnosis for unstable angina pectoris, myocardial infarction, or coronary intervention, within 6 months before the start date; number of patients with concurrent use of two or more platelet aggregation inhibitors at the start date and during follow-up

- Warnings and precautions: Patients with a history of arrhythmias, hypotension, or coronary heart disease recorded at any time before the start date will be followed to assess the rates of visits to general practitioners or specialists
- Posology: Reduction of daily dose to 100 mg will be assessed among patients who are prescribed a potentially interacting medication or a potent inhibitor of CYP3A4 or CYP2C19 during current use of cilostazol.

Use of cilostazol will be evaluated for the use in patients with diseases and conditions currently listed as contraindications in the SmPC that will be retained in the revised SmPC. These conditions are severe renal impairment, moderate to severe hepatic impairment, congestive heart failure, history of bleeding disorders, and history of arrhythmias.

Indications associated with treatment and off-label prescribing: In most databases, the indication for which the treatment is given is not recorded as a separate field and must be assessed by diagnosis codes recorded around the date of the first cilostazol prescription and/or by manual review of the computerised clinical information, including free-text comments from the prescriber when these are available (e.g., THIN). Because review of computerised information is very time- and-resource consuming, the indication associated with cilostazol treatment and off-label prescribing of cilostazol in THIN will be assessed in a random sample of about 200 patients stratified by age and strength of first prescription of cilostazol. For the rest of databases, which do not have free-text comments, indications for cilostazol will be evaluated for all patients by hospital discharge diagnoses.

Assessment of hospitalisations during treatment with cilostazol: The percentage of users of cilostazol who are hospitalised for any cause during treatment will be assessed.

Speciality of prescribers: The type of prescriber initiating treatment with cilostazol will be ascertained in the databases that have this information available: IACS, SIDIAP, GePaRD, Sweden.

Data sources: The study is proposed to be conducted in the following databases:

- The Aragón Health Sciences Institute (Instituto Aragonés de Ciencias de la Salud [IACS]) database, Spain
- The Information System for the Advancement of Research in Primary Care (Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària [SIDIAP]) database in Catalonia, Spain
- The German Pharmacoepidemiological Research Database (GePaRD), Germany. Conduct of the study in the GePaRD needs approval by the statutory health insurance providers (SHIs)
- The Health Improvement Network (THIN), United Kingdom (UK)
- The Swedish National Registers

Study size: We ascertained the preliminary number of new users of cilostazol in SIDIAP, THIN, and Swedish databases. For GePaRD, we estimated the number of new users in the database based on the reported use of cilostazol in Germany. For IACS in Spain, the number of new users is yet to be ascertained. Overall, the estimated total number of new users in the study databases is between 11,000 and 17,000 (pending the number of new users from IACS and confirmation from GePaRD and Sweden).

Data analysis: The use and patterns of use of cilostazol will be summarised by the total number of users, prescriptions, and number of defined daily doses (DDDs), and by the number of users according to daily dose and duration of use. Characteristics of users, comorbidity, comedications, use of interacting drugs, and conditions defined for the evaluation of risk minimisation measures, contraindications, indications, off-label use, hospitalisations, and prescriber speciality will be described as number and percentage of patients with each condition. All analysis will be stratified by age and sex. Shell tables of results for the planned analysis are presented in a separate file (Cilostazol shell analysis tables Final.xlsx).

Limitations: Drug utilisation studies conducted in automated health databases allow identification of patients who are prescribed or dispensed the drugs of interest and characterisation of these patients according to prior medical history, use of medications, and patterns of use of medications. Health care databases have become a standard tool for conducting research to study the safety of drugs as information on diagnoses and treatments is recorded on an ongoing basis. Thus, the proposed DUS will comply with the request of the Rapporteur Assessment (Joint Assessment Report, July 2012) to provide data on the use of cilostazol across several populations in Europe.

This study will address all the requirements with the exception of three components of the evaluation of risk minimisation measures: (1) smoking status and history, which is only partially available in THIN and GePaRD; (2) assessment of physical exercise, which is not recorded in the study databases; and (3) ascertainment of the indication of cilostazol (no direct indication information is available). For the indication, we will use proxy data (i.e., diagnosis around the date of prescriptions of cilostazol) in all populations and complemented with the clinical review of the full computerised information in the UK and, if possible, in Germany.

Milestones: The study will be initiated first in THIN in the first quarter of 2013 (1Q2013), with a final report expected by the fourth quarter of 2013 (4Q2013). Separate study reports adding results for the rest of the databases will be finalised on 30 June 2014 for IACS (Spain), 30 September 2014 for SIDIAP (Spain) and Sweden, and 31 March 2015 for Germany. A preliminary report is planned by 30 June 2014, with complete results from THIN and IACS and preliminary results from SIDIAP and Sweden.

5 Amendments and Updates

The protocol version 2 dated 28 February 2013, was the protocol endorsed by the EMA and first posted in the EMA PAS registry (ENCEPP).

Version 2.2, 30 January 2015

Amendments are described in Table 1 and reflect changes in data availability in the GePaRD (Germany), study timelines, and analysis plan. Shells of the analysis tables have also been updated (see the Excel file, Cilostazol shell analysis tables Final V02.xlsx). The file with the updated shells of tables includes a listing of the changes made.

Table 1. Summary of Amendments and Updates

Amend-ment Number	Date	Section of Study Protocol	Amendment or Update	Reason
Version 2.3	5 Nov 2015	9.7.5 Assessment of Changes to the Summary of Product Characteristics	Edits for clarification; corrected typos on assessment of visits between 2 and 4 months; reduction of daily dose	Clarification and correction of typos; does not affect DUS1 analyses
Version 2.3	5 Nov 2015	9.7.1 Number of Users and Patterns of Use	Clarification for calculating prevalence of use in DUS2	Clarification
Version 2.3	5 Nov 2015	9.7.1 Number of Users and Patterns of Use	Evaluation of number of users with less than 12 months of continuous enrolment	MHRA request
Version 2.3	5 Nov 2015	9.2.6 Follow-up	Included date of end of follow-up	Date of end of follow-up not included in prior version
Version 2.3	5 Nov 2015	9.2.3 Study Cohort; 9.2.5 Exclusion Criteria	Added definition of new users for DUS2	Definition of new users for DUS2 was not included in prior version
Version 2.3	5 Nov 2015	9.2.2 Study Period	Added figure and text for the conduct of DUS2	Clarification of study period
Version 2.3	5 Nov 2015	8 Research Question and Objectives	Added text to objectives for DUS2	Clarification of objectives

Amend-ment Number	Date	Section of Study Protocol	Amendment or Update	Reason
Version 2.3	5 Nov 2015	4 Abstract; 9.3.4 Concurrent Use of Medications That May Interact With Cilostazol; 9.7.3 Use of Medications Potentially Interacting With Cilostazol; 9.7.5 Assessment of Changes to the Summary of Product Characteristics	Evaluation of potent inhibitors of CYP3A4 and CYPC19	MHRA request
Version 2.3	5 Nov 2015	4 Abstract	Clarification of reduction of daily dose	Corrected error; does not affect DUS1 analyses
Version 2.3	5 Nov 2015	6 Milestones and Timeline	Clarification of deadline final report	Deadline is for submission of final report to the MHRA
Version 2.3	5 Nov 2015	3 Responsible Parties; 6 Milestones and Timeline	Updated acronym description for IACS	Change in acronym description
Version 2.2	30 Jan 2015	6.1 Milestones and Timeline for DUS1 9.4.2 Description of Databases 10 Protection of Human Subjects	Statutory health insurance providers (SHIs) contributing data to the GePaRD, Germany	One SHI denied approval for participating in the study. Data from another SHI, with 44 users of cilostazol, are considered inadequate due to data truncation
Version 2.2	30 Jan 2015	6.1 Milestones and Timeline for DUS1	Update status of study and preliminary reports submitted to the MHRA	Study is finalized in THIN (UK), IACS (Spain), SIDIAP (Spain), and Sweden, and two preliminary reports have been submitted to the MHRA
Version 2.1	30 Apr 2014	6, Milestones and Timeline	Timelines updated. Added timelines for DUS2	Delays in the start of the study in some databases because of the conduct of preliminary analysis, contractual issues, and approvals. Revised timelines for DUS2.

Amend-ment Number	Date	Section of Study Protocol	Amendment or Update	Reason
Version 2.1	30 Apr 2014	7, Rationale and Background 9.3.6, Baseline Characterisation of New Users for the Assessment of Planned Risk Minimisation Measures (SmPC Changes)	Clarifications on the conduct of DUS2 regarding cilostazol products and study protocol	Clarifications requested by MHRA
Version 2.1	30 Apr 2014	6, Milestones and Timeline	Clarification on study report	A cumulative report summarising results from all databases will be produced
Version 2.1	30 Apr 2014	9.3.3, Characterisation of New Users at the Start Date Table 4, Diagnostic Codes for Comorbid Conditions Analysis Table 8	Categorisation of cardiovascular disease, bleeding disorders, and renal disease	To obtain more detailed information on these diseases
Version 2.1	30 Apr 2014	9.3.4, Concurrent Use of Medications That May Interact With Cilostazol Analysis Tables 10-13	Additional analysis of concurrent use of any CYP2C19 and CYP3A4 metabolisers	To assess overall use of metabolisers
Version 2.1	30 Apr 2014	9.3.5, Concurrent Use of Selected Antithrombotic Agents 9.7.4, Concurrent Use of Antithrombotic Agents Analysis Tables 14-15	Analysis conducted during consecutive use of cilostazol instead of current use of cilostazol. Corrected codes for some antithrombotic agents	Consecutive use of cilostazol reflects better its chronic use according to descriptive analysis of consecutive prescriptions
Version 2.1	30 Apr 2014	9.3.6, Baseline Characterisation of New Users for the Assessment of Planned Risk Minimisation Measures (SmPC Changes) 9.7.5, Assessment of Changes to the Summary of Product Characteristics Analysis Tables 17B and 17C	Changes of period of assessment of visits (2-4 months after start date instead of 3-4 months). Unplanned analysis of visits between 1 and 6 months after start date. Unplanned analysis of visits using diagnosis/visit codes	To improve assessment of visits based on clinical review of patient profiles

Amend-ment Number	Date	Section of Study Protocol	Amendment or Update	Reason
Version 2.1	30 Apr 2014	9.3.6, Baseline Characterisation of New Users for the Assessment of Planned Risk Minimisation Measures (SmPC Changes) 9.7.5, Assessment of Changes to the Summary of Product Characteristics Analysis Table 17A	Assessment of discontinuation of cilostazol by survival analysis	Survival analysis used to take into account censoring
Version 2.1	30 Apr 2014	9.3.6, Baseline Characterisation of New Users for the Assessment of Planned Risk Minimisation Measures (SmPC Changes)	Analysis of reduction of dose conducted during consecutive use of cilostazol instead of current use of cilostazol	Consecutive use of cilostazol reflects better its chronic use according to descriptive analysis of consecutive prescriptions
Version 2.1	30 Apr 2014	9.3.6, Baseline Characterisation of New Users for the Assessment of Planned Risk Minimisation Measures (SmPC Changes) 9.7.7, Overall Assessment of Contraindications Analysis Table 28	Overall assessment of labelled and new 2013 SmPC contraindications	To assess overall number of users with any contraindication for cilostazol
Version 2.1	30 Apr 2014	9.7.1, Number of Users and Patterns of Use Analysis Table 29	Distribution of users by the number of prescriptions received	Additional analysis
Version 2.1	30 Apr 2014	9.7.1, Number of Users and Patterns of Use Analysis Table 30	Distribution of users by the year of start date	Additional analysis
Version 2.1	30 Apr 2014	9.7.1, Number of Users and Patterns of Use Analysis Table 25	Age- and sex-specific prevalence of use	Additional analysis
Version 2.1	30 Apr 2014	9.7.1, Number of Users and Patterns of Use Analysis Table 31	New analysis table for calculation of mean of age by sex	To document results of analysis

Amend-ment Number	Date	Section of Study Protocol	Amendment or Update	Reason
Version 2.1	30 Apr 2014	9.7.2, Characterisation of Users at the Start Date Analysis Table 24	New analysis table	To document results of analysis
Version 2.1	30 Apr 2014	9.7.3, Use of Medications Potentially Interacting With Cilostazol Analysis Table 27	Distribution of users by the number of interacting medications received	Additional analysis
Version 2.1	30 Apr 2014	PASS Information	Included EMA PAS registration number	Protocol submitted and EU PAS registration number obtained
Version 2.1	30 Apr 2014	Marketing Authorisation Holder(s)	Updated sponsor address and contact person	Changes in Otsuka organisation
Version 2.1	30 Apr 2014	Approval page	Updated Otsuka approval person	Changes in Otsuka organisation
Version 2.1	30 Apr 2014	3 Responsible Parties	Updated information	Changes in Otsuka organisation and confirmation of collaborating institutions

DUS = drug utilization study; EMA = European Medicines Agency; EU PAS Register = European Union electronic register of post-authorisation studies; GePaRD = German Pharmacoepidemiological Research Database; IACS = Aragón Health Sciences Institute; MHRA = Medicines and Health Products Regulatory Agency; PASS = post-authorisation safety study; SHI = statutory health insurance; SIDIAP = Information System for the Advancement of Research in Primary Care; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

6 Milestones and Timeline

6.1 Milestones and Timeline for DUS1

We anticipate that study results for each country will be available 9 to 12 months after study start, which is defined as the date when data are extracted, and thus may vary by country and database. Results from each database will be finalised according to the time the data become available in each database; the results from each database will be compiled into a cumulative report.

Initial anticipated timelines detailed in protocol version 2 dated 28 February 2013 have been revised to account for delays in the start of the study in some databases because of the need to conduct exploratory analysis (SIDIAP), contractual issues, and approvals. The revised timelines for DUS1 impact the finalisation of DUS2, resulting in about a 1-month delay (see Section 6.2 for DUS2 timelines).

At the time of the protocol amendment (30 January 2015), the study has been completed in THIN (UK), IACS (Spain), SIDIAP (Spain), and Sweden and is ongoing in the GePaRD (Germany).

A preliminary report with final results from THIN and IACS, and partial results from IACS, SIDIAP, and Sweden, was submitted to MHRA 30 June 2014. A second preliminary report adding final results from IACS, SIDIAP, and Sweden was submitted to the MHRA in November 2014. The final study report with final results from all databases will be submitted in April 2015.

Milestone	Original Anticipated Date	Actual/Revised Date
Registration in the EU PAS register	1Q 2013 – Prior to start of data collection	4 Mar 2013
Data availability - THIN	1Q 2013	1Q 2013
Start of data collection[a] - THIN	1Q 2013	1Q 2013
End of data collection[b] - THIN	2Q 2013	2Q 2013
Final report – THIN	4Q 2013	27 Sep 2013
Data availability – IACS, SIDIAP, Sweden	1Q 2013	1Q 2013
Start of data collection[a] - IACS, SIDIAP, Sweden	2Q 2013	IACS: 3Q 2013 SIDIAP, Sweden: 1Q 2014
End of data collection[b] - IACS, SIDIAP, Sweden	3Q 2013	IACS: 3Q 2013 SIDIAP, Sweden: 1Q-2Q 2014
Final report adding IACS, SIDIAP, Sweden	4Q 2013 - 1Q 2014	IACS: 30 Jun 2014 SIDIAP: Preliminary report: 30 Jun 2014 Final report: 30 Sep 1014 Sweden: Preliminary report: 30 Jun 2014 Final report: 30 Sep 1014
Data availability – GePaRD	3Q-4Q 2013	2Q 2014[c]
Start of data collection[a] - GePaRD	4Q 2013	2Q-3Q 2014[c]
End of data collection[b] - GePaRD	1Q 2014	3Q-4Q 2014[c] Analysis to be completed by 30 Jan 2015
Final study report adding GePaRD	2Q 2014	31 Mar 2015[d]

EU PAS Register = European Union electronic register of post-authorisation studies; GePaRD = German Pharmacoepidemiological Research Database; IACS = Aragón Health Sciences Institute; SIDIAP = Information System for the Advancement of Research in Primary Care database, Catalonia, Spain; THIN = The Health Improvement Network, United Kingdom.

[a] Date from which data extraction starts.

[b] Date from which the analytical data set is completely available.

[c] Conditional on approval by statutory health insurance providers (SHIs) and data availability. One SHI denied approval for conducting the study. Data from another SHI involving 44 users of cilostazol are truncated to the end of 2007 and will not be included in the study.

[d] Submission of the final study report is planned for 30 April 2015.

6.2 Milestones and Timeline for DUS2

DUS2 will be conducted after the implementation of changes to the summary of product characteristics (SmPC) and the follow-up communication activities with health care professionals. Anticipated timelines submitted to the EMA have been revised by the research institutions. The original and revised timelines for completing DUS2 are presented in the table below.

Timelines for finalising the study report in THIN, IACS, SIDIAP, and the Sweden databases have been confirmed by the researchers at each of these data sources. In THIN, the final report is planned to be finalised by 31 December 2015. In IACS, SIDIAP, and Sweden the final report is planned to be finalised by 30 September 2016. In Germany, the original timelines have been adapted based on experience from the implementation of DUS1. The analysis is expected to be completed by 1 November 2016, and the final report incorporating the cumulative results from all the data sources is expected to be completed for submission to the MHRA by 1 February 2017. This is about 1 month later than the originally planned date of completion.

Milestone	Anticipated Date	Revised Date
Approval SmPC changes	May 2013	May 2013
SmPC implementation period	May 2013 - Nov 2013	Jun-Dec 2013
Patient accumulation – 1 year	Nov 2014	1 Jan 2014 – 31 Dec 2014
Data availability – THIN	May 2015[a]	1Q 2015[b]
Start of data collection[c] – THIN	2Q 2015	1 Apr 2015
End of data collection[d] – THIN	3Q 2015	30 Jun 2015
Final report – THIN	4Q 2015	31 Dec 2015
Data availability – IACS, SIDIAP, Sweden[e]	3Q 2015-1Q 2016	Jan 2016
Final report – IACS, SIDIAP, Sweden	2Q 2016-3Q 2016	30 Sep 2016
Data availability – GePaRD[f]	1-2Q 2016	1 Jul 2016
Final report – THIN, IACS, SIDIAP, Sweden, and GePaRD[g]	3-4Q 2016	1 Feb 2017[h]

EU PAS Register = European Union electronic register of post-authorisation studies; GePaRD = German Pharmacoepidemiological Research Database; IACS = Aragón Health Sciences Institute; SIDIAP = Information System for the Advancement of Research in Primary Care database, Catalonia, Spain; THIN = The Health Improvement Network, United Kingdom.

Note: Timelines revised by IACS, IDIAP, Karolinska, and BIPS in March 2014. Contracts between sponsor and research organisations and approvals by data protection, data custodian, ethics committees, and scientific review bodies are pending. Timelines may be impacted by duration of contract reviews, approvals of mentioned bodies, and availability of data and staff at research institutions once contracts and approvals are finalised.

[a] Based on 6 months' lag time for data availability after patient accumulation.

[b] Based on communication with THIN.

[c] Date from which data extraction starts.

[d] Date from which the analytical data set is completely available.

[e] Based on 12 months' lag time for data availability after patient accumulation.

[f] Based on an expected 18 months' lag time for data availability after patient accumulation.

[g] Conditional to data availability.

[h] Final report ready for submission to the MHRA.

7 Rationale and Background

We present a study protocol for conducting a drug utilisation study on the use of cilostazol in several European populations in the context of the European Medicines Agency (EMA) cilostazol referral under Article 31 of Council Directive 2001/83/EC.

Cilostazol has been marketed in Europe for intermittent claudication since 2002. The EMA has recently reviewed cilostazol (Pletal, Ekistol) for intermittent claudication, prompted by a referral under Article 31 of Council Directive 2001/83/EC. The focus of the review was the role of cilostazol in current treatment of intermittent claudication and the balance of risks and benefits of the drug. The preliminary Joint Assessment Report (4 July 2012) recommended the conduct of a drug utilisation study (DUS) using database sources to understand the characteristics of users of cilostazol, duration and patterns of cilostazol use, and the prevalence of concomitant use of cilostazol and other drugs with which it may interact.

Prior research conducted in the region of Cantabria in Spain showed that 70% of users of cilostazol were elderly patients with underlying comorbidities who were treated concurrently with several other medications in addition to cilostazol (González-Ruíz et al., 2011).

The plan is to conduct the DUS in two phases. DUS1 will evaluate cilostazol as currently used in several European countries during the period from launch through 2011. DUS2 will be conducted after the implementation of changes to the summary of product characteristics (SmPC) and the follow-up communication activities with health care professionals (HCPs) and will evaluate the impact of these measures during the year 2014 in the same countries as DUS1. DUS2 will be conducted using the same protocol as DUS1. Both DUS1 and DUS2 will include all the marketed products containing cilostazol in the countries, irrespective of brand.

This protocol describes the study design and methods for conducting DUS1 and DUS2. The study is proposed to be conducted in populations covered in automated health databases from four European countries: Spain, the United Kingdom (UK), Germany, and Sweden. Adjustments may be made to the protocol after DUS1 is completed.

8 Research Question and Objectives

The primary objectives of the DUS are as follows:

- To describe the characteristics of new users of cilostazol according to the following factors:
  - Demographics (e.g., age and sex)
  - Baseline comorbidity including conditions listed in the SmPC and the risk management plan (RMP) as potential or identified safety concerns (Otsuka Pharmaceutical Europe Ltd, 2012).
  - Baseline and concurrent use of medications potentially interacting with cilostazol and other medications

  - Specific comorbidity and use of medications considered in the proposed risk minimisation measures, specifically those included in the proposed changes to the SmPC
- To describe the duration of the use of cilostazol and discontinuation patterns

Secondary objectives of the DUS are as follows:

- To quantify and describe off-label prescribing
- To describe dosage patterns of the use of cilostazol
- To assess the proportion of patients who are hospitalised for any cause while treated with cilostazol
- To describe the medical specialties of physicians prescribing cilostazol

The study objectives are the same for DUS1 and DUS2. DUS1 provides the baseline characteristics of users of cilostazol before the implementation of SmPC changes and communication with HCPs. DUS2 will be conducted after the implementation of these measures to evaluate their impact on the prescribing of cilostazol.

9 Research Methods

9.1 Study Design

The DUS is a cohort study of new users of cilostazol identified in five proposed European population-based automated health databases from four countries:

- The Aragón Health Sciences Institute (Instituto Aragonés de Ciencias de la Salud [IACS]) database, Spain
- The Information System for the Advancement of Research in Primary Care (Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària [SIDIAP]) database in Catalonia, Spain
- The German Pharmacoepidemiological Research Database (GePaRD), Germany
- The Health Improvement Network (THIN), United Kingdom (UK)
- The Swedish National Databases.

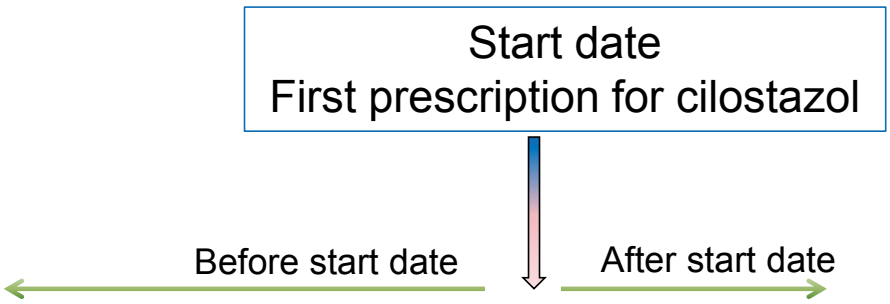
Study participation

- THIN has agreed to provide the data for conducting the study. The THIN Scientific Review Committee approved the study in February, 2013. IACS, SIDIAP, GePARD and Sweden confirmed interest in participating in the study. The principal investigator in IACS will be Dr. Francisca González Rubio.
- Conduct of the study in the GePaRD needs approval by the statutory health insurance providers (SHIs) to send individual patient–level data to BIPS to be used in the analysis.
- A detailed description of these databases is included in Section 9.4.

New users of cilostazol will be characterised in terms of demographics, comorbidity, and past and concurrent use of medications before and after receiving the first prescription

for cilostazol (start date) according to the time frame displayed in Figure 1. Comorbidity for each patient will be assessed for the whole medical history available in each database before the start date. Conditions and procedures that will be used to evaluate the risk minimisation measures based on changes in the SmPC (contraindications, posology, and warnings and precautions) will be assessed for the 6 months before the start date. Comedications will be evaluated for the 6 months before the start date. Concurrent use of potentially interacting medications will be assessed for the 3 months before the start date and during follow-up. Duration of use of cilostazol will be assessed during follow-up.

Figure 1. Overview of Study Design



Characterization of users of cilostazol	>6 months	6 months	3 months	Follow-up
Comorbidity	✓	✓	✓	
Comorbidity for risk minimization measures		✓	✓	
Comedications		✓	✓	
Interacting medications			✓	✓
Duration of use				✓

9.2 Setting

9.2.1 Source Population

The source population includes all individuals registered in the study databases since the date of the first recorded prescription of cilostazol in each database.

9.2.2 Study Period

The study period is defined in each database as the time between the date when cilostazol became available in the corresponding country and the latest date of data availability (Table 2). The estimated end of study period for IACS, GePaRD, and Sweden will be 31 December 2011. Partial data for the year 2012 are expected to be available in SIDIAP and THIN.

Table 2. Estimated Study Period in Each Study Database

	IACS, Spain	SIDIAP, Spain	GePaRD, Germany	THIN, UK	National Databases, Sweden
Cilostazol launch in country[a]	Jun 2009	Jun 2009	Jan 2007	Jun 2002	Apr 2008
Study period (based on cilostazol launch date and data availability, end of 2012 or early 2013)	Jan 2010 – Dec 2011	Jun 2009 – Apr 2012	Jan 2007 – Dec 2011	Jun 2002 – Dec 2012	Apr 2008 – Dec 2011

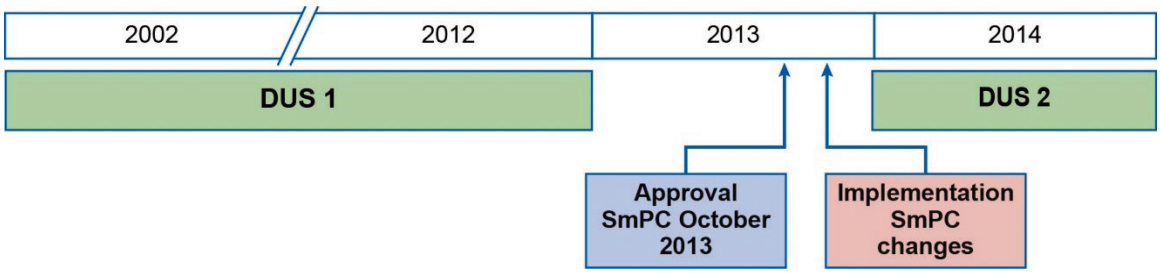
GePaRD = German Pharmacoepidemiological Research Database; IACS = Aragón Health Sciences Institute; SIDIAP = Information System for the Advancement of Research in Primary Care database, Catalonia, Spain; THIN = The Health Improvement Network, United Kingdom; UK = United Kingdom.

[a] Provided by Otsuka.

9.2.2.1 Study Period for DUS2

The study period for DUS 2 is from 1 January 2014 to 31 December 2014, following the implementation of changes to the summary of product characteristics (SmPC) and communication activities with HCPs that took place during 2013 (Figure 2).

Figure 2. Study Period for DUS 1 and DUS 2 in Relation to 2013 SmPC Changes



DUS 1 = first drug utilisation study; DUS 2 = second drug utilisation study; SmPC = summary of product characteristics.

9.2.3 Study Cohort

The study cohort includes all individuals from the source population who have a first recorded prescription of cilostazol during the study period and have been continuously enrolled in the database for at least 6 months. For each patient, the **start date** is defined as the date a patient receives a first prescription for cilostazol after 6 months of continuous enrolment in the database (see Section 9.2.4, Inclusion Criteria). Because the study period starts at the year cilostazol was available in each country, members of the study cohort are new users of cilostazol. For DUS2, the study cohort includes all individuals from the source population who have a **first ever** recorded prescription of cilostazol during the study period and have been continuously enrolled in the database for at least 6 months.

9.2.4 Inclusion Criteria

Members of the study cohort are required to have been continuously enrolled in the study database for an eligibility period of at least 6 months before the start date. This ensures that all patients will have at least 6 months of information recorded in the database.

9.2.5 Exclusion Criteria

Because the DUS seeks to characterise all new users of cilostazol, no exclusion criteria regarding age, sex, or comorbidity will be applied.

Patients who have their first recorded prescription for cilostazol during the eligibility period (6 months of continuous enrolment in the database) will be excluded as they will not be new users at the start date. In addition, for DUS2, patients who have a recorded prescription for cilostazol at any time before the start will also be excluded.

Patients with records flagged as incomplete or as substandard data quality according to each database-specific quality-control measures will be excluded.

9.2.6 Follow-up

Each member of the study cohort will be followed from the start date until the first of the following termination dates:

- End of enrolment in the database
- Death
- End of study period (for DUS2, 31 December 2014)

For each member of the study cohort, comorbidity will be assessed for the entire period of data availability before the start date.

9.3 Variables

9.3.1 Use of Cilostazol and Patterns of Use

The number of new users of cilostazol and the number of prescriptions, packages, and defined daily dose (DDD) will be ascertained overall and by strength, quantity, and year.

Current use of cilostazol will be ascertained according to the days of supply of each prescription for cilostazol. Days of supply of a prescription are defined as the number of days of intended duration of treatment for that prescription. If days of supply of prescriptions are not recorded in some databases, they will be estimated from descriptive analysis of the number of days between consecutive prescriptions.

Current use is defined as the time involving the days of supply of each prescription plus 7 days to allow for a potential delay in the start of treatment.

Duration of Use of Cilostazol

Duration of use refers to the duration of continuous treatment with cilostazol. Duration will be ascertained by the total number of days of supply of consecutive prescriptions, defined as those prescribed within a maximum interval of 60 days of each other. Sensitivity analyses will be conducted for a maximum interval of 90 days between prescriptions.

Daily Dose of Cilostazol

Daily dose of cilostazol will be calculated using the recorded information on strength and quantity prescribed and the days of supply of each prescription.

9.3.2 Characterisation of New Users—Overview

Characterisation of new users of cilostazol will include the following assessments:

- Characterisation at the start date
  - Demographics, comorbidity, comedications
- Concurrent use of medications
  - Medications that may interact with cilostazol
  - Selected antithrombotic agents
  - Use of platelet aggregation inhibitors
- Characterisation for risk minimisation measures
  - Restricted target population and other changes in the SmPC
- Assessment of contraindications
- Indications associated with treatment and off-label prescription
- Speciality of prescribers

Comorbidity and use of medications will be assessed through the codes for diagnoses, procedures, and medications specific to each database (Table 3).

Table 3. Types of Diagnosis, Procedure, and Medication Codes in the Study Databases

Type of Code	IACS, Spain	SIDIAP, Spain	GePaRD, Germany	THIN, UK	National Databases, Sweden
Diagnoses	Hospital: ICD-9 Primary health care: ICPC	ICD-10	ICD-10-GM	Read	ICD-10
Procedures	ICD-9	—	Hospital: OPS Ambulatory: EBS	Read	ICD-9
Medications	ATC	ATC	ATC	Multilex, British National Formulary	ATC

ATC = Anatomical Therapeutic Chemical; EBS = ambulatory operation or procedure codes; GePaRD = German Pharmacoepidemiological Research Database; IACS = Aragón Health Sciences Institute; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th Revision; ICD-10-GM = International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification; ICD-9 = International Classification of Diseases, 9th Revision; ICPC = International Classification of Primary Care; OPS = hospital operation or procedure codes; SIDIAP = Information System for the Advancement of Research in Primary Care; THIN = The Health Improvement Network; UK = United Kingdom.

Source: See Section 9.4.

9.3.3 Characterisation of New Users at the Start Date

New users of cilostazol will be characterised at the start date according to demographic, family history, comorbidity, and comedications. Comorbidity will be ascertained through primary care and/or hospital discharge diagnosis codes recorded in the study databases at any time before the start date. Comedications will be ascertained through medication codes recorded in the 6 months before the start date.

Some variables may not be available in all databases. For example, smoking status is available only in THIN, and the recording of data may be incomplete.

The following variables will be assessed:

Demographics and Lifestyle Habits

- Age
- Sex
- Calendar year of the start date
- Socioeconomic indicators (proxies: patient's postal code, zip code level)
- Smoking status

Family History

- Cardiovascular diseases

Comorbidity

Comorbidity will be ascertained through diagnosis codes recorded at any time before the start date.

Note: ICD-10 codes in Table 4 will be mapped to ICD-9, ICD-10-GM, and Read codes.

Table 4. Diagnostic Codes for Comorbid Conditions

Disease Description	ICD-10
A. Cardiovascular diseases and procedures	**All codes in Section A**
Diseases of arteries, arterioles, and capillaries	I70-I79
Intermittent claudication	I73.9
Other peripheral arterial disease	I70.2, I70.9, I73.1-I73.8
Atherosclerosis	I70
Other diseases of arteries, arterioles, and capillaries	I74.4
Revascularisation procedures	List of codes to be developed according to each database dictionary
Cardiovascular disease other than diseases of arteries, arterioles, and capillaries	All codes in this section, Cardiovascular disease other than diseases of arteries, arterioles, and capillaries
Ischaemic heart disease	I20-I25
Acute myocardial infarction	I21
Unstable angina pectoris	I20.0
Other acute or subacute ischaemic heart disease	I22,I23,I24
Angina pectoris	I20.1-I20.9
Chronic ischaemic heart disease	I25
Old myocardial infarction	I25.2
Coronary reperfusion surgery and procedures	List of codes to be developed according to each database dictionary
Arrhythmias	I47, I48, I49
Paroxysmal tachycardia	I47
Ventricular tachycardia	I47.0, I47.2
Supraventricular tachycardia and unspecified	I47.1, I47.9
Atrial fibrillation and flutter	I48
Other cardiac arrhythmias	I49
Ventricular fibrillation and flutter	I49.0
Other cardiac arrhythmias	I49.1-I49.9
Cardiac arrest	I46
Conduction disorders	I44-I45
Heart failure	I50
Cerebrovascular disease	I60-I69
Cerebral haemorrhage (subarachnoid, intracerebral, other nontraumatic)	I60, I61, I62

Disease Description	**ICD-10**
Ischaemic stroke	I63, I64, G46.5
Cerebral infarction	I63
Stroke, NOS	I64
Pure motor lacunar syndrome	G46.5
Sequelae of cerebrovascular disease	I69
Other cerebrovascular disease	I65-I69
TIA	G45
Hypertension and hypertensive heart disease	I10-I15
Hypotension	I95
Other form of heart diseases	I00-I09, I30-I43
Disorders of lipoprotein metabolism and other lipidaemias	E78
B. Bleeding disorders	**Any code in Section B**
Cerebral haemorrhage	I60, I61, I62
Gastrointestinal bleeding	Any code in the section Gastrointestinal bleeding
Gastroduodenal bleeding	Any code in the section Gastroduodenal bleeding
Gastroduodenal ulcer	K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6
Gastrointestinal bleeding unspecific	K92.0-K92.2
Acute haemorrhagic gastritis	K29.0
Oesophageal bleeding	K22.6, K22.8 , I85.0
Lower gastrointestinal bleeding[a]	K62.5, K66.1, I84.1, I84.4, I84.8
Genitourinary bleeding[a]	N02, R31, N92, N93
Other site bleeding[b]	I31.2, M25.0, R04
C. Blood dyscrasias	**Any code in Section C**
Haemolytic anaemias	D55-D59
Aplastic anaemia	D61.9
Acute posthaemorrhagic anaemia	D62
Other anaemias	D60, D61.0-D61.8, D63, D64
Thrombocytopenia	D69.6
Purpura and other haemorrhagic conditions	D69.0-D69.5, D69.8, D69.9
Haemorrhagic thrombocythaemia	D47.3
D. Renal diseases	**Any code in Section D**
Renal failure	N17-N19
Other renal diseases	N00-N08, N10-N16
Other disorders of kidney and ureter	N25-N39
E. Skin and subcutaneous tissue disorders	**Any code in Section E**
Dermatitis and eczema	L20-L30

Disease Description	ICD-10
Stevens-Johnson syndrome	L51.1
Toxic epidermal necrolysis	L51.2
Urticaria and erythaema	L50, L51.0, L51.8, L51.9, L52-L54
F. Other conditions	
Peptic ulcer disease	K25-K28
Liver disease	K70-K77
Diabetes mellitus	E10-E14
Chronic obstructive pulmonary disease (COPD), emphysema, respiratory insufficiency	J40-J44, J96
Asthma	J45, J46
Rheumatoid arthritis and other inflammatory arthropathies	M05-M14
Systemic connective tissue diseases	M30-M36
Malignancy	C00-C97
Human immunodeficiency virus disease	B20-B24

ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*.

[a] K62.5 = Haemorrhage of rectum and anus; K66.1 = Haemoperitoneum; I84.1 = Internal haemorrhoids with other complications; I84.4 = External haemorrhoids with other complications; I84.8 = Unspecified haemorrhoids with other complications; N02 = Recurrent and persistent haematuria; R31 = Unspecified haematuria; N92 = Excessive, frequent and irregular menstruation; N93 = Other abnormal uterine and vaginal bleeding.

[b] I31.2 = Haemopericardium, not elsewhere classified; M25.0 = Haemarthrosis; R04 = Epistaxis.

Comedications

Comedications will be ascertained through medication codes recorded in the 6 months before the start date.

Note: The Anatomical Therapeutic Chemical (ATC) codes in Table 5 will be mapped to Multilex/British National Formulary codes.

Table 5. Anatomical Therapeutic Chemical Codes for Comedications

Disease Description	ATC
Cardiovascular medications	C
Cardiac glycosides	C01A
Antiarrhythmics, Class I and III	C01B
Cardiac stimulants excluding cardiac glycosides	C01C
Vasodilators used in cardiac diseases	C01D
Other cardiac preparations	C01E
Diuretics	C03
Peripheral vasodilators	C04
Pentoxifylline	C04AD03
Beta blocking agents	C07

Disease Description	ATC
Calcium channel blockers	C08
Antihypertensives	C02
Agents acting on the renin-angiotensin system	C09
Angiotensin-converting-enzyme inhibitors	C09A, C09B
Angiotensin II receptor antagonists	C09C, C09D
Renin-inhibitors	C09X
Lipid-modifying agents	C10
Statins	C10AA
Simvastatin	C10AA01
Lovastatin	C10AA02
Other lipid-modifying agents	C10AB, C10AC, C10AD, C10AX, C10BA
Statin combinations with ASA	C10BX
Antithrombotic agents	B01
Platelet aggregation inhibitors	B01AC
Clopidogrel	B01AC04
Acetylsalicylic acid	B01AC06, B01AC30, B01AC56
Other platelet aggregation inhibitors	B01AC01-B01AC03, B01AC05, B01AC07-B01AC22, B01AC24
Vitamin K antagonists	B01AA
Heparins	B01AB
Other antithrombotic agents	B01AD, B01AE, B01AX
Iron preparations	B03A
Proton pump inhibitors	A02BC
Omeprazole	A02BC01
Drugs used in diabetes	A10
Insulins	A10A
Blood glucose lowering drugs	A10B, A10X
Drugs for obstructive airway diseases	R03
Drugs for musculoskeletal system	M01A, N02BA, M01B, M01C
Non-steroidal anti-inflammatory drugs	M01A
Acetylsalicylic acid (other analgesics and antipyretics)	N02BA
Other antirheumatic agents	M01B-M01C
Antidepressants	N06A
Selective serotonin reuptake inhibitors	N06AB
Antineoplastic agents	L01
Immunosuppressants	L04
Antivirals for systemic use	J05
Other medications	
Systemic corticosteroids	H02

Disease Description	ATC
Hormone replacement therapy	G03C, G03D, G03F
Drugs used in nicotine dependence	N07BA

ATC = Anatomical Therapeutic Chemical.

9.3.4 Concurrent Use of Medications That May Interact With Cilostazol

Cilostazol is extensively metabolised by cytochrome P-450 (CYP450) enzymes, particularly CYP3A4 and to a lesser extent by CYP2C19. Medications potentially interacting with cilostazol are listed in the risk management plan and in the summary of product characteristics and include CYP3A4 and CYP2C19 substrates and inhibitors and CYP3A4 inducers. A summary of these medications is presented in Table 6. A complete list of clinically relevant medications interacting with CYP450 is presented in Annex 3.

Table 6. Medications Potentially Interacting With Cilostazol

	Substrates		Inhibitors		Inducers
Medication	**CYP2C19**	**CYP3A4**	**CYP2C19**	**CYP3A4**	**CYP3A4**
Proton pump inhibitors					
Lansoprazole	X		X		
Omeprazole	X		X		
Antiepileptics					
Phenytoin	X				X
Carbamazepine					X
Macrolide antibiotics					
Clarithromycin		X		X	
Erythromycin		X		X	
Protease inhibitor antivirals					
Indinavir		X		X	
Ritonavir		X		X	
Nelfinavir				X	
Gastrointestinal					
Cisapride		X			
Calcium channel blockers					
Diltiazem		X		X	
Statins					
Simvastatin		X			
Antimycotics					
Ketoconazole			X	X	
Itraconazole				X	
Antimycobacterials					
Rifampin					X

	Substrates		Inhibitors		Inducers
Medication	**CYP2C19**	**CYP3A4**	**CYP2C19**	**CYP3A4**	**CYP3A4**
Antipsychotics					
Pimozide		X			

CYP = cytochrome P-450.

For each user of cilostazol, the use of each medication listed in Annex 3 will be ascertained at the start date and during follow-up for current use of cilostazol (Section 9.3.1).

- Concurrent use at the start date:
  - Patients who have at least one prescription for a potentially interacting medication recorded within 3 months before the start date
- Concurrent use during follow-up:
  - Patients who have at least one prescription for a potentially interacting medication recorded during the time of current use of cilostazol.
  - Patients who have at least one prescription for a potentially interacting medication recorded during the time of consecutive use of cilostazol as defined in Section 9.3.1 (duration of use of cilostazol).

9.3.4.1 Concurrent Use of Potent Inhibitors of CYP3A4 and CYP2C19

Concurrent use of potent inhibitors of CYP3A4 and CYP2C19 will also be evaluated. Potent inhibitors are those identified as such by the Indiana Classification (Trustees of Indiana University, 2013) and the United States Food and Drug Administration Drug Development and Drug Interactions website.[1] Potent inhibitors are lansoprazole, fluvoxamine, nefazodone, ticlopidine, clarithromycin, troleandomycin, indinavir, ritonavir, nelfinavir, mibefradil, ketoconazole, and itraconazole.

9.3.4.2 Concurrent Use of Other Acting Medications

In addition of the assessment of individual medications listed in Annex 3, the following groups of medications and ATC codes will be assessed at the start date and during follow-up as described above:

- Cardiovascular system – C
  - Antihypertensives – C02
  - Lipid-modifying agents – C10
- Drugs used in diabetes – A10
- Drugs for obstructive airway diseases – R03
- Non-steroidal anti-inflammatory drugs – M01A
- Antidepressants – N06A

[1] http://medicine.iupui.edu/clinpharm/ddis/clinical-table/ (accessed February 2015)
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm (accessed February 2015)

9.3.5 Concurrent Use of Selected Antithrombotic Agents

In addition to potentially interacting drugs, the concurrent use of cilostazol with platelet aggregation inhibitors and antithrombotic agents will be assessed. Antithrombotic agents are listed in Table 5.

Use of each antithrombotic agent will be defined, similarly to cilostazol use, according to the days of supply of each prescription. If days of supply of prescriptions are not recorded in some databases, they will be estimated from descriptive analysis of the number of days between consecutive prescriptions. Current use of each antithrombotic agent is defined as the time involving the days of supply of each prescription plus 7 days to allow for a potential delay in the start of treatment.

Concurrent use of cilostazol and antithrombotic agents will be ascertained as follows:

- At the start date:
  - Use of antithrombotic agents at the start date will be ascertained according to the days of supply of the most recent prescription for each antithrombotic agent before the start date (date of first prescription for cilostazol).
- Overall:
  - Patients simultaneously contributing time to consecutive use of cilostazol and current use of antithrombotic agents at the start date and during follow-up.

Use of Platelet Aggregation Inhibitors

New users of cilostazol who are concurrently treated with platelet aggregation inhibitors at the start date will be followed to assess the proportion of patients discontinuing the use of platelet aggregation inhibitors. Current use of platelet aggregation inhibitors at the start date will be assessed according to the days of supply of the most recent prescription before the start date. Days of supply of a prescription is defined as the number days of intended duration of treatment for that prescription. If days of supply of prescriptions for platelet aggregation inhibitors are not recorded in some databases, they will be estimated from descriptive analysis of the number of days between consecutive prescriptions.

Discontinuation of platelet aggregation inhibitors will be assessed during the time of consecutive use of cilostazol. Discontinuation is defined as any concurrent user of cilostazol and platelet aggregation inhibitors at the start date who does not have a recorded prescription for a platelet aggregation inhibitor after 60 days of ending the days of supply of the prior prescription. Sensitivity analyses for periods of 30 and 90 days after the end of the prior prescription will be conducted.

9.3.6 Baseline Characterisation of New Users for the Assessment of Planned Risk Minimisation Measures (SmPC Changes)

New users of cilostazol will be characterised to evaluate the impact of the risk minimisation measures that Otsuka submitted to the EMA in October 2012. The risk minimisation measures include SmPC changes to identify a more restricted target population and to decrease the daily dose when cilostazol is used with potentially interacting medications. The risk minimisation measures also include communication initiatives to HCPs.

To evaluate the impact of the risk minimisation measures, a second DUS (DUS2) will be initiated 6 months after the implementation of the SmPC changes, and results will be compared with those obtained in the first DUS (DUS1).

The SmPC changes and the characteristics of users that will be evaluated in DUS1 and DUS2 are detailed in Table 7.

Table 7. Proposed Changes in the Labelling of Cilostazol and Characterisation of Users

Proposed Change to Summary of Product Characteristics	Characterisation in DUS
Restricted target population	
Indication	
4.1 Cilostazol is for second-line use in patients in whom life-style modifications (including smoking cessation and [supervised] exercise programmes) and other appropriate interventions have failed to sufficiently improve their intermittent claudication symptoms	Smoking status[a]
4.2 The physician should reassess the patient after 3 months of treatment with a view to discontinuing cilostazol where an inadequate effect is observed.	Number of patients seen by the treating physician after 3 months[b] Number of patients discontinuing after 3 months[b]
Contraindications	
4.3 Patients with unstable angina pectoris, myocardial infarction within the last 6 months, or a coronary intervention in the last 6 months	Unstable angina Myocardial infarction Coronary intervention
Patients treated concomitantly with two or more additional antiplatelet agents (e.g., aspirin, clopidogrel)	Concurrent use of two or more platelet-aggregation inhibitors
Other SmPC changes	
Warnings and precautions	
4.4 Based on its mechanism of action, cilostazol may induce tachycardia, palpitation, tachyarrhythmia, and/or hypotension. The increase in heart rate associated with cilostazol is approximately 5 to 7 beats per minute; in patients at risk, this may induce angina pectoris. Patients who may be at increased risk for serious cardiac adverse events as a result of increased heart rate, e.g., patients with stable coronary disease or a history of tachyarrhythmias, should be monitored closely during the treatment with cilostazol; the use of cilostazol in patients with unstable coronary disease or coronary intervention within the last 6 months is contraindicated (see SmPC Section 4.3).	Number of visits to general practitioner and/or specialist

Proposed Change to Summary of Product Characteristics	Characterisation in DUS
Posology	
4.2 Reduction of the dose to 50 mg twice daily is recommended in patients receiving medicines that strongly inhibit CYP3A4, e.g., several macrolides, azole antifungals, protease inhibitors, or medicines that strongly inhibit CYP2C19, e.g., omeprazole.	Daily dose

CYP = cytochrome P-450; DUS = drug utilisation study; SmPC = Summary of Product Characteristics.

[a] Smoking is available partially in THIN but not in the other study databases. A record of supervised physical exercise programmes is not available in any of the study databases.

[b] Physicians' reassessment of patients and discontinuation because of lack of effect cannot be measured directly in the study databases. The number of patients monitored and the number of patients discontinuing after 3 months will be used as proxies of reassessment and lack of effect.

Evaluation of the impact of the risk minimisation measures will be conducted through diagnosis and medication codes according to the following variables (by SmPC section):

- Indication
  - Smoking at the start date: Smoking status is partially available in THIN and GePARD but not in the other study databases.
  - Number of patients monitored after 2 months: The number of patients with a visit to the general practitioner and/or to a specialist (e.g., cardiologist, vascular specialist, endocrinologist) between (1) 2 months and 4 months after the start date and (2) 1 month and 6 months after the start date. To assess if the visit to the general practitioner (GP) or specialist is related to intermittent claudication, we will manually review the computerised information and free-text comments (THIN) of a random sample of 200 patients. According to the data available in each database, evaluation of visits will also be conducted using diagnosis codes for all users of cilostzol included in the study.
  - Number of patients discontinuing after 3 months: The number of patients discontinuing cilostazol between 3 months and 4 months after the start date will be ascertained using Kaplan-Meier survival curves. This variable will be used as a proxy of lack of efficacy of cilostazol.
- Contraindications
  - Number of patients with a recorded diagnosis for any of the following conditions within 6 months before the start date:
    - Unstable angina pectoris
    - Myocardial infarction
    - Coronary intervention
  - Concurrent use of two or more platelet aggregation inhibitors
    - Concurrent use of two or more platelet aggregation inhibitors will be ascertained at the start date and during follow-up through the simultaneous contribution of person-time to current use of cilostazol and to current use of two or more platelet aggregation inhibitors.

- Warnings and precautions
  - Monitoring of patients at increased risk of serious cardiac events (e.g., arrhythmias, coronary heart disease)
  - Patients with a history of arrhythmias, hypotension, or coronary heart disease recorded at any time before the start date will be followed to assess the rates of visits to general practitioners or specialists. Visit rates for these patients will be used as a proxy of intensified monitoring and compared with the rates for the patients who do not have a history of arrhythmias, hypotension, or coronary heart disease.
- Posology
  - Daily dose of cilostazol at the start date will be assessed among concurrent users of potentially interacting medications at the start date
  - Reduction of daily dose to 50 mg will be assessed among patients who are prescribed a potentially interacting medication during continuous use of cilostazol.

The diagnosis, procedure, and medication codes that will be used to define the variables for the evaluation of the risk minimisation measures are included in Table 4 and Table 5.

Assessment of Contraindications

Use of cilostazol will be additionally evaluated for the use in patients with diseases and conditions listed as contraindications in the SmPC. These contraindications are the following:

- Severe renal impairment
- Moderate to severe hepatic impairment
- Congestive heart failure
- History of bleeding disorders: active peptic ulcer, recent haemorrhagic stroke, proliferative diabetic retinopathy, poorly controlled hypertension
- History of arrhythmias: ventricular tachycardia, ventricular fibrillation or multifocal ventricular ectopics, prolongation of the QT interval

The diagnosis codes that will be used to define the variables for the evaluation of contraindications are included in Table 4.

Overall Assessment of Contraindications

Overall assessment will be conducted by evaluating the number of users who are current smokers at the start date, have a labelled contraindication for the use of cilostazcol, or have a new 2013 SmPC contraindication.

9.3.7 Indications Associated With Treatment and Off-Label Prescribing

Indication for the initiation of treatment with cilostazol and off-label use will be assessed according to the type of data available in each database. In most databases, the indication for which the treatment is given is not recorded as a separate field and must

be assessed by diagnosis codes recorded around the date of the first cilostazol prescription and by manual review of the computerised clinical information including free-text comments from the prescriber, when these are available (e.g., THIN).

Because of these limitations, the indication associated with cilostazol treatment and off-label prescribing of cilostazol at the start date will be assessed in a random sample of about 200 patients in databases with available primary care diagnosis. The computerised information from these patients, including free-text comments (THIN), will be manually reviewed to assess the indication and off-label prescribing of cilostazol. The random sample will be identified using simple random sampling stratified by age (< 70 years and ≥ 70 years) and strength of first prescription (50 mg and 100 mg).

For databases that do not have free-text comments or those with only hospital discharge diagnoses, indications for cilostazol will be evaluated by hospital discharge diagnoses.

The definition of off-label use of cilostazol will be based on diagnoses for a disease or medical condition other than the labelled indications in the SmPC. In the absence of labelled indications, potential off-label use may include, among others, prevention of secondary stroke and prevention of ischaemic heart disease.

9.3.8 Assessment of Hospitalisations During Treatment With Cilostazol

Users of cilostazol will be followed to assess the proportion of users who are hospitalised for any cause during consecutive use of cilostazol. For the THIN database, hospitalisations will be assessed through the hospital diagnoses recorded by GPs. It should be noted that the date of hospitalisation recorded by GPs may not reflect the exact date of hospital admission. This can lead to some misclassification.

9.3.9 Speciality of Prescribers

The type of prescriber initiating treatment with cilostazol will be ascertained in the databases that have this information available: IACS, SIDIAP, GePaRD, Sweden. THIN captures prescriptions only from general practitioners. Type of prescriber will include the following specialities: general practitioner, cardiologist, vascular surgeon, endocrinologist, and other specialities.

9.4 Data Sources

To investigate the use of cilostazol, the DUS requires an efficient means to identify large numbers of users of this drug. At present, the largest and most readily accessible drug utilisation data come from automated databases that record prescriptions, diagnoses, and procedures on an individual-patient basis. Such databases accumulate records longitudinally so that patient experience can be observed before and after prescription of a drug of interest.

Based on usage and reimbursement of cilostazol in European countries with population-based databases, we plan to conduct the DUS in five population-based automated health databases from four European countries:

- The Aragón Health Sciences Institute (Instituto Aragonés de Ciencias de la Salud [IACS]) database in Aragón, Spain

- The Information System for the Advancement of Research in Primary Care (Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària [SIDIAP]) database in Catalonia, Spain
- The German Pharmacoepidemiological Research Database (GePaRD), Germany
- The Health Improvement Network (THIN), United Kingdom
- The Swedish National Databases

9.4.1 Status of Contacts With the Study Databases

Contacts with the database researchers to explore interest in and availability for conducting this study are ongoing. The status in each database is listed in Table 8.

Table 8. Status in Each Database

Database	Shared Study Protocol Synopsis	Interest in Participating
IACS, Spain	Yes	Confirmed
SIDIAP, Spain	Yes	Confirmed
THIN, UK	Yes	Agreed to provide the data[a]
GePaRD, Germany	Yes	Confirmed
National Databases, Sweden	Yes	Confirmed

[a] After scientific committee approval and registration of the study in ENCePP. The THIN Scientific Review Committee approved the study in February, 2013.

9.4.2 Description of Databases

The characteristics of the study databases in Spain, Germany, the UK, and Sweden are summarised in this section and also in Table 9 at the end of this section.

Spain

Aragón: A group of researchers in Public Health and Health Services Research of the Aragón Health Sciences Institute (Instituto Aragonés de Ciencias de la Salud [IACS]) has linked the electronic medical and administrative databases in the region. These databases contain administrative and clinical information from outpatient clinics (primary care health centres), specialty clinics, emergency departments, hospitals, and pharmacies. From 2010 onwards, data are available for 1.2 million patients covered by all outpatient practices in Aragón. The following types of data are available: administrative and clinical information from outpatient clinics (primary care health centres), administrative and clinical information from specialty clinics, emergency department diagnoses and care, hospital procedures and discharge diagnoses, and pharmacy prescription data.

Studies are conducted in collaboration with the Institute of Public Health and Health Services Research; ethics committee approval is needed for the study. The principal investigator in IACS will be Dr. Francisca González Rubio.

Catalonia: The Information System for the Advancement of Research in Primary Care (SIDIAP) currently collects information from 274 primary health care centres, including more than 5.8 million patients, about 80% of the Catalan population covered by the Catalan Institute of Health (Bolíbar et al., 2012). Primary care physicians with an up-to-standard quality of care provide information on approximately 1.9 million patients (García-Gil et al., 2011). Information from different data sources can be accessed through linkage by an individual's national security number, including demographic information from the Catalan Health Services database, electronic primary care clinical and laboratory test records, drugs dispensed in community pharmacies, hospital discharge codes from an external database on hospital admissions (CMBD-AH), date and cause of death from the National Office of Statistics, and other available disease or procedural registries. The current primary care database includes data from the year 2000 through April 2012; however, the start of data availability of elements from other linkable data sources varies from 2003 for mortality data to 2006 for laboratory data. Availability of pharmacy dispensed drug information is available since 2005.

Studies are conducted in collaboration with the Institute of Research in Primary Health Care; ethics committee approval is needed for the study.

Germany

The German Pharmacoepidemiological Research Database (GePaRD) is a population-based database obtained from statutory health insurance agencies (SHIs) in Germany (Jobski et al., 2012; Kraut et al, 2010; Pigeot and Ahrens, 2008). Ninety percent of the population in Germany is insured with the SHIs. The database covers over 15 million SHI members from all regions of Germany, approximately 17% of the German population (population data from Eurostat, 2012). Membership in SHIs is fairly stable over time. The GePaRD includes the following types of data from all patients enrolled in one of the SHIs: demographics, hospital diagnoses, ambulatory care diagnoses and procedures (coded in the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification [ICD-10-GM]), and ambulatory prescriptions including date of prescription and date of pharmacy dispensing. Although information on dose is not available, the number of boxes prescribed is recorded for each medication.

The German version of the ICD-10-CM is used for coding diagnoses, and OPS (Operationen- und Prozedurenschlüssel) codes are used for surgical and diagnostic procedures. Types of treatments and diagnostic procedures with exact date are registered according to EBM (Einheitlicher Bewertungsmaßstab) codes, developed for payment of physicians for the outpatient treatment of German SHI patients.

Studies are conducted in collaboration with the Bremen Institute for Prevention Research and Social Medicine (BIPS), University of Bremen, Germany; SHI and health ministry approval is needed for the study.

A total of four SHIs contribute data to the GePaRD. Two of these SHIs, involving approximately 4,000 users of cilostazol, approved participation in the study. Data from a third SHI, which also approved participation and included 44 users of cilostazol, are considered inadequate as follow-up is truncated at the end of 2007. These data will not be included in the study. The fourth SHI denied participation in the study. This SHI denied approval because the study protocol did not include an evaluation of current treatment recommendations from the Federal Joint Committee (G-BA) concerning

cilostazol. Submission of a revised protocol that included additional analyses to evaluate these recommendations was unsuccessful.

United Kingdom

In the UK, nearly all residents are registered in a general medical practice that uses electronic medical records. Based on those records, there are two main databases available for research purposes: the Clinical Practice Research Datalink (CPRD), formerly the General Practice Research Database (GPRD), and the The Health Improvement Network (THIN). Both databases have similar information recorded by general practitioners (GPs). Furthermore, there is an overlap of GP practices and patients between CPRD and THIN of approximately 30%. The CPRD database is available through the UK Medicines and Health Care Products Regulatory Agency (MHRA). The THIN database is available through Cegedim Strategic Data.

Established in 2002, THIN now collects data from more than 400 practices, covering 5% of the general population, with more than 57 million patient-years of experience (Cegedim Strategic Data Medical Research UK, 2012). Ten million individual patients are represented in the data; of those, approximately one-third are active at any one time. THIN records information on all services provided by the general practitioner.

All practices record information received on hospital admissions, discharge diagnoses, and medications; outpatient specialist visits; and outcomes of treatment. For some of the practices, THIN offers additional hospital episode data linked to the general practice patients. When a drug is prescribed, a computer record is immediately created and added to the database. The THIN database has been validated as accurately recording a patient's health care (Denburg et al., 2011), and pharmacoepidemiologic studies using THIN data have been published in scientific journals (e.g., Choi et al., 2012; Hayes et al., 2011).

THIN supplies de-identified data for approved drug safety and epidemiological studies. Such research needs to be approved by the South East Multicentre Research Ethics Committee (http://www.thin-uk.com/contributing_data.htm).

Sweden

In Sweden, the national health care system provides universal coverage to all residents (9.4 million inhabitants[1]). Health care coverage includes visits to general practitioners (GPs), specialists, hospital admissions, and hospital outpatient visits; drug costs are either partially or completely covered. A centralised civil registration system has been in place for many years, allowing for personal identification of each person in the entire population and for the possibility of linkage to all national registers containing civil registration numbers, e.g., patient register, cancer register, prescription databases, register of causes of death, and population registers (Furu et al., 2010). The National Inpatient Register covers all publicly run in-patient care in Sweden from 1987 and includes information on diagnoses, surgical procedures, and in-hospital deaths. Since 2001, the government has empowered the National Board to collect information on out-patient hospital care as well. The register includes about 1.5 million discharges annually. Since 1997, diagnoses have been coded using ICD-10 codes. Whereas coverage of the

[1] Population data from Eurostat. 2011. Available at: http://epp.eurostat.ec.europa.eu/portal/page/portal/population/data/database. Accessed 22 August 2012.

inpatient register is currently almost 100%, coverage of hospital-based outpatient care is considerably lower (about 80%) (Ludvigsson et al., 2011). Visits to GPs and specialists outside the hospitals are not included in the registers. Data collected in these registers can be made available for research purposes under the principles for protection and release of sensitive data (Ludvigsson et al., 2011; Ministry of Justice, 2009; 2012).

The Swedish National Prescription Database provides patient-level data on all dispensed and prescribed drugs (reimbursed and nonreimbursed) in ambulatory care to the whole population of Sweden since July 2005. The following data on drugs are available: drug substance, brand name, formulation and package, dispensed amount, dosage, expenditure and reimbursement, date of prescribing and dispensing, place of residence of the patient, practice issuing the prescription, and prescriber's specialty (Wettermark et al., 2007).

Data requests for research purposes require collaboration with university or affiliated researchers and ethics committee approval.

Table 9. Main Features of Selected European Databases

	Database and Size of Population Size of the Country				
Feature	**IACS, Aragón, Spain (N = 1,346,293)[a]**	**SIDIAP, Catalonia, Spain (N = 7,565,603)[b]**	**German Pharmacoepidemiological Research Database (GePaRD) (N = 81,751,602)[c]**	**THIN, United Kingdom (N = 62,435.709)[c]**	**Swedish Prescription and Inpatient National Databases (N = 9,415,570)[c]**
Database type	Primary health care electronic medical record database; link to hospital discharge and pharmacy data	Primary health care electronic medical record database; link to hospital discharge, pharmacy, and mortality data	Claims databases, 4 Statutory Health Insurance (SHI) plans[d]	Primary health care electronic medical record database	National health record databases capable of linkage though the unique civil personal registration number
Database population	1.3 million	5.8 million (1.9 million in up-to-standard practices)	14 million (fewer patients might be included in research projects)	3.4million	9.4 million
Proportion of the country's population covered by the database	2.8%	12.2% (4.0%; refers to the 1.9 million in up-to-standard practices)	17%	5%	100%
Representativeness of patients	Total population covered	Pending	Representative of sex and age of German population	Representative of sex and age of UK population	Total population covered
Data on medica-tions	Reimbursed pharmacy-dispensed prescriptions	All drugs prescribed in primary health centres; all reimbursed drugs dispensed by community pharmacies	Reimbursed pharmacy-dispensed prescriptions	All prescriptions by GPs	All pharmacy-dispensed prescriptions
Dose	Formulation strength	Prescribed dose	Formulation strength	Prescribed dose	Formulation strength

	Database and Size of Population Size of the Country				
Feature	**IACS, Aragón, Spain (N = 1,346,293)[a]**	**SIDIAP, Catalonia, Spain (N = 7,565,603)[b]**	**German Pharmacoepidemiological Research Database (GePaRD) (N = 81,751,602)[c]**	**THIN, United Kingdom (N = 62,435.709)[c]**	**Swedish Prescription and Inpatient National Databases (N = 9,415,570)[c]**
Duration	Based on prescriptions	Based on prescriptions	Based on prescriptions	As indicated in the prescription	Based on prescriptions
Drug dictionary codes/ therapeutic classification	ATC	ATC	ATC	Multilex/British National Formulary	ATC
Clinical indication	Not specifically recorded but based on proxies	Not specifically recorded but based on proxies	Not specifically recorded but based on proxies	Associated with new courses of medications, but completeness is variable Computerised free-text information is available for review	Not specifically recorded but based on proxies
Primary care diagnosis	Yes	Yes	Yes Since January 2004	Yes	No. Diagnoses from outpatient hospital clinics are available
Hospital diagnosis	Yes	Yes (CMBD-AH)	Yes	Recorded by GPs	Yes
Recorded by primary care physicians	No	No	No	Yes	No
Available from hospital database or hospital claims	Yes CMBD-AH	Yes CMBD-AH	Yes	Partial linkage to HES	Yes

	Database and Size of Population Size of the Country				
Feature	**IACS, Aragón, Spain (N = 1,346,293)[a]**	**SIDIAP, Catalonia, Spain (N = 7,565,603)[b]**	**German Pharmacoepidemiological Research Database (GePaRD) (N = 81,751,602)[c]**	**THIN, United Kingdom (N = 62,435.709)[c]**	**Swedish Prescription and Inpatient National Databases (N = 9,415,570)[c]**
Disease and procedure codes	Primary health care: ICPC Hospital: ICD-9	ICD-10-CM	ICD-10-GM	Read codes	ICD-10-CM
Lifestyle risk factors	No	Yes	No	Yes	No
Data availability	Partial since 2005; Complete since 2010	Since 2006	Since 2004	Since 1980	Since July 2005
Approximate time lag (updates)	1 year	1 year	1.5 years	6 months	2012 data will be available in 3-4Q 2013
Approval process for database research	Data application and ethics committee approval required	Data application and ethics committee approval required	Approvals by SHI and Health Ministry are required	Ethics or scientific approval is required	Data application and ethics committee approval required

ATC = Anatomical Therapeutic Chemical; CMBD-AH = Catalan Health Services database of hospital admissions; GP = general practitioner; HES = Hospital Episode Statistics; IACS = Aragón Health Sciences Institute ; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th Revision; ICD-10-CM = International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification; ICD-10-GM = International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification; ICPC = International Classification of Primary Care (codes); SHI = Statuary Health Insurance (Germany); SIDIAP = Information System for the Advancement of Research in Primary Care; THIN= The Health Improvement Network Database; UK = United Kingdom.

[a] Gobierno de Aragón [Government of Aragón]. Available at: http://www.aragon.es/DepartamentosOrganismosPublicos/Organismos/InstitutoAragonesEstadistica/AreasTematicas/Demografia/CifrasPoblacion/ci.02_Cifras_oficiales_poblacion.detalleDepartamento?channelSelected=448c2135fc5fa210VgnVCM100000450a15acRCRD. Accessed 19 November 2012.

[b] Generalitat de Catalunya. Available at: http://www.gencat.cat/catalunya/eng/coneixer-poblacio.htm. Accessed 19 November 2012.

[c] Population data from Eurostat. 2011. Available at: http://epp.eurostat.ec.europa.eu/portal/page/portal/population/data/database. Accessed 22 August 2012.

[d] Two SHIs agreed to contribute data to the study, providing approximately 4,000 users of cilostazol. One SHI denied approval for participation, and data from a second SHI involving 44 users of cilostazol are truncated to the end of 2007 and are considered inadequate.

9.5 Study Size

The study size is driven by the uptake of cilostazol in the populations from which the automated databases obtain data. For each database, we will identify all new users of cilostazol since the drug became available in the country.

We ascertained the preliminary number of users of cilostazol in SIDIAP, THIN, and Swedish databases (Table 10). For the GePaRD, we estimated the number of users of cilostazol in the database based on the sales data in Germany provided by Otsuka. For IACS in Spain, the number of users is yet to be ascertained. Overall, the estimated total number of users in the study databases is approximately between 11,000 and 17,000 (pending number of users from IACS and confirmation from the GePaRD and Sweden). This estimation does take into account the study exclusion criterion of 6 months of continuous enrolment in the database.

Table 10. Preliminary Number of Users of Cilostazol in the Study Databases

Database	Preliminary Number of Users	Comment
IACS, Spain	Pending	
SIDIAP, Spain	3,375	Identified in the database
GePaRD, Germany	4,867 to 9,735	Estimated from sales data in Germany
THIN, UK	1,640	Identified in the database
Sweden (users by year)		Identified in the Swedish National Pharmacy Register[a]
2008	441	
2009	934	
2010	1,170	
2011	1,067	
2008-2011	1,800 to 2,200	Estimated minimum and maximum number of unique users for the period 2008-2011

[a] National Board of Health and Welfare. Statistics database. Available at: http://www.socialstyrelsen.se/statistik/statistikdatabas and Drug statistics. Available at: http://192.137.163.49/sdb/lak/val.aspx. Accessed November 2012.

In Table 11 we present the level of precision in different scenarios of available number of users of cilostazol for different prevalence of diseases and conditions including off-label use. In general, the 95% level of confidence is adequate for prevalences as low as 1% and 1,500 users of cilostazol.

Table 11. Binomial Confidence Intervals for Different Study Sizes and Prevalence of Disease and Conditions Including Off-Label Use

Number of Patients	Lower and Upper Bounds of 95% Confidence Intervals for Various Prevalences of Diseases (%)									
	1%		2%		5%		7%		10%	
1,500	0.6	1.6	1.4	2.8	4.0	6.2	5.8	8.4	8.6	11.6
2,000	0.6	1.5	1.4	2.7	4.1	6.0	5.9	8.2	8.7	11.4
4,000	0.7	1.4	1.6	2.5	4.3	5.7	6.2	7.8	9.1	11.0
6,000	0.8	1.3	1.7	2.4	4.5	5.6	6.4	7.7	9.3	10.8
8,000	0.8	1.2	1.7	2.3	4.5	5.5	6.5	7.6	9.4	10.7

Note: Calculated with Episheet (Rothman, 2011).

9.6 Data Collection and Management

Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks of all programs. Each database custodian will maintain any patient-identifying information securely on site according to internal standard operating procedures.

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.

Appropriate data storage and archiving procedures will be followed (i.e., storage on CD-ROM or DVD), with periodic backup of files to tape. Standard procedures will be in place at each research centre to restore files in the event of a hardware or software failure.

9.7 Data Analysis

The use of cilostazol will be ascertained by the following analysis. Draft shells of the analysis tables are provided in separate Excel files (DUS1: Cilostazol shell analysis tables Final.xlsx; DUS2: Cilostazol shell analysis tables DUS2.xlsx).

9.7.1 Number of Users and Patterns of Use

Analysis Tables 1, 2, and 29: Use of cilostazol during the study period. Number of users; number of prescriptions; number of packages; total number of DDDs; mean number and standard deviation (SD) of packages and DDDs per prescription; and mean (SD) number of prescriptions, packages, and DDDs per user. Analyses will be stratified by year of start of cilostazol (DUS1 only) and formulation: 50 mg and 100 mg (Analysis Table 1), and by formulation and package size (Analysis Table 2). The number and percentage of users by the number of prescriptions received during follow-up will be calculated (Analysis Table 29). The number of users of cilostazol with less than 12 months of continuous enrolment in the database will also be ascertained (Analysis Table 1A).

Analysis Tables 3 and 30: Distribution of users at the start date. Number of users, number of prescriptions, number of packages, number of DDDs, mean (SD) number of packages per user, and mean (SD) number of DDDs per user will be ascertained at the start date for each combination of formulation and package size. The distribution of users by year of start date will be generated (DUS1 only) (Analysis Table 30).

Analysis Tables 4, 25, and 31: Age and sex distribution of users at the start date. The number and percentage of users at the start date will be described by sex and the following groups of age (in years): (1) < 18, 18-29, 30-39, 40-49, 50-59, 60-69, 70-79, ≥ 80 and (2) < 70 and ≥ 70 (Analysis Table 4). Age- and sex-specific prevalence of users of cilostazol during the study period will be calculated (Analysis Table 25). For DUS2, prevalence of use will be calculated as the proportion of patients from the source population who received at least one prescription for cilostazol during 2014 (includes new users and prevalent users). In addition, the mean (SD) of age by sex among cilostazol users at first use will be calculated (Analysis Table 31).

Analysis Table 5: Daily dose at the start date. Daily dose prescribed at the start date will be calculated using the recorded information on strength and quantity prescribed and the days of supply of the first prescription for cilostazol. The daily dose prescribed at the start date will be described by sex and age group (< 70 years, ≥ 70 years).

Analysis Table 6: Person-years of use. Person-years of use will be accumulated for each user of cilostazol and across all users. Person-years of use will be described by sex and age (< 70 years, ≥ 70 years). The mean (SD), median, 25th percentile, and 75th percentile (P75) of person-years will be calculated by sex and age group (< 70 years, ≥ 70 years).

Analysis Table 7: Duration of continuous use. Duration of use refers to the duration of continuous treatment with cilostazol. Duration will be ascertained by the total number of days of supply of consecutive prescriptions, defined as those prescribed with a maximum interval of 60 days between dates of consecutive prescriptions. Sensitivity analyses will be conducted for a maximum interval of 90 days between dates of consecutive prescriptions. Person-years of consecutive use will be accumulated for each user of cilostazol and across all users. Person-years of consecutive use will be described by sex and age group (< 70 years, ≥ 70 years). The mean (SD), median, 25th percentile, and 75th percentile of person-years of consecutive use will be calculated by sex and age group (< 70 years, ≥ 70 years).

9.7.2 Characterisation of Users at the Start Date

Analysis Tables 8 and 24: Comorbidity at the start date. Users of cilostazol will be characterised according to the presence of comorbidity at any time before the start date. Comorbidity will be assessed for each disease/condition detailed in Table 4 (Section 9.3.3). The number and percentage of users with comorbidity at the start date will be calculated by sex and age group (< 70 years, ≥ 70 years). The distribution of users by socioeconomic indicators will be calculated (Analysis Table 24).

Analysis Table 9: Comedications at the start date. Users of cilostazol will be characterised according to the use of other medications within 6 months before the start date. Comedications to be assessed are those listed in Table 5 (Section 9.3.3). The number and percentage of users treated with other medications at the start date will be calculated by sex and age group (< 70 years, ≥ 70 years).

9.7.3 Use of Medications Potentially Interacting With Cilostazol

Analysis Tables 10, 11, 12, 13, and 27: Use of medications potentially interacting with cilostazol will be assessed at the start date (Analysis Table 10), during current use of cilostazol (Analysis Table 11), during consecutive use of cilostazol (Analysis Table 12), and at any of these times (Analysis Table 13). The list of relevant medications potentially interacting with cilostazol is presented in Table 6 (Section 9.3.4) and protocol Annex 3. The number and percentage of concurrent users of each potentially interacting medication will be calculated by sex and age group (< 70 years, ≥ 70 years). Concurrent use of cilostazol and potent inhibitors of CYP3A4 and CYP2C19 will also be evaluated. Potent inhibitors are lansoprazole, fluvoxamine, nefazodone, ticlopidine, clarithromycin, troleandomycin, indinavir, ritonavir, nelfinavir, mibefradil, ketoconazole, and itraconazole. The distribution of users by the number of interacting medications received concurrently with cilostazol will be calculated (Analysis Table 27).

9.7.4 Concurrent Use of Antithrombotic Agents

Analysis Tables 14 and 15: Concurrent use of cilostazol and antithrombotic agents including platelet aggregation inhibitors will be assessed at the start date (Analysis Table 14) and during continuous use of cilostazol (Analysis Table 15). The number and percentage of concurrent users of antithrombotic agents will be calculated by sex and age group (< 70 years, ≥ 70 years).

Analysis Table 16: Users of cilostazol treated with platelet aggregation inhibitors. The number and percentage of users of cilostazol concurrently treated with platelet aggregation inhibitors at the start date who discontinue treatment with platelet aggregation inhibitors during continuous use of cilostazol will be calculated by sex and age group (< 70 years, ≥ 70 years).

9.7.5 Assessment of Changes to the Summary of Product Characteristics

Analysis Tables 17, 18, and 26: The number and percentage of users by sex and age group (< 70 years, ≥ 70 years) will be calculated for the following conditions:

- Smoking: current, past, non-smoker (Analysis Table 17A)
- Number and percentage of users with at least one visit for any reason with a general practitioner or specialist between (a) 2 months and 4 months after the start date and (b) 1 month and 6 months after the start date, evaluated by the clinical review of a sample of patient profiles (Analysis Table 17B) and by diagnosis codes in all users (Analysis Table 17C). Analysis is restricted to patients who are current users of cilostazol at 3 months after the start date.
- Number and percentage of users with at least one visit for intermittent claudication with a general practitioner or specialist between (a) 2 months and 4 months after the start date and (b) 1 month and 6 months after the start date, evaluated by the clinical review of a sample of patient profiles (Analysis Table 17B) and by diagnosis codes in all users (Analysis Table 17C). Analysis is restricted to patients who are current users of cilostazol at 3 months after the start date.
- Discontinuation of cilostazol between 3 months and 4 months after the start date, evaluated using Kaplan-Meier survival curves (Analysis Table 17A and 26)

- Diagnosis within 6 months before the start date: unstable angina, myocardial infarction, or coronary intervention (Analysis Table 17A)
- Concurrent use of cilostazol and two or more platelet aggregation inhibitors (Analysis Table 17A)
- Reduction of daily dose of cilostazol from 200 mg to 100 mg among concurrent users of cilostazol and (a) potentially interacting medications (Analysis Table 18A) or (b) potent inhibitors of CYP3A4 or CYP2C19 (Analysis Table 18B) during continuous use of cilostazol

Analysis Table 19: Rates of visits to general practitioners and/or specialists among users at increased risk of serious cardiac events (patients with history of arrhythmias, coronary heart disease, or hypotension). Rates of visits per 100 person-years and 95% confidence intervals (CI) will be calculated for these patients and for those who are not considered at increased risk of serious cardiac events. Rate ratios and 95% CIs will be estimated comparing the rates in patients with increased risk with rates in patients without increased risk.

9.7.6 Assessment of Contraindications

Analysis Table 20: Contraindications for cilostazol currently listed in the SmPC will be assessed at the start date according to the following time frames:

- Diagnosis recorded at any time before the start date: renal failure, liver disease, congestive heart failure, diabetic retinopathy, arrhythmias
- Diagnosis recorded within 6 months before the start date: active peptic ulcer, recent cerebral haemorrhage

The number and percentage of patients with contraindications will be calculated by sex and age group (< 70 years, ≥ 70 years).

9.7.7 Overall Assessment of Contraindications

Analysis Table 28. Number and percentage of users with new 2013 SmPC contraindications and contraindications labelled before 2013.

9.7.8 Indications and Off-Label Use

Analysis Table 21: The number and percentage of users by sex and age group (< 70 years, ≥ 70 years) will be calculated for each indication associated with the initiation of treatment according to the on-label and off-label use of cilostazol. The overall number, percentage, and 95% CI of patients prescribed according to the on-label and off-label use of cilostazol will be calculated by sex and age group (< 70 years, ≥ 70 years).

9.7.9 Assessment of hospitalisations during treatment with cilostazol

Analysis Table 22: Percentage of users of cilostazol with at least one hospitalisation for any cause during consecutive use of cilostazol.

9.7.10 Speciality of Prescribers at the Start Date

Analysis Table 23: New users of cilostazol will be described according to the type of prescriber of the first prescription for cilostazol. The number and percentage of users by sex and age group (< 70 years, ≥ 70 years) will be calculated according to each prescriber speciality: general practitioner, cardiologist, vascular specialist, endocrinologist, other.

9.8 Quality Control

Standard operating procedures at each research centre will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

All programming written by one study analyst will be reviewed independently by a different analyst, with oversight by a senior statistician. All key study documents, such as the analysis plan, abstraction forms, and study reports, will undergo quality-control review, senior scientific review, and editorial review.

For work conducted at RTI Health Solutions, an independent Office of Quality Assurance will perform audits and assessments that involve various aspects of the project, including but not limited to education and training documentation, data entry and data transfer procedures and documentation, and institutional review board (IRB) documentation. Such audits will be conducted by the Office of Quality Assurance according to established criteria in standard operating procedures and other applicable procedures.

9.9 Limitations of the Research Methods

Drug utilisation studies conducted in automated health databases allow identification of patients who are prescribed or dispensed the drugs of interest and characterisation of these patients according to prior medical history, use of medications, and patterns of use of medications. Health care databases have become a useful tool for conducting research to study the safety of drugs as information on diagnoses and treatments is recorded on an ongoing basis (Schneeweiss and Avorn, 2005).

However, the use of automated health databases for research has some limitations, mainly related to the type and completeness of the recorded information. Regarding prescription data, databases provide detailed information on prescribed and/or dispensed medications but not on the actual use of the medications by patients. Thus, patients may be classified as exposed when they are not actually taking the drug. Databases often do not record the intended duration of use of each prescription (days of supply), and this needs to be estimated from the interval between consecutive prescriptions. Overall, this can result in misclassification of drug exposure. Sensitivity analysis assuming different lengths of duration of use can help to address exposure misclassification. In this DUS, we plan to assess the duration of each prescription of cilostazol through the interval between consecutive prescriptions and the total duration of use by assuming two interval scenarios of 60 days and 90 days between prescriptions. Another limitation on the assessment of medication use in databases is that over-the-counter medications are usually not recorded. Therefore, we are not able to ascertain the concomitant use of

cilostazol and non-prescribed aspirin. The use of external data (e.g., health surveys), when available, might help to quantify the use of over-the-counter medications.

Regarding the recording of clinical information, databases based on electronic medical records (e.g., THIN) usually provide data on findings of physical examinations and results of diagnostic tests. Health habits (e.g., smoking, use of alcohol) are usually recorded, at least partially, in these databases. In other databases, clinical information is restricted to clinical diagnoses such as hospital discharge diagnoses, and health habits are not recorded. For the conduct of this DUS, smoking can be partially assessed in THIN and GePaRD. Regarding the indication of treatment and off-label use, this can be evaluated in the THIN database by manual review of computerised information and free-text comments. General practitioners in the UK usually record the indication for new treatments although the recording may be incomplete. In the other study databases, the assessment of treatment indication and off-label use will be approximated by looking at diagnosis codes and use of medications before and at the start date.

10 Protection of Human Subjects

This is a retrospective, noninterventional study and does not pose any risks for patients. All data collected in the study will be de-identified with no breach of confidentiality with regards to personal identifiers or health information. Each database research partner will apply for an independent ethics committee review and/or other approvals according to local regulations; in addition, RTI Health Solutions as the coordinating centre will obtain approval from the RTI International institutional review board.

Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

RTI International

RTI International holds a Federal-Wide Assurance from the Department of Health and Human Services, Office for Human Research Protections, that allows the organisation to review and approve human subjects protocols through its IRB committees. RTI International currently has three IRB committees available to review research protocols. One IRB committee is constituted to review medical research and has two members who are MDs. These IRBs have been audited by the United States Food and Drug Administration and are fully compliant with applicable regulatory requirements. RTI Health Solutions will obtain approval for the study from the RTI International IRB.

IACS, Aragón, Spain

The final study protocol will be submitted to the local ethics committee.

SIDIAP, Catalonia, Spain

The final study protocol will be submitted to the local ethics committee.

GePaRD, Germany

For the GePaRD, approval is needed from the four SHI agencies providing data to the GePaRD. A summary of the protocol will be provided to the SHI agencies, outlining the public health importance of the research question. After obtaining approval from the SHI agencies, approval of the project has to be obtained from the Federal Ministry of Health. Approval from an IRB is not required in Germany because this study is based on pseudonymous data.

At the time of the protocol amendment (30 January 2015), one SHI has denied approval to participate in the study, and data from another SHI involving 44 users of cilostazol are truncated to the end of 2007 and will not be included in the study.

THIN, UK

In the UK, all research involving data collected from National Health Service patients must be approved by a research ethics committee. The research ethics committee is convened to provide independent advice to participants, researchers, funding bodies, sponsors, employers, care organisations, and professionals on the extent to which proposals for research studies and clinical audit projects comply with recognised ethical standards.

The Multicentre Research Ethics Committee (MREC) reviews studies and clinical audit (data collection) projects that involve patients from several local areas. Several MRECs are located throughout the country; however, the THIN Data Collection Scheme was approved by the South-East Multicentre Research Ethics Committee (SE-MREC).

The final study protocol will be submitted to the MREC. THIN requires that any study using THIN data that will be published or for which results will be communicated to third parties must receive MREC approval before proceeding (http://www.thin-uk.com/mrec.htm).

Sweden

The Swedish National Inpatient Register (IPR) is regulated by the Health Care Data Register Act (1998:543; Lag om hälsodataregister) and the IPR ordinance (2001:707; Förordning om patientregister hos Socialstyrelsen). It is mandatory for all physicians, private and publicly funded, to deliver data to the IPR. Data from the IPR are subjugated to the Health and Medical Services Act (1982:763; Hälso och sjukvårdslag) and the Patient Data Act (2008:355; Patientdatalag). Of special importance to the regulation of Swedish medical research and health care is also the Public Access to Information and Secrecy Act (2009:400, Offentlighets-och sekretesslagen).

The final study protocol will be submitted to the ethics committee and the Statistical Authority (Centre for Epidemiology, National Board of Health and Welfare).

10.1 Other Good Research Practice

The study will be conducted in accordance with Guidelines for Good Pharmacoepidemiology Practices (GPP) developed by the International Society for Pharmacoepidemiology (ISPE) (2007).

The study will be conducted in accordance to the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (ENCePP, 2012a). The ENCePP Checklist for Study Protocols has been completed (ENCePP, 2011); see Annex 2.

The study is a postauthorisation safety study (PASS) and will comply with the definition of the noninterventional (observational) study provided in the 2012 Guideline on Good Pharmacovigilance Practice (GVP): Module VIII – Post-Authorisation Safety Studies (EMA, 2012a).

The study will be registered in the ENCePP electronic register of studies (ENCePP, 2010).

11 Management and Reporting of Adverse Events/Adverse Reactions

Based on current guidelines from ISPE (2007, Section VI) and the EMA (2012b, Section VI:C.1.2.1), noninterventional studies such as the one described in this protocol, conducted using medical chart reviews or electronic claims and health care records, do not require expedited reporting of suspected adverse events/reactions. Based on the data used for this study, no suspected adverse events/reactions are expected.

12 Plans for Disseminating and Communicating Study Results

The study protocol, study progress reports, and final study report will be included in regulatory communications in line with the risk management plan, Periodic Safety Update Reports (PSURs), and other regulatory milestones and requirements. Study reports will be prepared using a template following GVP Module VIII, Section B.6.3 (European Medicines Agency, 2012a).

In its Guidelines for Good Pharmacoepidemiology Practices (GPP), ISPE (2007, Section V) contends that "there is an ethical obligation to disseminate findings of potential scientific or public health importance"; for example, results pertaining to the safety of a marketed medication. Publication of study results will be considered. Publications will follow guidelines, including those for authorship, established by the International Committee of Medical Journal Editors (2013). When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be followed (STROBE, 2007).

Communication via appropriate scientific venues, e.g., International Society for Pharmacoepidemiology, will be considered.

The marketing authorisation holder and the principal investigators (e.g., the principal investigators at the study coordinating centre and database research centres) will agree

upon a publication policy allowing the principal investigators to independently prepare publications based on the study results, irrespective of data ownership. The marketing authorisation holder will be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication (European Medicines Agency, 2012a, Section VIII.B.7).

13 References

Bolíbar B, Fina Avilés F, Morros R, Garcia-Gil MDELM, Hermosilla E, Ramos R, et al.; Grupo SIDIAP. SIDIAP database: electronic clinical records in primary care as a source of information for epidemiologic research [Article in Spanish]. Med Clin (Barc). 2012 May 19;138(14):617-21.

Cegedim Strategic Data Medical Research UK. About us. 2012. Available at: http://csdmruk.cegedim.com/our-data/our-data.shtml. Accessed 28 August 2012.

Choi HK, Soriano LC, Zhang Y, Rodríguez LA. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. BMJ. 2012 Jan 12;344:d8190.

Denburg MR, Haynes K, Shults J, Lewis JD, Leonard MB. Validation of The Health Improvement Network (THIN) database for epidemiologic studies of chronic kidney disease. Pharmacoepidemiol Drug Saf. 2011 Nov;20(11):1138-49.

European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies. 9 July 2012a. Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf. Accessed 3 October 2012.

European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VI – Management and reporting of adverse reactions to medicinal products. 22 June 2012b. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129135.pdf. Accessed 3 October 2012.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). ENCePP checklist for study protocols (revision 1). 19 August 2011. Available at: http://www.encepp.eu/standards_and_guidances/index.html. Accessed 3 October 2012.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). ENCePP study seal. Last updated: 15 May 2012b. Available at: http://www.encepp.eu/encepp_studies/index.html. Accessed 3 October 2012.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on methodological standards in pharmacoepidemiology. 11 July 2012a. Available at: http://www.encepp.eu/standards_and_guidances/index.html. Accessed 3 October 2012.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Electronic register of studies. Version 3.0.49. 2010. Available at: http://www.encepp.eu/encepp/studiesDatabase.jsp. Accessed 3 October 2012.

Eurostat. Population data for Germany. 2012. Available at: http://epp.eurostat.ec.europa.eu/tgm/table.do?tab=table&language=en&pcode=tps00001&tableSelection=1&footnotes=yes&labeling=labels&plugin=1. Accessed 11 May 2012.

Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sorensen HT. The Nordic countries as a cohort for pharmacoepidemiological research. Basic Clin Pharmacol Toxicol. 2010 Feb;106(2):86-94.

García-Gil MDELM, Hermosilla E, Prieto-Alhambra D, Fina F, Rosell M, Ramos R, et al. Construction and validation of a scoring system for the selection of high-quality data in a Spanish population primary care database (SIDIAP). Inform Prim Care. 2011;19(3):135-45.

González-Ruíz A, Cuaresma-Lasheras ME, Blanco-Ramos IV, Rodríguez-Dichico GP, Montero-Corominas D. Cilostazol: from spontaneous reports of cardiovascular and haemorrhagic reactions to a thorough benefit-risk evaluation in Europe. A signal generation (abstract). Basic Clin Pharmacol Toxicol. 2011 Oct;109(Suppl. 3):36.

Hayes J, Prah P, Nazareth I, King M, Walters K, Petersen I, et al. Prescribing trends in bipolar disorder: cohort study in the United Kingdom THIN primary care database 1995-2009. PLoS One. 2011;6(12):e28725.

International Committee of Medical Journal Editors (ICMJE). Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. International Committee of Medical Journal Editors; August 2013. Available at: http://www.icmje.org/urm_main.html. Accessed 25 February 2014..

International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP). Revision 2. April 2007. Available at: http://www.pharmacoepi.org/resources/guidelines_08027.cfm. Accessed 3 October 2012.

Jobski K, Schmid U, Behr S, Andersohn F, Garbe E. 3-year prevalence of alcohol-related disorders in German patients treated with high-potency opioids. Pharmacoepidemiology Drug Saf. 2012 Apr 19. doi: 10.1002/pds.3268.

Kraut AA, Schink T, Schulze-Rath R, Mikolajczyk RT, Garbe E. Incidence of anogenital warts in Germany: a population-based cohort study. BMC Infect Dis 2010 Dec 23;10:360.

Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011 Jun 9;11:450. Available at: http://www.biomedcentral.com/1471-2458/11/450. Accessed 30 August 2012.

Ministry of Justice. Government offices of Sweden. Data protection. Last updated 20 March 2012. Available at: http://www.sweden.gov.se/sb/d/2771. Accessed 30 August 2012.

Ministry of Justice. Government offices of Sweden. Public access to information and secrecy act (2009:400, Offentlighets- och sekretesslagen). 2009. Available at: http://www.sweden.gov.se/content/1/c6/13/13/97/aa5c1d4c.pdf. Accessed 30 August 2012.

Otsuka Pharmaceutical Europe Ltd. Pletal® (cilostazol) EU risk management plan. Version 4. July 2012.

Pigeot I, Ahrens W. Establishment of a pharmacoepidemiological database in Germany: methodological potential, scientific value and practical limitations. Pharmacoepidemiol Drug Saf. 2008 Mar;17(3):215-23.

Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol. 2005;58(4):323-37.

Rothman KJ. Episheet—spreadsheets for the analysis of epidemiologic data. October 25, 2011, version. Available at: http://www.epidemiolog.net/studymat/. Accessed 14 December 2012.

STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement. STROBE checklist. 2007. Available at: http://www.strobe-statement.org/index.php?id=available-checklists. Accessed 3 October 2012.

Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register—opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf. 2007;16(7):726-35.

Annex 1.
List of Stand-Alone Documents

None.

Annex 2.
ENCePP Checklist for Study Protocols

London, 25 July 2011
Doc.Ref. EMEA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 1)

Adopted by the ENCePP Steering Group on 19/08/2011

The purpose of the Checklist developed by ENCePP is to stimulate consideration of important epidemiological principles when designing a pharmacoepidemiological or pharmacovigilance study and writing a study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. ENCePP welcomes innovative designs and new methods of research. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each of the questions of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

Section 1: Research question	Yes	No	N/A	Page Number(s)
1.1 Does the formulation of the research question clearly explain:				
1.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	x			8,19
1.1.2 The objectives of the study?	x			8,19-20

Section 1: Research question	Yes	No	N/A	Page Number(s)
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	x			8, 20-21
1.2.2 Which formal hypothesis(-es) is (are) to be tested?			x	
1.2.3 if applicable, that there is no *a priori* hypothesis?			x	

Comments:

Drug utilisation study with the objective of characterising users of cilostazol

Section 2: Source and study populations	Yes	No	N/A	Page Number(s)
2.1 Is the source population described?	x			8, 21
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	x			21-22
2.2.2 Age and sex?	x			8, 19-20
2.2.3 Country of origin?	x			20-21
2.2.4 Disease/indication?	x			19-20
2.2.5 Co-morbidity?	x			8-12, 19-20
2.2.6 Seasonality?			x	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	x			22-23

Comments:

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?			x	
3.2 Is the study design described? (e.g., cohort, case-control, randomised controlled trial, new or alternative design)	x			8, 20-21
3.3 Does the protocol describe the measure(s) of effect? (e.g., relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)			x	
3.4 Is sample size considered?	x			8-12,44-45
3.5 Is statistical power calculated?	x			44-45

Comments:

Drug utilisation: no medication effect will be evaluated.

Section 4: Data sources	Yes	No	N/A	Page Number(s)
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	x			36-44
4.1.2 Endpoints? (e.g., clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc)			x	
4.1.3 Covariates?	x			36-44
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	x			36-44
4.2.2 Endpoints? (e.g., date of occurrence, multiple event, severity measures related to event)			x	
4.2.3 Covariates? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	x			36-44
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g., International Classification of Diseases (ICD)-10)	x			24-25, 36-44
4.3.2 Endpoints? (e.g., Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)			x	
4.3.3 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	x			24-25, 36-44
4.4 Is the linkage method between data sources described? (e.g., based on a unique identifier or other)	x			36-44

Comments:

No endpoints included, this is a drug utilisation study

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g., operational details for defining and categorising exposure)	x			23-25
5.2 Does the protocol discuss the validity of exposure measurement? (e.g., precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	x			44-45
5.3 Is exposure classified according to time windows? (e.g., current user, former user, non-use)	x			8-12, 23
5.4 Is exposure classified based on biological mechanism of action?			x	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	x			8-12, 23

Comments:

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?			x	

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

No endpoints included, this is a drug utilisation study

Section 7: Biases and Effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address: 7.1.1 Selection biases?	☒	☐	☐	49-50
7.1.2 Information biases? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	49-50
7.2 Does the protocol address known confounders? (e.g., collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.3 Does the protocol address known effect modifiers? (e.g., collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	
7.4 Does the protocol address other limitations?	☒	☐	☐	49-50

Comments:

Assessment of confounders and effect modifiers does not apply as this is a drug utilisation study and no study endpoints are included. However, the study describes factors that are relevant to the use of medications such as comorbidity, comedications, age, and sex.

Section 8: Analysis plan	Yes	No	N/A	Page Number(s)
8.1 Does the plan include measurement of absolute effects?	☐	☐	☒	
8.2 Is the choice of statistical techniques described?	☐	☐	☒	
8.3 Are descriptive analyses included?	☒	☐	☐	45-49
8.4 Are stratified analyses included?	☒	☐	☐	45-49
8.5 Does the plan describe the methods for identifying: 8.5.1 Confounders?	☐	☐	☒	
8.5.2 Effect modifiers?	☐	☐	☒	
8.6 Does the plan describe how the analysis will address: 8.6.1 Confounding?	☐	☐	☒	
8.6.2 Effect modification?	☐	☐	☒	

Comments:

No measures of effect are estimated.

Section 9: Quality assurance, feasibility and reporting	Yes	No	N/A	Page Number(s)
9.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	x			45, 49
9.2 Are methods of quality assurance described?	x			49
9.3 Does the protocol describe quality issues related to the data source(s)?	x			49-50
9.4 Does the protocol discuss study feasibility? (e.g., sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	x			44-45
9.5 Does the protocol specify timelines for 9.5.1 Study start?	x			8-12, 16-19
9.5.2 Study progress? (e.g., end of data collection, other milestones)	x			8-12, 16-19
9.5.3 Study completion?	x			8-12, 16-19
9.5.4 Reporting? (i.e. interim reports, final study report)	x			8-12, 16-19
9.6 Does the protocol include a section to document future amendments and deviations?	x			12-16
9.7 Are communication methods to disseminate results described?	x			52-53
9.8 Is there a system in place for independent review of study results?	x			49, 50, 52-53

Comments:

Section 10: Ethical issues	Yes	No	N/A	Page Number(s)
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	x			50-52
10.2 Has any outcome of an ethical review procedure been addressed?			x	
10.3 Have data protection requirements been described?	x			50

Comments:

Name of the coordinating study entity[1]: RTI-HS

Name of (primary) lead investigator[2]: Jordi Castellsague, MD, MPH

Date: 18 February, 2015

Signature: _____

[1] A legal person, institution or organisation which takes responsibility for the design and/or the management of a study. The (primary) lead investigator is the person authorised to represent the coordinating study entity.

[2] A person with the scientific background and experience required for the conduct of a particular pharmacoepidemiological or pharmacovigilance study. The lead investigator is responsible for the conduct of a study at a study site. If a study is conducted at several study sites by a team of investigators, the (primary) lead investigator is the investigator who has overall responsibility for the study across all sites.

Annex 3.
List of Medications Interacting With Cytochrome P450

		Substrates		Inhibitors		Inducers
Therapeutic Class	**Drug**	**CYP2C19**	**CYP3A4**	**CYP2C19**	**CYP3A4**	**CYP3A4**
Proton pump inhibitors	Lansoprazole	X		X		
	Omeprazole	X		X		
	Pantoprazole	X				
	Rabeprazole	X				
Antiepileptics	Phenytoin	X				X
	Phenobarbital	X				X
	Carbamazepine					X
Antidepressants	Amitriptyline	X				
	Clomipramine	X				
	Fluoxetine			X		
	Fluvoxamine			X	X	
	Nefazodone				X	
	Trazodone		X			
Platelet aggregation inhibitors	Clopidogrel	X				
	Ticlopidine			X		
Antineoplastic agents	Cyclophospha-mide	X				
	Imatinib		X			
	Tamoxifen		X			
	Vincristine		X			
Progestogens	Progesterone	X				
Macrolide antibiotics	Clarithromycin		X		X	
	Erythromycin		X		X	
	Telithromycin		X			
	Troleandomycin				X	
Anti-arrhythmics	Quinidine		X			
	Amiodarone				X	

		Substrates		Inhibitors		Inducers
Therapeutic Class	**Drug**	**CYP2C19**	**CYP3A4**	**CYP2C19**	**CYP3A4**	**CYP3A4**
Anxiolytics	Diazepam	X	X			
	Alprazolam		X			
	Midazolam		X			
	Triazolam		X			
	Buspirone		X			
Immunosuppressants	Cyclosporine		X			
	Tacrolimus		X			
Protease-inhibitor antivirals	Indinavir		X		X	
	Ritonavir		X		X	
	Saquinavir		X			
	Nelfinavir				X	
	Boceprevir		X			
	Telaprevir		X			
Gastrointestinal	Cisapride		X			
	Cimetidine				X	
Antihistaminics	Astemizole		X			
	Chlorpheniramine		X			
Calcium-channel blockers	Amlodipine		X			
	Diltiazem		X		X	
	Felodipine		X			
	Nifedipine		X			
	Nisoldipine		X			
	Nitrendipine		X			
	Verapamil		X		X	
	Mibefradil				X	
Statins	Atorvastatin		X			
	Lovastatin		X			
	Simvastatin		X			
Antimycotics	Ketoconazole			X	X	
	Itraconazole				X	
Oral hypoglycemic agents	Pioglitazone					X
	Troglitazone					X
Antimycobacterials	Rifabutin					X
	Rifampin					X

		Substrates		Inhibitors		Inducers
Therapeutic Class	**Drug**	**CYP2C19**	**CYP3A4**	**CYP2C19**	**CYP3A4**	**CYP3A4**
Antipsychotics	Aripiprazole		X			
	Haloperidol		X			
	Pimozide		X			
Drugs for addictive disorders	Methadone		X			
Antimalarials	Quinine		X			
	Halofantrine[a]		X			
Drugs for erectile dysfunction	Sildenafil		X			

CYP = cytochrome P-450.

[a] From cilostazol summary of product characteristics.

Source (unless noted otherwise): Drug interactions. P450 drug interaction table: abbreviated "clinically relevant" table. School of Medicine, Department of Medicine, Division of Clinical Pharmacology, Indiana University. 2009. Available at: http://medicine.iupui.edu/clinpharm/ddis/ClinicalTable.aspx. Accessed 16 November 2012.