PASS INFORMATION

Title	Ivabradine Drug Utilisation Study in Select European Countries: A Multinational, Retrospective, Observational Study to Assess Effectiveness of Risk-Minimisation Measures
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Product reference	EMEA/H/C/597-598-4187
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Marketing authorisation holder(s)	Les Laboratoires Servier 50 rue Carnot 92284 Suresnes Cedex - France
Joint PASS	No
Research question and objectives	The overall objective of this drug utilisation study is to assess how ivabradine is used in patients with chronic stable angina pectoris in routine clinical practice and to evaluate the effectiveness of the new risk-minimisation measures. The specific objectives of the study are as follows: - To describe the characteristics of new users of ivabradine before and after implementation of the risk-minimisation measures - To describe the patterns of use of ivabradine before and after implementation of the risk-minimisation measures according to (1) dose of ivabradine at treatment initiation and changes of dose within a 6-month follow-up period from treatment start and (2) concurrent use of verapamil or diltiazem at baseline and within a 6-month follow-up period
Country(ies) of study	France, Germany, Italy, Spain, United Kingdom
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2. LIST OF ABBREVIATIONS

bpm	Beats per minute
CCTIRS	Comite consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNIL	Commission nationale de l'informatique et des libertés
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
DHPC	Direct Healthcare Professional Communication
DUS	Drug utilisation study
EC	Ethics Committee
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ESC	European Society of Cardiology
EU	European Union
EU PAS Register	European Union electronic register of post-authorisation studies
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
MAH	Marketing Authorisation Holder
PASS	Post-authorisation safety study
PBRER	Periodic Benefit Risk Evaluation Reports
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
RTI-HS	RTI Health Solutions
SmPC	Summary of product characteristics
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UK	United Kingdom

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title

Ivabradine Drug Utilisation Study in Select European Countries: A Multinational, Retrospective, Observational Study to Assess the Effectiveness of Risk-Minimisation Measures

Version 2.1

Emmanuelle Jacquot, MD

Rationale and background

Procoralan/Corlentor (ivabradine hydrochloride) was granted a marketing authorisation in Europe in October 2005 for the symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm who have a contraindication or intolerance for beta-blockers. In October 2009, an extension of the ivabradine indication, for use in combination with beta-blockers in patients whose angina is inadequately controlled with beta-blockers and whose heart rate is > 60 bpm, was approved.

In May 2014, a benefit-risk re-evaluation of Procoralan/Corlentor was initiated, and a direct health care professional communication (DHPC) was disseminated in European Union (EU) countries in June 2014 to inform prescribers and remind them of the current conditions of use of the product, especially regarding dosing recommendations and heart rate threshold in patients with angina pectoris.

On 06 November 2014, the benefit-risk ratio of ivabradine was reassessed as favourable by the PRAC, which recommended new risk-minimisation measures, a summary of product characteristics (SmPC) update (including a change in the threshold of resting heart rate before treatment initiation and a new contraindication), and a drug utilisation study (DUS) to assess the effectiveness of the new risk-minimisation measures.

Research question and objectives

The objective of this DUS is to assess how ivabradine is used in patients with chronic stable angina pectoris in routine clinical practice and to evaluate the effectiveness of new risk-minimisation measures. The specific objectives of the study are as follows:

- To describe the characteristics of new users of ivabradine before and after implementation of the risk-minimisation measures according to (1) demographics and specific comorbidities at baseline and (2) baseline heart rate at treatment initiation
- To describe the patterns of use of ivabradine before and after implementation of the risk-minimisation measures according to (1) dose of ivabradine at treatment initiation and dose changes within 6 months after treatment start and (2) concurrent use of verapamil or diltiazem at baseline and within 6 months after starting ivabradine

Study design

This will be a multinational retrospective cohort study that will collect data from patient medical records for patients with chronic stable angina pectoris initiating treatment with

ivabradine in routine clinical practice in selected European countries. Patient data will be collected through health care professionals at the start of treatment and during a 6-month follow-up period.

The study will comprise the following two periods:
- The first study period will capture information before implementation of the new risk-minimisation measures: from January 2010 to the end of 2013 (corresponding to a period in which the use of ivabradine in combination with beta-blockers in patients whose angina is inadequately controlled with beta-blockers was approved).
- The second study period will cover a period after implementation of the new risk-minimisation measures (DHPC December 2014 and revised SmPC approved in January 2015): from approximately 6 months following these changes of the SmPC, corresponding to the end of 2Q 2015, to 1 year later.

Population

The source population will be all patients with chronic stable angina initiating treatment with ivabradine in regular clinical practice during each study period in France, Germany, Italy, Spain, and the United Kingdom (UK).

Variables

For each study period, the following data will be abstracted from medical records of selected patients:
- At baseline: date of abstraction, age, sex, ivabradine prescription (start date and dose), diagnosis of chronic stable angina at start date, specific comorbidities (hypertension, heart failure, arrhythmias, peripheral vascular disease, smoking, obesity, diabetes, hyperlipidaemia), heart rate at start date, and concomitant prescription of verapamil or diltiazem at start date
- During the follow-up period: ivabradine prescription (all prescription dates and doses), concomitant prescription of verapamil or diltiazem (all prescription dates)

For each study period, the following outcomes will be derived from the collected variables:
- Distribution of patient demographic characteristics and comorbidities at start date
- Distribution of ivabradine prescription dose at start date and during follow-up
- Distribution of heart rate at start date
- Patients who used ivabradine treatment according to the revised SmPC:
  - Heart rate at baseline: Patients whose heart rate at treatment initiation was ≥ 70 bpm
  - Dose: Patients with no dose higher than the SmPC doses at treatment initiation and during follow-up[1]
  - Concomitant prescriptions for use of verapamil or diltiazem: patients who did not concurrently use verapamil or diltiazem at treatment initiation and during follow-up

[1] SmPC dose recommendations: "*The starting dose of ivabradine should not exceed 5 mg twice daily in patients aged below 75 years. After three to four weeks of treatment, if the patient is still symptomatic, if the initial dose is well tolerated and if resting heart rate remains above 60 bpm, the dose may be increased to the next higher dose in patients receiving 2.5 mg twice daily or 5 mg twice daily. The maintenance dose should not exceed 7.5 mg twice daily….In patients aged 75 years or more, a lower starting dose should be considered (2.5 mg twice daily i.e. one half 5 mg tablet twice daily) before up-titration if necessary.*"

- Patients who were prescribed ivabradine according to heart rate recommendation at initiation, no doses higher than the SmPC doses at treatment initiation and during follow-up, and with no concomitant use of verapamil/diltiazem.

Data sources

Medical records of patients.

Study size

The study will target 600 patients treated with ivabradine in each study period. As closely as is feasible, the sample size to be achieved in each country will be proportional to the volume of prescriptions per country and prescriber specialty.

Data analysis

Continuous variables will be reported as mean, standard deviation, median, and range. Categorical variables will be summarised as number and proportion of the total study population, with missing data counted as one of the categories. Separate analyses will be performed for each study period and to estimate the change, the 95% confidence interval of the difference between the two study periods will be calculated. A chi-square test or a t-test will be used, according to the nature of the assessed variable, to test the differences in patient characteristics and observed study outcomes between the two study periods. Results will be presented overall, and subgroup analyses by country and physician specialty, as well as overall analyses including and excluding the general practitioners, will be reported.

Estimated milestones

- Protocol endorsement by EMA/PRAC June 2015
- Pilot study phase: evaluate feasibility requirements of sites (i.e., potential number of participant health care professionals and estimate of the number of ivabradine-treated patients); explore local regulatory and ethics requirements; pilot test study materials; and conduct user acceptance testing of data collection form: June 2015-February 2016
- Amended protocol endorsement by EMA/PRAC 13 May 2016
- Registration in the EU PAS Register/ENCePP Register: 31 May 2016, prior to the start of data collection
- Start of study implementation (i.e., preparation of study materials, submission documents for IRB/EC approval, and training materials; set up of study processes; and other operational activities): 01 June 2016 (no contacts with sites/physicians will take place until after the post-RMM study period reaches its end)
- Start of data collection: 31 December 2016
- End of data collection: 30 September 2017
- Study report: 31 December 2017

5. AMENDMENTS AND UPDATES

Version number	Date	Section(s) of study protocol	Amendment or update	Reason
2.1	28 Apr 2016	Section 9.2.2, Physicians and sampling frame; Section 9.5, Study size	Targeted physicians and recruitment plan	To clarify the distribution of physicians and patients by prescriber specialty and per country (response to PRAC Rapporteur assessment, 11 April 2016).
2.1	28 Apr 2016	Section 4, Abstract; Section 6, Milestones; Section 9.1, Study design; Section 9.7, Data analysis	The timelines and milestones have been revised Removal of the interim report	To provide a final study report by the end of 2017 (at the request of PRAC, 11 April 2016).
2.0	25 Feb 2016	Section 9.2, Setting; Section 9.7, Data analysis; Section 9.9, Limitations of the research methods	Targeted physicians and sampling Addition of a sensitivity analysis	Based on the pilot results, to account for the shared care management practices between specialists and general practitioners
2.0	25 Feb 2016	Section 4, Abstract; Section 9.1, Study design; Section 9.2.1, Countries; Section 9.2.2, Physicians and sampling frame; Section 9.5, Study size	To remove the Netherlands from the study countries and to add Italy	Following additional information from the Dutch subsidiary on sales and prescription modalities in angina, it was concluded that the study could not be performed in the Netherlands
2.0	25 Feb 2016	Section 4, Abstract; Section 6, Milestones; Section 9.1, Study design; 9.7, Data analysis	The timelines and milestones have been revised Addition of an interim report	Based on the pilot phase, it is proposed to revise the timelines to extend the site recruitment period to allow adequate time for site/physician recruitment activities and to extend the data collection period
1.2	19 May 2015	Section 4, Abstract; Section 9.7, Data analysis	Updated to add statistical tests to the analysis to be performed to evaluate the change between the periods before and after implementation of the risk-minimisation measures	To identify statistically significant differences between the two study periods (at the request of PRAC, 30 April 2015)
1.2	19 May 2015	Section 4, Abstract; Section 6, Milestones; Section 9.1, Study design; Section 9.9, Limitations of the research methods	The timelines and milestones have been revised to start the study implementation by the end of 1Q 2016 and ensure that the recruitment activities start only after the second study period has ended	To avoid potential bias due to health care professional awareness of study goals (response to PRAC assessment, 30 April 2015)
1.2	19 May 2015	Section 4, Abstract; Section 6, Milestones; Section 9.1, Study design	Updated to clarify that country-specific regulatory and ethics requirements will be ascertained during the pilot phase in each country, prior to study implementation	To explore regulatory and ethics requirements in due time to meet the study timelines (suggestion of PRAC, 30 April 2015)

Version number	Date	Section(s) of study protocol	Amendment or update	Reason
1.2	19 May 2015	Section 4, Abstract; Section 9.7, Data analysis	Updated to provide overall results including and excluding general practitioners	To have stratified analyses including and excluding general practitioners (suggestion of PRAC, 30 April 2015)
1.1	22 Apr 2015	Section 4, Abstract; Section 9.1, Study design	The timelines and milestones have been revised to complete the study by the end of Q2 2017; the description of the study overview was expanded to clarify the study timelines and milestones	To deliver the study final report 2Q 2017 (response to PRAC assessment, 9 April 2015)
1.1	22 Apr 2015	Section 9.2.2, Physicians and sampling frame	Text was added to consider increasing the number of sites and physicians, if needed to achieve the proposed target within the proposed timelines	Reaching the proposed target sample size, particularly in the second study period, might be difficult. A strategy to overcome this challenge needs to be included (response to PRAC assessment, 9 April 2015)
1.1	22 Apr 2015	Section 9.5, Study size	Updated to provide different sample size scenarios and assess a smaller sample size in the second period that would enable achievement of the study objective	Reaching the proposed target sample size in the second study period might be difficult. A strategy to overcome this challenge needs to be included (response to PRAC assessment, 9 April 2015)
1.1	22 Apr 2015	Section 4, Abstract; Section 9.7, Data analysis	Updated to clarify the analysis to be performed to evaluate the change between the periods before and after implementation of the risk-minimisation measures	Comparison analyses between the two study periods have to be included (response to PRAC assessment, 9 April 2015)

6. MILESTONES

Milestone	**Actual/Planned date**
Protocol endorsement by EMA/PRAC	June 2015
Pilot study phase: evaluate feasibility requirements of sites; explore local regulatory and ethics requirements; pilot test study materials; and conduct user acceptance testing of data collection form	June 2015-February 2016
Amended protocol endorsement by EMA/PRAC	13 May 2016[a]
Registration in the EU PAS Register	31 May 2016[b]
Start of study implementation: preparation of study materials, submission documents for IRB/EC approval, and training materials; set up of study processes; and other operational activities[c]	01 June 2016
Start of data collection[d]	31 December 2016
End of data collection[e]	30 September 2017
Final report of study results	31 December 2017

[a] *The date of amended protocol approval by EMA/PRAC will drive the timing of subsequent study milestones.*
[b] *Prior to start of data collection.*
[c] *No contacts with sites/physicians will take place until after the post-RMM study period reaches its end.*
[d] *Date from which data collection for the first study subject starts. For secondary use of data, the date from which data extraction starts (EMA GVP Module VIII terminology).*
[e] *Date from which the analytical data set is completely available. (EMA GVP Module VIII terminology).*
Note: Final timelines may be impacted by delays in obtaining ethical and scientific approvals in the targeted countries and in establishing contracts with participant physicians, amongst others. Data collection will be initiated after the risk-minimisation measures have been implemented in the source population, and will take into account the expected lag-time for observing the impact of the risk-minimisation measures on prescribing patterns in each country. Therefore, the timing of study initiation in the different countries might differ.

7. RATIONALE AND BACKGROUND

Ivabradine is a pure heart rate–lowering agent, acting by selective and specific inhibition of the cardiac pacemaker I_f current that controls the spontaneous diastolic depolarisation in the sinus node and regulates heart rate. The cardiac effects are specific to the sinus node with no effect on intra-atrial, atrioventricular, or intraventricular conduction times, nor on myocardial contractility or ventricular repolarisation (Procoralan summary of product characteristics [SmPC], 2015). The main pharmacodynamic property of ivabradine in humans is a specific dose-dependent reduction in heart rate. At usual recommended doses, heart rate reduction is approximately 10 bpm at rest and during exercise. This leads to a reduction in cardiac workload and myocardial oxygen consumption (Procoralan SmPC, 2015).

Procoralan/Corlentor (ivabradine hydrochloride) was granted a marketing authorisation in Europe in October 2005 for the symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm who have a contraindication or intolerance for beta-blockers. In October 2009, an extension of the ivabradine indication was approved for the use in combination with beta-blockers in patients whose angina is inadequately controlled with beta-blockers and whose heart rate is > 60 bpm. In February 2012, ivabradine was approved for the treatment of New York Heart Association class II to IV chronic heart failure with systolic dysfunction in patients with sinus rhythm and heart rate ≥ 75 bpm in combination with standard therapy, including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated. In both indications, the ivabradine starting dose is 5 mg twice daily (alternative starting dose of 2.5 mg twice daily if aged ≥ 75 years), with possible titration up to 7.5 mg twice daily.

The SIGNIFY study was performed in 19,102 patients with coronary artery disease without clinical heart failure. The posology used was higher than the posology recommended in the Procoralan (ivabradine) SmPC (starting dose 7.5 mg twice daily [5 mg twice daily if age ≥ 75 years] and maintenance dose 10 mg twice daily). In April 2014, the preliminary results of the SIGNIFY study showed an increased risk of cardiovascular death and non-fatal myocardial infarction possibly due to bradycardia in a subgroup of patients with angina of Canadian Cardiovascular Society class II or higher who were treated with ivabradine.

In May 2014, the benefit-risk re-evaluation of Procoralan/Corlentor was triggered by the European Commission via a referral under Article 20 of Regulation (EC) No 726/2004. Following a PRAC assessment of the need for provisional measures, a direct health care professional communication (DHPC) was disseminated in European Union (EU) countries in June 2014 to inform prescribers and remind them of the current conditions of use of the products, especially regarding dosing recommendations and heart rate threshold in patients with angina pectoris.

The benefit-risk ratio of ivabradine was reassessed as favourable by the PRAC in November 2014 (EMA, 2014), which recommended the following actions:

- Implement new risk-minimisation measures with an SmPC update in Sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, and 5.1, including a change of the threshold of resting heart rate before treatment initiation in angina pectoris patients from > 60 to ≥ 70 bpm, a contraindication for the concomitant use of ivabradine with verapamil or diltiazem, reinforcement of current posology including initial and maintenance doses not to be exceeded and heart rate monitoring, and new recommendations regarding atrial fibrillation.

- Conduct a drug utilisation study (DUS) to assess the effectiveness of these new risk-minimisation measures.

On 20 November 2014, the CHMP endorsed these recommendations and confirmed that "The benefit-risk balance of Procoralan/Corlentor remains positive for its authorised indications." To inform health care professionals of these changes, a DHPC was disseminated in EU countries in December 2014.

To evaluate the effectiveness of the new risk-minimisation measures, a DUS will be conducted in several European countries. This study will aim to assess how ivabradine is used in patients with chronic stable angina pectoris in routine clinical practice, with a focus on whether the new contraindications (heart rate at treatment initiation lower than 70 bpm and concomitant use of verapamil or diltiazem) are followed. It was determined that a multinational retrospective medical chart review study was preferred as opposed to using population-based health care databases because some key information, in particular heart rate measures, will not be accurate enough or is partially available in such databases. In addition, ivabradine may be prescribed in some countries by physicians whose prescriptions are not captured in the available databases.

8. RESEARCH QUESTION AND OBJECTIVES

The overall objective of this DUS is to assess how ivabradine is used in patients with chronic stable angina pectoris in routine clinical practice and to evaluate the effectiveness of the new risk-minimisation measures. The study will comprise two periods: before and after implementation of the risk-minimisation measures.

The specific objectives of the study are as follows:
- To describe the characteristics of new users of ivabradine before and after implementation of the risk-minimisation measures according to (1) demographics and specific comorbidities at baseline and (2) baseline heart rate at treatment initiation.
- To describe the patterns of use of ivabradine before and after implementation of the risk-minimisation measures according to (1) dose of ivabradine at treatment initiation and changes of dose within a 6-month follow-up period from treatment start and (2) concurrent use of verapamil or diltiazem at baseline and within a 6-month follow-up period.

9. RESEARCH METHODS

9.1. Study design

This will be a multinational retrospective cohort study that will collect data from patient medical record abstraction (chart review) for patients with chronic stable angina pectoris initiating treatment with ivabradine in routine clinical practice in selected European countries. Patients' data will be collected through their health care professionals at the start of treatment and during a 6-month follow-up period.

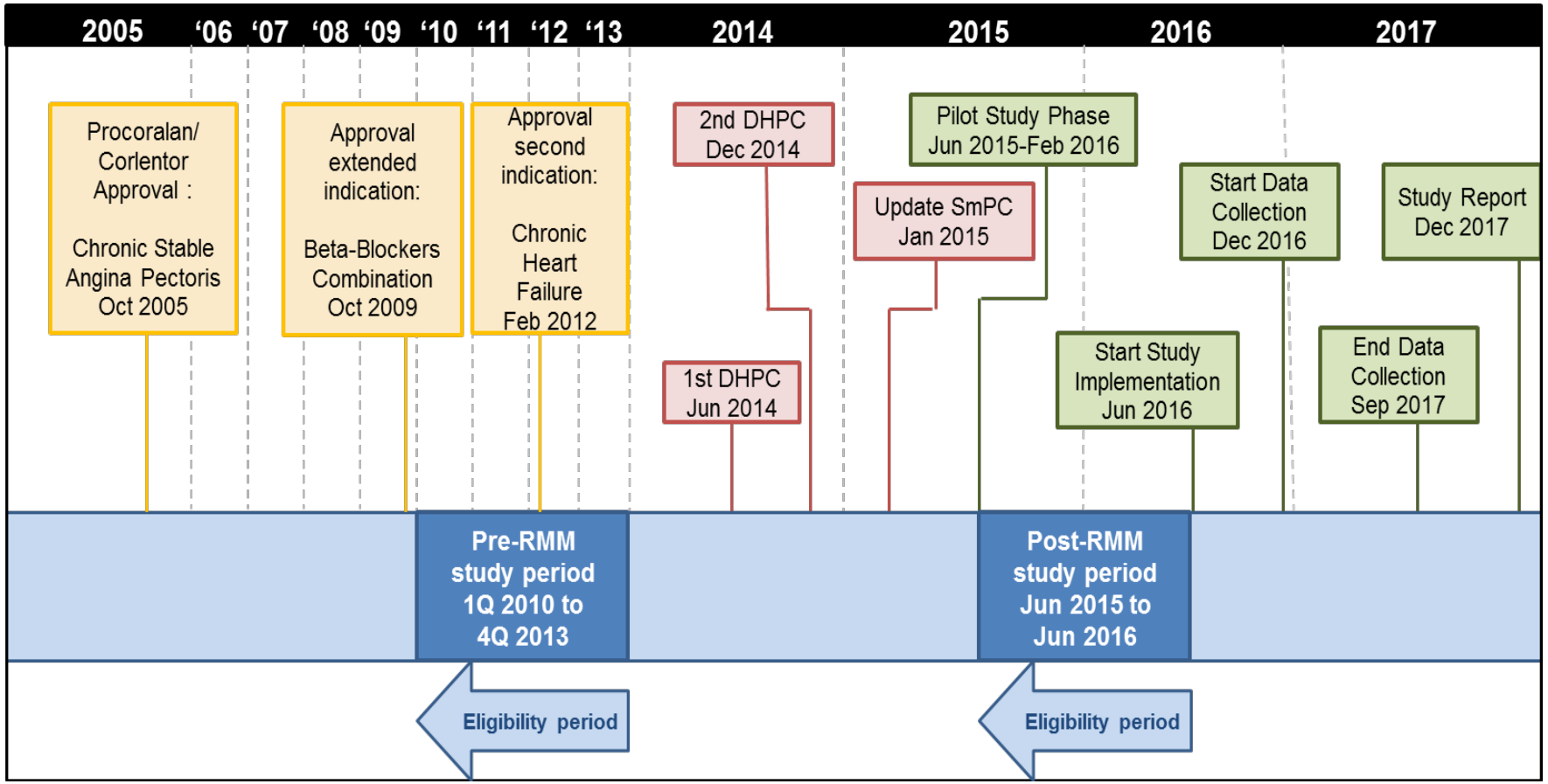
The study will comprise the following two periods (Figure 1):
- The first study period will capture information before the implementation of risk-minimisation measures: from January 2010 to the end of 2013, corresponding to a period

during which the use of ivabradine in combination with beta-blockers in patients whose angina is inadequately controlled with beta-blockers alone was approved; communications regarding the new risk-minimisation measures started in June 2014.

- The second study period will cover a period after implementation of the risk-minimisation measures (DHPC December 2014 and revised SmPC approved in January 2015): from 6 months following the changes of the SmPC, corresponding to the 30 June 2015, to 1 year later, which corresponds to 30 June 2016.

For each study period, the start date for the use of ivabradine will be defined as the first date in which a patient initiated treatment with ivabradine.

Figure 1. Study overview



DHPC = direct health care professional communication; SmPC = summary of product characteristics; RMM = risk-minimisation measures.

** Early activities include preparation of study materials and documentation for institutional review board/ethics committee submission. No contacts with sites/physicians will take place until after the post-RMM study period reaches its end.*

For the main study, in each country, a lead investigator will be recruited to help organise the research effort in the country. Country lead investigators will be expected to provide support for ethics committee (EC) submissions in each country, and input to engage other potential physician investigators to participate in the study.

The timing of study initiation in the different countries might differ. Study implementation is planned to start in June 2016. Initial activities will consist of the preparation of study materials and documentation for institutional review board (IRB)/ethics committee (EC) submissions, and the set up of study processes. The first IRB/EC submission is targeted starting June2016. Recruitment activities will start only after the post-RMM study period has concluded. Data collection can start at each site in all countries only after the approvals from the French competent authorities (CCTIRS and CNIL) have been obtained as well as local regulatory and ethics committee approvals and investigators' agreements are in place. In some countries, the set-up phase, including activities such as site recruitment and EC approval, requires an average of up to 6 months. Therefore, the timing of the start of data collection is expected to vary across countries. Data collection is anticipated to start at least 6 months after the end of the post-RMM period (30 June 2016), which corresponds to 31 December 2016. This will allow collecting the data over the 6-month follow-up period for patients who are included towards the end in the post-RMM period.

The end of the data collection, including data lock and cleaning, is planned by the end of September 2017 in all participating countries. We propose to submit the final report by the end of December 2017.

9.2. Setting

9.2.1. Countries

Based on the protocol submitted to the PRAC and approved in June 2015, five countries were planned to be included: France, Germany, Spain, the United Kingdom and the Netherlands. However, as a result of the specific reimbursement conditions in the Netherlands, the estimated number of patients initiating treatment with ivabradine in this country is very limited and is restricted to a limited subset of patients with angina pectoris. For this reason, it was decided not to perform the study in the Netherlands and to include Italy to keep five countries involved in the DUS.

The final targeted countries are France, Germany, Italy, Spain, and the UK. The selection of countries was based on the volume of sales of ivabradine per country, a diverse geographic representation of European countries following the current European Society of Cardiology (ESC) guidelines for the management of stable coronary artery disease (Montalescot et al., 2013), and their ability to represent a variety of medical practices (i.e., specialty of prescriber). Table 1 shows the estimated number of patient-years of ivabradine exposure based on sales data since the marketing authorisation in the targeted countries.

Table 1. Estimated patient-years of ivabradine exposure based on sales data through 25 April 2015

Countries	Date of market authorisation	Number of patient-years	
		From market authorisation to 25 Apr 2015	PSUR 13 period 26 Oct 2014 to 25 Apr 2015
France	03 Sep 2007	461,852	52,399
Germany	16 Dec 2005	255,898	30,249
Italy	08 Feb 2008	263,830	39,176
Spain	23 Feb 2007	255,898	27,843
United Kingdom	23 Dec 2005	141,844	13,693
Total of the selected countries[a]		1,379,322 (74.9%)	163,360 (74.0%)
Total in EU countries		1,842,119	220,616

Source: Institut de Recherches Internationales Servier (I.R.I.S). 13th periodic safety update report for ivabradine [data on file]. 24 June 2015.

a The denominator for the percentage is the total in EU countries.

9.2.2. Physicians and sampling frame

Patients will be identified across a variety of physician specialities, including general practitioners (GPs), cardiologists (office and hospital outpatient clinics), and specialists in internal medicine (office and hospital outpatient clinics). Representation by each physician group should reflect, to the extent possible, prescribing patterns in each country (Table 2).

Table 2. Ivabradine market experience and prescribing pattern in selected countries

Country	Ivabradine sales[a]		Percentage of prescriptions to new users by prescriber speciality	Mean number of patients initiated by prescriber specialty each year
	n	%[b]		
France	307,398	32	GP, 42 Cardiologist, 51 Other, 7	0.2 GP 1.7 Cardiologist, private 1.9 Cardiologist, hospital
Germany	188,599	19	n.a	n.a.
Italy	264,648	27	GP or internist, 6 Cardiologist, 94	0.01 GP or internist 0.6 Cardiologist
Spain	159,599	16	GP, 9 Cardiologist, 81 Internist, 9	0.02 GP 2.7 Cardiologist 0.15 Internist
United Kingdom	52,812	5	GP, 94 Cardiologist/Internist, 6	n.a.
Total	973,056		—	—

n.a. = not available.

[a] Total number of Procoralan/Corlentor boxes (5 mg and 7.5 mg), April-June 2015.

[b] Sum is greater than 100 due to rounding.

We will target patients who initiated treatment with ivabradine during the study periods by prescriptions written by specialists or GPs.

Following the physicians' feedback during the pilot phase, the distribution of sales (Table 2) by type of prescribers in each country does not appear to correspond to the accurate distribution of patients to be targeted, particularly in France and the UK. Based on the pilot study findings, the management of ivabradine-treated patients by the different specialties and the target physicians is as follows:

- In France, Italy, and Spain, initiation of ivabradine treatment seems to be done exclusively by specialists. Most of these specialists follow their patients over a period of at least 6 or 12 months, allowing us to retrieve both initiation and follow-up data from their medical records. We will primarily target specialists. However, general practitioners will also be targeted in these countries in order to assess their prescription modalities. Therefore, we plan to recruit 60% of specialists and 40% of GPs. This distribution will allow recruiting 80% of patients identified through specialists and 20% through GPs, assuming a mean number of 12 patients per specialist and 5 patients per GP.
- In Germany, the shared care management between specialists and GPs is more pronounced. Initiation of ivabradine treatment seems to be done exclusively by specialists, while follow-up and subsequent prescriptions are done mostly by GPs. Therefore, we plan to recruit 40% of specialists and 60% of GPs. This distribution will allow recruiting 50% of patients identified through specialists and 50% through GPs, assuming a mean number of 12 patients per specialist and 6 patients per GP.
- As for the UK, the initiation of ivabradine treatment is mainly decided by specialists, even when GPs issue the initial prescription. Data at initiation could be missing since its collection will depend on whether the GP has access to information from the initial specialist prescriber or not. Thus, we plan to recruit 40% of specialists and 60% of GPs in order to capture both data at initiation and data at follow-up. This distribution will allow recruiting 50% of patients identified through specialists and 50% through GPs, assuming a mean number of 12 patients per specialist and 6 patients per GP.

Therefore, the number of physicians sampled per country will be proportional to the physician specialty and practice type distributions described earlier and with sampled physicians treating a minimum number of patients with ivabradine per study period, i.e., 10 for specialists and 4-5 for GPs, using a nonprobability sampling strategy.
Thus, the number of ivabradine-treated patients followed by physicians is expected to be higher for the specialists than for the GPs.

Overall, based on these assumptions, we estimate that 38 sites of specialists and 32 sites of GPs will be involved. The total number of patients identified through GPs will be 165 (28%) and 435 (72%) through specialists per period (see section 9.5, Study Size, table 3).

It is worth noting that the feedback from the specialties and clinical settings during the pilot study does not reflect primary care settings in Germany, Italy, and Spain or secondary care settings in the UK.

This sampling strategy will have the objective of achieving a generally representative sample of physicians prescribing ivabradine as well as of ivabradine new users. In addition to country and specialty, practice type and other characteristics (as available) will be taken into consideration, an approach that is supported by the findings in the pilot study.

Identification of participating physicians will be performed based on lists of centres/physician prescribers in each of the relevant specialties that are purchased by the MAH for the targeted

countries. Based on the prescription of ivabradine in each country, a multistage approach will be taken to identify potential practices or centres and physicians in each country, targeting those known to prescribe ivabradine. The sampled physicians will be contacted through regular mail, e-mail when available, or phone otherwise, focusing on high-volume prescribers to enhance the efficiency.

In countries where, as a result of a longer set-up phase, the period for data collection has been shortened so that the ability to achieve the target sample size may be limited, as well as in countries with slow recruitment, an increase in the number of sites and physicians will be considered.

The study feasibility questionnaire will be completed by each physician who expressed interest in study participation. The site/physician-specific feasibility information will help inform the final decision regarding physician recruitment into the study. Consistent with local laws and regulations, each eligible participating physician who agrees to participate will provide a list of consecutive patients who were treated with ivabradine within the study periods. The medical records of the patients who fulfil the eligibility criteria will be obtained. The physician or designated health care provider will contact patients to obtain informed consent if local regulations require patient informed consent for the use of patient medical records for the study (at this time, this applies to France and Germany).

9.2.3. Patients

The source population will include all patients with chronic stable angina initiating treatment with ivabradine in regular clinical practice. A patient initiating ivabradine (new user) will be defined as a patient without documented use of ivabradine during the previous 6 months and who receives a first prescription for ivabradine by their prescribing physician during (one of) the study periods.

Inclusion criteria
- Documented initiation of treatment with ivabradine during one of the study periods
- Diagnosis of chronic stable angina as the indication for treatment initiation
- Patient (or legal representative) has provided informed consent to participate in the study, where required

Exclusion criteria
- Patients treated with ivabradine for an indication other than chronic stable angina
- Patients with documented use of ivabradine in the 6 months prior to the first prescription of ivabradine in a study period
- Patients who were participating in ivabradine clinical trials for the study period during which they would have contributed data

9.3. Variables

9.3.1. Collected data

An electronic data collection form will be used to collect study data.

The following data will be collected from contacted physicians who indicate willingness to participate in the feasibility questionnaire:

- Physician characteristics: demographics, specialty, years in practice
- Practice setting
- Number of patients initiated with ivabradine during the study period
- Internet access, availability of an automated data system to identify patients for the study

Physicians who are provided the feasibility questionnaire and who refuse to participate will be asked the reason for refusal.

For each study period, the following data will be abstracted from medical records of selected patients:
- At baseline
  - Date of abstraction
  - Age, sex
  - Ivabradine prescription: start date and dose
  - Diagnosis of chronic stable angina at start date
  - Specific comorbidities: hypertension, heart failure, arrhythmias, peripheral vascular disease, smoking, obesity, diabetes, hyperlipidaemia
  - Heart rate at start date
  - Concomitant prescription of verapamil or diltiazem at start date
- During the follow-up period
  - Ivabradine prescription: all prescription dates and doses
  - Concomitant prescription of verapamil or diltiazem: all prescription dates

9.3.2. Outcomes

For each study period, the following outcomes will be derived from the collected variables:
- Distribution of patient demographic characteristics and comorbidities at start date
- Distribution of ivabradine prescription dose at start date and during follow-up
- Distribution of heart rate at start date
- Patients who used ivabradine treatment according to the revised SmPC (main and secondary analyses in Section 9.7):
  - Heart rate at baseline: patients whose heart rate at treatment initiation is ≥ 70 bpm
  - Doses: patients with no dose higher than the SmPC doses at treatment initiation and during follow-up
  - Concomitant prescriptions for verapamil or diltiazem: patients who did not concurrently use verapamil or diltiazem at treatment initiation and during follow-up
  - Patients who were prescribed ivabradine according to the heart rate recommendation at baseline, no doses higher than the SmPC doses at treatment initiation and during follow-up, and with no concomitant use of verapamil or diltiazem

9.4. Data sources

The source of information for the study will be the medical records of patients with chronic stable angina pectoris who initiated treatment with ivabradine in the period before and after implementation of the risk-minimisation measures in the selected countries.

Medical records of patients initiating treatment with ivabradine will be identified by participating study physicians in each country. Fully anonymised data will be collected from the patients' records by designated site health care professionals using a standard data collection form tailored to the study objectives. Health care professionals will not be required

to contact patients to obtain information on study variables that are not recorded in the patient's record.

9.5. Study size

The study will target a sample size of 600 patients treated with ivabradine in each study period (before and after implementation of the new risk-minimisation measures). To the extent possible, the sample size to be achieved in each country will be proportional to the volume of prescriptions per country and prescriber specialty.

The following formula to calculate the number of subjects required for a proportion has been used to estimate the target sample size.

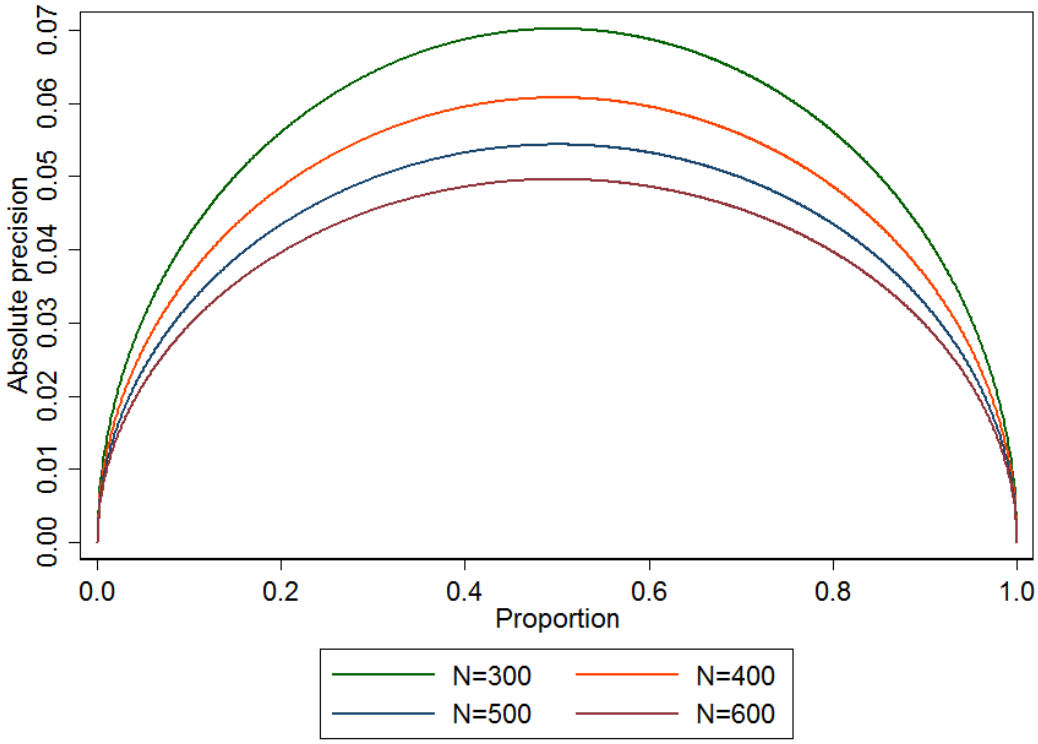
$$N = t^2 * \frac{p\,(1-p)}{e^2}$$

Where *t* is the t-test value for a confidence interval level at 95%; *e* is the margin of error (absolute precision); and *p* the proportion to be measured, assumed to be 50%, which results in the largest sample size, since there is no evidence that supports the expected proportion of patients compliant with the SmPC. Assuming a margin of error at 5%, the required sample size would be up to 384 patients overall for the five selected countries.

The sample of patients will not be a random sample because the selection will be based on a non-probabilistic sample of physicians. Thus, the probability for a patient to be selected depends on the practice or centre (cluster effect), the physician speciality, and the availability of medical charts. To correct for the difference in design, the sample size is multiplied by the design effect, assumed to be 1.4 for this study (Korn and Graubard, 1991; Park et al., 2003). The required sample size would be 384 * 1.4 = 538. The sample size is further increased by 10% to account for a number of contingencies (e.g., medical record not located, non-response, other). The required sample size would be 538 + (538 * 10 / 100) = 592 (final target rounded to 600) for the five selected countries, which results in 1,200 patients for the two study periods.

The absolute precision for a 95% confidence interval with different target sample sizes according to the proportion of patients with a specific outcome is shown in Figure 2. For a target sample size of 600 patients, and a proportion of 50% (worst hypothesis) in the measurement, the absolute precision would be 5%.

Figure 2. Absolute precision for a 95% confidence interval and four sample size scenarios



Medical practices or centres, including general practitioners, cardiologists, and internists, will be targeted in each country. To achieve the target sample in each country, the number of practices or centres and the number of patients per practice or centre will be adapted according to the potential for recruitment and the physician speciality. It is assumed that 10% of physicians contacted will agree to participate in the study and that they will be able to collect information on 90% of eligible patients. The number of physicians that will need to be contacted to achieve the target sample of patients per country will take into account the relative distribution of specialty of prescriber physicians and the estimated mean number of new users of ivabradine with chronic stable angina by specialty per year.

All reasonable efforts will be made to reach the target sample size of 600 patients for the second period. However, a target sample size of 400 patients will be considered acceptable to meet the study objective, as the absolute precision would be 6%, i.e., for the worst precision scenario of a proportion of 50%, the 95% confidence interval would be 44%-56% rather than the 45%-55% confidence interval for the same proportion if 600 patients are targeted.

Based on the sales volume per country, the theoretical number of patients by country and for each period is presented in Table 3.

Table 3. Study sample size and estimated mean number of sites per country

Country	Ivabradine sales[a]		Target sample size	Target sample size per physicians' specialty		Estimated mean number of sites[b]	
	n	%		Specialists	GPs	Specialists[c]	GPs [d]
France	307,398	31.6	190	152	38	13	8
Germany	188,599	19.4	116	58	58	5	10
Italy	264,648	27.2	163	130	33	11	7
Spain	159,599	16.4	98	78	20	7	4
United Kingdom	52,812	5.4	33	17	16	2	3
Total	973,056		600	435	165	38	32

[a] *Total number of Procoralan/Corlentor boxes (5 mg and 7.5 mg), April-June 2015.*
[b] *The number of sites per specialty and per country will be adjusted according to the actual inclusions*
[c] *Assumes a mean number of 12 patients per site (specialists)*
[d] *Assumes a mean number of 5 patients per site for GPs in France, Italy and Spain and 6 patients per site for GPs in UK and Germany*

9.6. Data management

An electronic data capture system will be used to collect patient data. Use of the electronic data capture technology minimises the burden on the physician and the site and maximises the quality of the data while ensuring that participant privacy is maintained throughout the process. Using an electronic data capture system will improve data collection efficiency, decrease response error, and facilitate physicians' contributions. However, if some sites are anticipated to have limited access to a computer, a pen-and-paper CRF option could also be considered.

Data collection will be performed by physicians or designated site support staff through the abstraction of data from the patients' medical records.

9.7. Data analysis

The statistical analysis plan, developed and finalised before the study database lock, will include a description of the statistical methods, data structure, the analyses planned, and planned tables and figures.

Continuous variables will be described as mean, standard deviation, median, and range. Categorical variables will be summarised as number and proportion of the total study population, with missing data counted as one of the categories. Confidence intervals (95% CI) will be calculated for key variables.

Separate analyses will be performed for each study period. The difference, before and after implementation of the additional risk-minimisation measures, between the proportions of the study outcomes defined in the main analysis will be calculated as an estimate of the change. The upper and lower limits of the 95% confidence interval for the difference will be calculated using the most appropriate method described by Newcombe (1998). A chi-square test or a t-test will be used, according to the nature of the assessed variable, to test the differences in patient characteristics and observed study outcomes between the two study periods (Fisher and van Belle, 1993). Results will be presented overall, and subgroup analyses by country and physician specialty, as well as overall analyses including and excluding the general practitioners, will be reported.

The main analysis will estimate the proportion of the following:
- Patients with a heart rate threshold at treatment initiation ≥ 70 bpm
- Patients with no ivabradine dose higher than the SmPC doses at treatment initiation and during follow-up
- Patients who did not concurrently use verapamil or diltiazem at ivabradine treatment initiation and during follow-up
- Patients who were prescribed ivabradine according to the heart rate recommendation at baseline, no doses higher than the SmPC doses at treatment initiation and during follow-up, and had no concomitant use of verapamil or diltiazem at treatment initiation nor during follow-up

Secondary analyses will be as follows:
- Characteristics of participating and non-participating physicians will be described
- Characteristics of ivabradine users (age, sex, and specific comorbidities) will be described as the number and percentage of patients
- Ivabradine treatment discontinuation figures will also be presented using survival analysis and Kaplan-Meier graphs.

In analyses, dose of ivabradine at start and over the 6-month follow-up will be stratified by age group.

Sensitivity analysis:
- Subanalyses will be conducted for the main outcome stratified by the setting in which treatment was initiated (i.e., in the same participating practice vs. initiation in another practice)

Programming will be conducted using SAS statistical software (SAS Institute, Cary, North Carolina).

9.8. Quality control

Standard operating procedures will 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.

Quality assurance activities will be performed to assess various aspects of the project according to established criteria in standard operating procedures and other applicable procedures. A quality assurance audit of this study may be conducted by the sponsor or the sponsor's designees.

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.

All programming written by one study analyst will be independently reviewed by a different analyst, with oversight by a senior statistician. The programmer(s) will review all analysis program log files for errors and warning messages and retain electronic copies of all final program log files in the project folder. The programmer will account for the number of observations reported at each executed data step and note in the program code when the number of observations increases or decreases. Listings of observations/results from the final

data sets will be printed and reviewed. Listings or output used to verify results will be preserved in the quality-control folder or in the program folder. A quality-control checklist will be maintained for the project; a hard copy will be printed, signed, and retained in the project folder.

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

9.9. Limitations of the research methods

There are some challenges and limitations in performing the study based on data abstracted retrospectively by health care professionals from patient medical records. The study will rely on the site health care professionals abstracting the data, which may influence their willingness to participate in the study and subsequently affect the representativeness of the sample. The involvement of a lead country investigator in each country could be a strategy to enhance the selection and responsiveness of centres and health care professionals and their willingness to participate in the study. On the other hand, health care professionals may influence the selection of patients, with potentially better information recorded in the medical records or with better adherence to the ESC guidelines. This can be minimised by using selection strategies such as enrolment of consecutive patients during the study period until a target number is reached or random selection of new users of ivabradine, if the available number of eligible patients is large. Having the site health care professionals perform the medical chart abstraction also has some advantages. The clinical experience and knowledge about the medical records and site-specific process for medical record retrieval and easy navigation through the medical record can ultimately make the data collection process more efficient and minimise any issues due to data protection and data privacy and confidentiality requirements, compared with data abstraction by external independent data abstractors.

Data on actual distribution of new users of ivabradine across physician specialties is lacking, and the final targeted sample will be approximated on the basis of the sales distribution. Shared care management practices may result in missing information either on treatment initiation or follow-up depending on the countries. Stratified analyses by physician specialty and sensitivity analyses are planned. These analyses will allow assessment of whether the source of initiation and subsequent prescription of ivabradine has any impact on the main study endpoints.

It is expected that the same physicians will contribute data on new users of ivabradine from both study periods. Pilot study phase activities were concurrent with the physicians' recording of information about patients during the second study period. Participation and awareness of the study objective amongst the lead investigator physicians might influence their prescribing behaviour and subsequently affect the study results (Hawthorne effect) (Fletcher and Fletcher, 1988). However, this effect is expected to be minimal, and to a large extent will be neutralised by the retrospective nature of the study; timing of the start of site and physician recruitment activities to occur only after the end of the post-RMM period; and timing of the start of data collection, which will be performed at the same time for both study periods.

Another limitation of the study relates to the underrecording of relevant information about the baseline conditions (e.g., heart rate, comorbidities, concomitant medications) at the time of ivabradine treatment initiation.

A potential and critical challenge for timely inclusion of patients during the second study period following the new risk-minimisation recommendations with the increased threshold in heart rate is that, if effective, this will result in lower number of patients using ivabradine, which may impact the number of patients eligible for this second study period.

10. PROTECTION OF HUMAN SUBJECTS

This is a non-interventional study with retrospective secondary data collection; therefore, the risks for patients linked to their participation in the study is limited to a breach of confidentiality with regard to personal identifiers or health information. The study will collect de-identified information from patients' medical records without any involvement or participation of patients.

Compliance with local regulations concerning the provision of patient informed consent/patient approval for the retrospective collection of medical record data will be followed. We anticipate that no patient informed consent will be required in some countries, whereas in others (e.g., France, Germany), a verbal or written informed consent will be required from eligible patients to access their medical records or from relatives (of deceased patients), or each participating physician depending on local laws and regulations.

The study protocol and consent form, where required, will be submitted to the IRB or independent ethics committee for review and approval (as required) according to the guidance of each country's research ethics requirements.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS / ADVERSE REACTIONS

Based on current guidelines from the International Society for Pharmacoepidemiology (ISPE) (ISPE, 2007) (Section VI) and the EMA Guideline on Good Pharmacovigilance Practices: Module VI – Management and Reporting of Adverse Reactions to Medicinal Products (EMA, 2012) (Section VI:C.1.2.1 Module VI), non-interventional 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 adverse events or reactions.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study protocol, and final study report will be included in regulatory communications in line with the risk management plan, Periodic Benefit Risk Evaluation Reports (PBRER), and other regulatory milestones and requirements. Study reports will be prepared using a template following the Guideline on Good Pharmacovigilance Practices (GVP): Module VIII Section B.6.3 (EMA, 2013).

Study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors (ICMJE, 2014). Communication in appropriate scientific venues (e.g., ISPE) will be considered. When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be followed (von Elm et al., 2008).

13. OTHER GOOD RESEARCH PRACTICE

This study adheres to the Guidelines for Good Pharmacoepidemiology Practices (GPP) (ISPE, 2007) and has been designed in line with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (ENCePP, 2014). The ENCePP Checklist for Study Protocols (ENCePP, 2013a) has been completed (see Appendix 2).

The study is a post-authorisation safety study (PASS) and will comply with the definition of the non-interventional (observational) study referred to in the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use tripartite guideline Pharmacovigilance Planning E2E (ICH, 2004) and provided in the EMA Guideline on GVP Module VIII: Post-Authorisation Safety Studies (EMA, 2013), and with the 2012 EU pharmacovigilance legislation, adopted June 19, 2012 (European Commission, 2012). The study will comply with the study-reporting requirements specified in Module VIII section VIII.B.6.3.1. “Progress Reports” and VIII.B.6.3.2. “Final Study Report” of the Guideline on Good Pharmacovigilance Practices (EMA, 2013).

The study will be registered in the EU PAS Register (ENCePP, 2015) before the start of data collection.

14. REFERENCES

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Appendix 1: LIST OF STAND-ALONE DOCUMENTS

None.

Appendix 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMEA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. 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 question 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.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Ivabradine Drug Utilisation Study in Select European Countries: A Multinational, Retrospective, Observational Study to Assess Effectiveness of Risk-Minimisation Measures

Study reference number:
Product reference: EMEA/H/C/597-598-4187

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	☒	☐	☐	12
1.1.2 End of data collection[3]	☒	☐	☐	12
1.1.3 Study progress report(s)	☒	☐	☐	12
1.1.4 Interim progress report(s)	☒	☐	☐	12
1.1.5 Registration in the EU PAS Register	☒	☐	☐	12
1.1.6 Final report of study results	☒	☐	☐	12

Comments:

The protocol will be registered following European Medicines Agency endorsement and prior to start of data collection

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 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)	☒	☐	☐	13-14
2.1.2 The objectives of the study?	☒	☐	☐	14
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	14
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 if applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

This is a drug utilisation study; no hypotheses will be tested.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	14-18
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	22
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)	☐	☐	☒	

Comments:

This is a drug utilisation study; no effect will be measured.

[3] Date from which the analytical dataset is completely available.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	18-23
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	18-23
4.2.2 Age and sex?	☒	☐	☐	18-23
4.2.3 Country of origin?	☒	☐	☐	18-23
4.2.4 Disease/indication?	☒	☐	☐	18-23
4.2.5 Co-morbidity?	☒	☐	☐	18-23
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	18-21

Comments:

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)	☒	☐	☐	21-22
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)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

This is a drug utilisation study; no biological effect will be measured, and validity testing of exposure will not be performed.

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?	☐	☐	☒	
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:

This is a drug utilisation study; no endpoints will be assessed.

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

This is a drug utilisation study; no effects will be measured, and confounding will not be assessed.

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	18-23
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☐	☐	☒	
8.1.3 Covariates?	☐	☐	☒	
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	18-23
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

This is a drug utilisation study with secondary data collection.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	23-25

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	25-26
10.3 Are descriptive analyses included?	☒	☐	☐	25-26
10.4 Are stratified analyses included?	☒	☐	☐	25-26
10.5 Does the plan describe the methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

This is a drug utilisation study; no effects or effect modification will be measured, and confounding will not be assessed.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☐	☒	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	25-27
11.3 Are methods of quality assurance described?	☒	☐	☐	26-27
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	26-27
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	26-27

Comments:

This is a drug utilisation study with secondary data collection.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	26-27
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	26-27
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	18-25
12.3 Does the protocol address other limitations?	☒	☐	☐	26-27

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/ Institutional Review Board approval been described?	☒	☐	☐	28

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	28
13.3 Have data protection requirements been described?	☒	☐	☐	28

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	10-11

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	28
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	28

Comments:

Name of the main author of the protocol: Emmanuelle Jacquot, MD

Date: 28/Apr/2016

Signature:

Appendix 3: PILOT STUDY REPORT