Study Protocol

Drug utilization study of mirabegron (Betmiga®) using real-world healthcare databases from the Netherlands, Spain, United Kingdom and Finland

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PHARMO Institute in collaboration with SIDIAP, CPRD and EPID Research

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PASS information

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Research question and objectives	The objectives of the study are to assess the effectiveness of the Direct Healthcare Professional Communication (DHPC) letter as a risk minimization measure in the participating countries by quantifying the proportions of mirabegron initiators with documented severe uncontrolled hypertension (primary objective) and the frequency of blood pressure recordings at baseline and during mirabegron treatment, especially in hypertensive patients (secondary objective) before and after DHPC dissemination.
Countries of study	The Netherlands, Spain, United Kingdom, Finland
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2 List of used abbreviations

ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BNF	British National Formulary
CCMO	Centrale Commissie Mensgebonden Onderzoek
CHMP	Committee for Medicinal Products for Human Use
CKD	Chronic Kidney Disease
CPRD	Clinical Practice Research Datalink
DBP	Diastolic Blood Pressure
DDD	Defined Daily Dose
DHPC	Direct Healthcare Professional Communication
DUS	Drug Utilization Study
EMA	European Medicines Agency
EMR	Electronic Medical Record
GP	General Practitioner
HUS	Hospital District of Helsinki and Uusimaa
ICD	International Classification of Diseases
ID	Social Security Number
IQR	Interquartile Range
MAH	Marketing-Authorisation Holder
MI	Myocardial Infarction
OAB	Over Active Bladder
PAD	Peripheral Artery Disease
PAS	Post-Authorisation Studies
PDD	Prescribed Daily Dose
PRAC	Pharmacovigilance Risk Assessment Committee
SD	Standard Deviation
SBP	Systolic Blood Pressure
SIDIAP	Sistema d' Informació per al Desenvolupament de la Investigació en Atenció Primària
SPAT	Suomalainen perusterveydenhuollon avohoidon toimintoluokitus
UK	United Kingdom
WHO	World Health Organization
WMO	Wet medisch-wetenschappelijk onderzoek met mensen

3 Responsible parties

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4 Abstract

Title: Drug utilization study of mirabegron (Betmiga®) using real-world healthcare databases from the Netherlands, Spain, United Kingdom and Finland.

Rationale and background: The mirabegron (Betmiga®) Summary of Product Characteristics (SmPC) states that the drug is contraindicated in patients with "Severe uncontrolled hypertension defined as systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg". In accordance and compliance with the European Medicines Agencies (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) request, a Direct Healthcare Professional Communication (DHPC) letter was disseminated on 7 September 2015 as a risk minimization activity in 30 countries in EU. In line with the EMA CHMP guideline Module IX, an effectiveness check of this risk minimization activity was proposed by Astellas. A drug utilization study (DUS) on the use of mirabegron in the Netherlands, Spain, United Kingdom and Finland will be performed as a risk minimization effectiveness check measure.

Research question and objectives: The objectives of the study are to assess the effectiveness of the Direct Healthcare Professional Communication (DHPC) letter as a risk minimization measure in the participating countries by quantifying the proportions of mirabegron initiators with documented severe uncontrolled hypertension (primary objective) and the frequency of blood pressure recordings at baseline and during mirabegron treatment, especially in hypertensive patients (secondary objective) before and after DHPC dissemination.

Study design: An observational retrospective cohort study among patients initiating mirabegron (Betmiga®) treatment using real-world data from the Netherlands, Spain, the United Kingdom and Finland will be performed. The study will compare the time periods relative to the DHPC letter dissemination.

Population: Mirabegron initiators during the years 2012-2016 will be selected from the databases by prescriptions of mirabegron (ATC code G04BD12) since first authorisation (20 December 2012) and until end of data availability (31 December 2016). The date of the first mirabegron prescription will be the index date. A baseline period of 12 months preceding the index date will be defined to capture information on blood pressure and hypertension before the index date. Users with less than 12 months recorded history in the database prior to the index date will be excluded. No other exclusion criteria apply.

Variables: Patient characteristics will be assessed at the index date. Diagnoses of and treatment for hypertension and values of recorded diastolic and systolic blood pressure (DBP

and SBP) measurements will be assessed during the 6 months preceding the index date in order to assign hypertension status at index date. The frequency of blood pressure recordings will be assessed before initiation of and during mirabegron treatment among initiators with hypertension at index date and also among initiators without hypertension in order to allow interpretation of the data.

Data sources: The study will be conducted utilizing the PHARMO Database Network (PHARMO) from The Netherlands, the Sistema d' Informació per al Desenvolupament de la Investigació en Atenció Primària database (SIDIAP) from Catalonia (Spain), the Clinical Practice Research Datalink (CPRD) from the United Kingdom and the National registers and electronic medical record (EMR) data from Finland.

Study size: In preliminary analyses, about 3,000 mirabegron users were identified in the PHARMO GP Database up to December 2014; over 7,000 users in SIDIAP up to December 2014; 12,000 users in CPRD up to April 2016; and altogether 20,000 users in Finland during the year 2015 with about 4,000 in the Helsinki-Vantaa-Espoo area where blood pressure information from EMR data will be collected.

Data analysis: Patient characteristics and outcomes will be reported descriptively. Categorical data will be presented as counts (n) and proportions (%). Continuous data will be presented as means with standard deviation (SD) and as medians with interquartile range (IQR), when appropriate. To determine the duration of mirabegron usage, prescriptions of mirabegron between index date and end of follow-up will be converted into treatment episodes of uninterrupted use. Results will be presented pre- and post-DHPC letter dissemination period and in specified time intervals before and after dissemination, taking the dissemination date of 7 September 2015 as the reference date. An interrupted time series approach will be applied to estimate incremental changes in the distributions of hypertension status among mirabegron initiators over time relative to the DHPC letter dissemination. The frequency of blood pressure recordings will be compared before and after DHPC dissemination.

Milestones: Data for 2016 will become available in Q2 2017 for SIDIAP and CPRD and in Q3-Q4 2017 for PHARMO and EPID. An interim report will be delivered in September 2017 including results from PHARMO up to 2015 and SIDIAP and CPRD up to 2016 (not EPID). The final report will include data up to 2016 for all databases and will be delivered in December 2017.

5 Amendments and updates

None, this is the first version.

6 Milestones

Table 1: Milestones

Milestone	Planned date
Study Protocol - first draft for investigators (prepared by PHARMO)	05 September 2016
Study Protocol - investigator feedback	22 September 2016
Study Protocol - first draft, to Astellas	29 September 2016
Study Protocol - Astellas feedback	13 October 2016
Study Protocol - second draft for investigators	07 November 2016
Study Protocol - investigator feedback	09 November 2016
Study Protocol - second draft, to Astellas	11 November 2016
Study Protocol - Astellas feedback	19 November 2016
Study Protocol – final for Astellas PAC review	23 November 2016
Study Protocol - feedback to Astellas PAC	18 January 2017
Study Protocol - approved by Astellas PAC	24 January 2017
Registration in the EU PAS register	24 January 2017
Table shells - first draft for investigators (prepared by PHARMO)	18 January 2017
Table shells - investigator feedback	01 February 2017
Table shells – final	04 February 2017
Data dictionary	04 February 2017
Start of data collection (interim) *	04 February 2017
Database-specific Interim reports - draft to PHARMO ***	28 June 2017
Database-specific Interim reports - PHARMO feedback ***	12 July 2017
Database-specific Interim reports - final	26 July 2017
Interim Report - first draft for investigators (prepared by PHARMO)	02 August 2017
Interim Report - investigator feedback	19 August 2017
Interim Report - first draft, to Astellas	26 August 2017
Interim Report - Astellas feedback	09 September 2017
Interim Report - final	16 September 2017
Start of data collection (final) *	25 June 2017
End of data collection**	22 November 2017
Database-specific final reports - draft to PHARMO ***	13 December 2017
Database-specific final reports - PHARMO feedback ***	20 December 2017
Database-specific final reports - final	27 December 2017
Final Report - first draft for investigators (prepared by PHARMO)	17 November 2017
Final Report - investigator feedback	04 December 2017
Final Report - first draft, to Astellas*	11 December 2017
Final Report - Astellas feedback	25 December 2017
Final Report	01 January 2018
Dissemination (manuscript & abstract): to be planned	

* the date from which data extraction starts (see Module VIII of the GVP[1])

** the date from which the analytical dataset is completely available (see Module VIII of the GVP[1])

*** delivery of the last report, as databases differ in timelines

7 Rationale and background

Mirabegron (European brand name Betmiga®) (25 mg and 50 mg prolonged-release tablets) is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urinary incontinence, urgency, and urinary frequency. In clinical trials, a modest increment of pulse rate and blood pressure was observed[2] and therefore the mirabegron Summary of Product Characteristics (last updated in April 2016) states that, "Mirabegron can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with Betmiga, especially in hypertensive patients" and that use is contraindicated for patients with "Severe uncontrolled hypertension defined as systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg"[3].

The new recommendations followed a review by the European Medicines Agency (EMA) of cumulative data associated with mirabegron and increased blood pressure. Serious cases of hypertension and increased blood pressure have been reported in patients on mirabegron treatment[2].

In accordance and compliance with the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) request, a Direct Healthcare Professional Communication (DHPC) letter was disseminated as a risk minimization activity in 30 countries in EU, where Astellas is marketing-authorisation holder (MAH), on or before 7 September 2015. This DHPC letter contains the contra-indication for use in patients with severe uncontrolled hypertension as well as a recommendation to measure blood pressure prior to start of mirabegron and regularly during use of mirabegron, especially in hypertensive patients. According to the EMA CHMP guideline Module IX, an effectiveness check of the risk minimization activity, DHPC dissemination in this case, is subsequently required.

Astellas requested the PHARMO Institute to perform this effectiveness check of the risk minimization activity in multiple countries in Europe, This Study Protocol describes the patient selection and methods, including definitions and analyses, for a multi-database study in the Netherlands, Spain, the United Kingdom and Finland.

8 Research questions and objectives

The objectives of the study are to assess the effectiveness of the Direct Healthcare Professional Communication (DHPC) letter as a risk minimization measure in the participating countries by quantifying the proportions of mirabegron initiators with documented severe uncontrolled hypertension (primary objective) and the frequency of blood pressure recordings at baseline and during mirabegron treatment, especially in hypertensive patients (secondary objective) before and after DHPC dissemination.

For the primary objective we will assess whether the proportions of mirabegron initiators with documented hypertension (severe uncontrolled hypertension but also controlled hypertension or non-severe uncontrolled hypertension) differ between the time periods before and after DHPC dissemination. To answer the research question we will asses, among mirabegron initiators from each database:

- the proportion of users with severe uncontrolled hypertension
- the proportion of users with non-severe uncontrolled hypertension
- the proportion of users with controlled hypertension

For the secondary objective we will asses whether the frequency of blood pressure recordings at initiation and during mirabegron treatment among initiators with documented hypertension at index date differ between the time periods before and after DHPC dissemination. To answer the research question we will assess, among all mirabegron initiators:

- the proportion of users with a blood pressure recording during the 6 months preceding and including the index date
- the frequency of blood pressure recordings during mirabegron treatment

This will be reported separately for users with and without hypertension at index date.
These assessments will be performed pre- and post-DHPC dissemination (7 September 2015).

9 Research methods

9.1 Study design

Retrospective cohort study.

9.2 Setting

The source population will include all individuals aged ≥18 years and registered in the databases receiving mirabegron (ATC G04BD12) between 20 December 2012 (first authorisation) and 31 December 2016 (end of data availability). The date of receiving the first prescription of mirabegron will be defined as the index date.

A baseline period of 12 months preceding the index date will be defined:

- to ensure that patients have no evidence of mirabegron use before the index date
- to capture information on blood pressure and hypertension before the index date

The study population will include all users with at least 12 months recorded history in the database prior to the index date. No other inclusion or exclusion criteria apply.

Patients will be followed from 12 months before index date until the earliest of 1) end of mirabegron treatment (see section 9.3.2), 2) transfer out of the database (death or end of database follow-up available/censoring) or 3) end of study period (this is the "study follow-up"). Assessments will be performed on the pre- and post-DHPC dissemination period and in specified time intervals, taking the dissemination date of 7 September 2015 as the reference date (see section 9.3.4).

9.3 Variables

9.3.1 Patient characteristics

The following general characteristics will be assessed at the index date:

- Age, calculated as year of index minus year of birth (in years, categorized, mean (± standard deviation (SD)), median (interquartile range (IQR)))
- Gender (male, female)
- Database follow-up available after the index date (in months, categorized, mean (± SD), median (IQR))
- Duration of uninterrupted use of mirabegron following the index date (in months, categorized and median (IQR)) (see section 9.3.2)
- Duration of use of mirabegron following the index date, including interruptions shorter than 12 months (in months, categorized and median (IQR)) (see section 9.3.2)

The following lifestyle characteristics and conditions will be assessed during the 12 months preceding the index date (baseline period):

- Smoking
- Obesity
- Chronic respiratory disease
- Diabetes
- Hyperlipidaemia

The following events and conditions will be assessed ever before index date (or as long before as data is available):

- Acute myocardial infarction (MI)I
- Ischemic heart diseases (excl. MI)
- Cardiac arrhythmias
- Congestive heart failure
- Cerebrovascular events
- Chronic kidney disease (CKD)
- Peripheral artery disease (PAD)

Age (year of birth), gender, duration of follow-up and duration of use are always filled. Smoking and obesity are expected to be underreported in the databases. Diagnoses of comorbidities may also be missing. When a characteristic is not recorded in the database, it cannot be determined whether it was not present or whether it was not recorded.

Chronic respiratory disease, diabetes and hyperlipidaemia will be identified by diagnoses as well as drug treatment.

Patient characteristics will be presented pre- and post-DHPC dissemination and quarterly.

9.3.2 Mirabegron exposure

Mirabegron initiators will be patients with no documented evidence of Mirabegron use in the 12 months preceding the index date (baseline period). Mirabegron exposure will be assessed by GP prescriptions in PHARMO, by community pharmacy dispensings in SIDIAP, by GP prescriptions in CPRD and by community pharmacy dispensings in Finland. Hereafter, all are referred to as “prescriptions”. Prescriptions of mirabegron from index date until end of database follow-up will be converted into treatment episodes of uninterrupted use.

First, the duration of each mirabegron prescription will be calculated by dividing the number of units prescribed by the number of units to be used per day (prescribed daily dose, PDD). If the PDD is not available from the prescription record, the defined daily dose (assumed average maintenance dose per day for a drug used for its main indication in adults, DDD) is

used instead. The DDD for mirabegron, according to the WHO Collaborating Centre for Drug Statistics Methodology [4], is 50 mg.

In case of an interruption between two prescriptions, use of the drug will be considered uninterrupted if the duration of this gap is less than half the period of the prescription preceding the gap, or seven days, whichever is greater, according to the method of Catalan [5]. Otherwise, use of the drug will be considered interrupted and the treatment episode ended. The end date of an episode includes the permissible gap following the final prescription within that episode.

The end date of mirabegron treatment will be defined as the end date of an episode after which no mirabegron exposure is observed for at least 12 months. Patients with multiple episode of use of mirabegron interrupted by at least 12 months will be included as initiators multiple times. See also Figure 9.3.

9.3.3 Blood pressure and hypertension

Information about hypertension and its severity at index date is available from diagnoses of or treatment for hypertension as well as from blood pressure measurements as recorded in medical records. Hypertension status at index date will be defined from recorded diagnoses any time before and including the index date and from information on blood pressure levels and antihypertensive treatment extracted from the databases during the baseline period and on the index date;

- A diagnosis of hypertension can be identified any time before and on the index date and is valid from the date of recording and identified by diagnosis codes as listed in Annex 3. Codes for hypertension or free text search terms (PHARMO). All types of hypertension are included. The diagnosis is valid until normal blood pressure in the absence of treatment is observed.
- Treatment of hypertension is assessed per prescription date (not by episodes as will be done for mirabegron exposure) and will be assessed during the 6 months preceding and including the index date. A prescription is valid for its duration (i.e. prescriptions will be included when either the prescription date or end of the duration is within 6 months before the index date) and is identified by prescription of drugs with codes as listed in Annex 4. Drug codes for antihypertensives. The duration of a prescription will be calculated by dividing the number of units prescribed by the number of units to be used per day (prescribed daily dose, PDD) or, if the PDD is not available from the prescription record, the DDD is used instead (see section 9.3.2). In the absence of a diagnosis for hypertension, at least two distinct antihypertensives should be prescribed within the 6 months preceding the

index date to qualify as antihypertensive treatment, to reduce the likelihood that antihypertensive drugs are prescribed for other indications.

- The most recent blood pressure value during the 6 months preceding and including the index date will be valid if no new antihypertensive prescription is observed between the measurement and the index date.

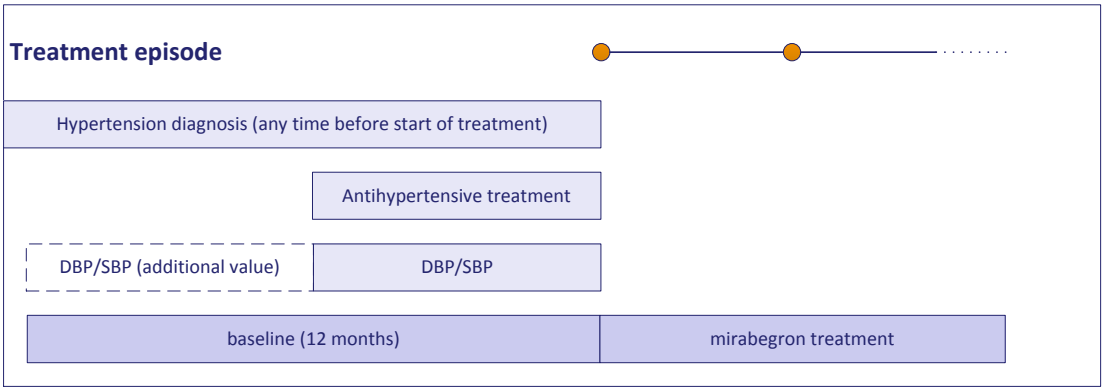

Figure 9.1: Assessment of hypertension diagnoses, treatment and measurements

Normal blood pressure will be defined as DBP < 90 mm Hg and SBP <140 mm Hg in the absence of treatment for hypertension. When no blood pressure value, diagnosis or treatment is recorded, it is assumed that the value was also normal. The rationale for this assumption is that physicians tend to record the abnormal values rather that the normal values in daily practice.

Hypertension will be defined as DBP ≥ 90 mm Hg or SBP ≥140 mm Hg.

The definitions of normal blood pressure, controlled/uncontrolled hypertension and severity of uncontrolled hypertension are based on the combination of diagnosis, treatment and blood pressure and are presented in Figure 9.2.

- Hypertension status unknown: a previous diagnosis of or current treatment for hypertension but no blood pressure value
- Controlled hypertension: DBP < 90 mm Hg and SBP <140 mm Hg during treatment for hypertension
- Non-severe uncontrolled hypertension: DBP ≥ 90 - <110 mm Hg or SBP ≥140 - <180 mm Hg regardless of diagnosis or treatment
- Severe uncontrolled hypertension: DBP ≥ 110 mm Hg or SBP ≥180 mm Hg regardless of diagnosis or treatment

The reference values for hypertension are based on the European product information[3], local guidelines[6-8] and instructions for use[9] and are the same in the participating countries.

	Recorded diagnosis of hypertension			
	yes		No	
	Antihypertensive treatment		**Antihypertensive treatment**	
Blood pressure	yes	no	yes	No
Unknown	Hypertension status unknown	Hypertension status unknown	Hypertension status unknown	Normal blood pressure
DBP <90 mm Hg and SBP <140 mm Hg	Controlled hypertension	Normal blood pressure	Controlled hypertension	Normal blood pressure
DBP ≥90-<110 mm Hg or SBP ≥ 140-<180	Non-severe uncontrolled hypertension	Non-severe uncontrolled hypertension	Non-severe uncontrolled hypertension	Non-severe uncontrolled hypertension*
DBP ≥110 mm Hg or SBP ≥180 mm Hg	Severe uncontrolled hypertension	Severe uncontrolled hypertension	Severe uncontrolled hypertension	Severe uncontrolled hypertension*

*Patients in these categories need to have at least two subsequent abnormal blood pressure values (on different dates but no more than 6 months apart.

Figure 9.2: Definitions of normal blood pressure and (severity of) hypertension

In the absence of a prior diagnosis of or current treatment for hypertension, an additional abnormal blood pressure value should be observed in order to be classified as hypertensive. Relative to an abnormal value observed during the 6 months preceding and including the index date, this additional value should be recorded not more than 6 months earlier and with no normal values in between:

- If only one value is recorded a user is classified as:
  - Normal blood pressure when DBP < 90 mm Hg and SBP <140 mm Hg
  - Hypertension status unknown when DBP ≥ 90 mm Hg or SBP ≥140 mm Hg
- If multiple values are recorded a users is classified as:
  - Normal blood pressure when only one value is abnormal (DBP ≥ 90 mm Hg or SBP ≥140 mm Hg)
  - Non-severe uncontrolled hypertension when at least two values are abnormal (DBP ≥ 90 mm Hg or SBP ≥140 mm Hg) and the most recent value is DBP < 110 mm Hg and SBP <180 mm Hg
  - Severe uncontrolled hypertension when at least two values are abnormal and the most recent value is DBP ≥ 110 mm Hg or SBP ≥180 mm Hg

9.3.4 Outcomes

The analysis will be performed on the pre- and post-DHPC dissemination period, taking the dissemination date of 7 September 2015 as the reference date. Because some lag time is

expected after the DHPC dissemination, September 2015 will be taken as the intervention period. Time intervals for analysis will be defined before and after September 2015 and as defined in section 9.7. For each time interval, the hypertension status of patients initiating mirabegron during that interval will be assessed.

For the primary outcome, the proportion of mirabegron initiators with normal blood pressure, controlled hypertension, non-severe uncontrolled hypertension, severe uncontrolled hypertension or unknown hypertension status at index date will be assessed pre- and post-DHPC dissemination and quarterly.

For the secondary outcome, the number of blood pressure recordings before initiation of and during mirabegron treatment (including the time during treatment gaps <12 months) will be explored among mirabegron initiators with any hypertension and also separately among initiators with controlled hypertension, non-severe uncontrolled hypertension or severe uncontrolled hypertension. For the definition of duration of mirabegron treatment and the assessment of blood pressure recordings see Figure 9.3. The number of blood pressure recordings will also be assessed among initiators with normal blood pressure at index date, in order to allow interpretation of the data. The number of blood pressure recordings will be assessed pre- and post-DHPC dissemination.

9.4 Data sources

The study will be conducted in four databases: the PHARMO Database Network (PHARMO) in The Netherlands, the Sistema d' Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) database in Catalonia (Spain), the Clinical Practice Research Datalink (CPRD) in the United Kingdom and the national registers and electronic medical record (EMR) data from Finland (lead by EPID). These are existing electronic databases and have also been used in previous studies registered in the EU PAS register [10].

9.4.1 PHARMO GP Database (Netherlands)

Data will be used from the General Practitioner (GP) Database of the PHARMO Database Network. This database comprises data from electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists and healthcare product/drug prescriptions. The prescription records include information on type of product, date, strength, dosage regimen, quantity and route of administration. Drug prescriptions are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System (WHO Anatomical Therapeutic Chemical Classification System [4]). Diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC) (International Classification of Primary Care [11]), which

can be mapped to ICD codes, but can also be entered as free text. GP data cover a catchment area representing 2.5 million residents.

9.4.2 SIDIAP database (Spain)

The SIDIAP database (Sistema d' Informació per al Desenvolupament de la Investigació en Atenció Primària) includes the information coded by GPs using ICD-10 codes and some structured forms for registering common clinical variables (smoking, alcohol drinking, body mass index, blood pressure, etc.), and linked pharmacy invoice data from the official reimbursement database.

SIDIAP has been collecting data from 2000 (research usable data from 2006 onwards), and the database is updated on an annual basis. Currently data are available up to end 2015. The SIDIAP database is comprised of electronic medical records of a representative sample of patients attended by GPs in Catalonia (North-East Spain), covering a population of more than 5.8 million active patients (approximately 80% of the total of 7.5 million population of Catalonia).

9.4.3 CPRD database (United Kingdom)

Primary care data for patients in the United Kingdom will be sourced from the Clinical Practice Research Datalink (CPRD). CPRD primary care data are collected anonymously from the electronic medical records of contributing GPs. The records include clinical events (coded using Read codes) including symptoms and diagnoses, laboratory tests and referrals to specialists, and prescription events (coded using Gemscript codes). The prescription records include information on the type of product, date of prescription, strength, dosage, quantity and route of administration. CPRD have traditionally collected data from GPs using the Vision software system, but are now additionally able to collect and analyse data from practices using the EMIS system. This study will be the first ever to use Vision and EMIS data in combination for an investigation of drug utilisation. Data is available for over 20 million patients, including over 5.2 million currently registered patients.

9.4.4 National registers and EMR data (Finland)

Finnish data are accessed and managed by EPID Research. The data sources include the nationwide the electronic e-Prescription Register (drug exposure data), Care Register for Health Care (in- and outpatient hospital care data), Register of Primary Health Care Visits (primary care data), Population Register Centre (place of residence, migration information) and Causes of Death Registry (time of death) in Finland. The e-Prescription Register was introduced in Finland in April 2013. In the beginning the coverage was 50 % but since 2014 it has been close to 100 % (outpatient use). Due to this, some data on mirabegron users during 2013 might be missing. The e-Prescription Register does not cover drugs used in some

institutions and elderly homes or during hospitalizations. The coverage of the other national registers utilized in this study is close to 100%. Through national registers data on treatment (ATC codes), diagnoses (ICD-10 codes) and hospitalisations can be collected. In addition to national registers, healthcare data from electronic medical record (EMR) databases will be accessed.

Baseline data (age, gender, diagnoses and medical treatment) is available for all mirabegron users in nationwide registers. The information on blood pressure measurements will be gathered from local EMR databases for the mirabegron users included in the study. The primary option is to include mirabegron user in cities of Helsinki, Espoo, and Vantaa as well as the Hospital District of Helsinki and Uusimaa (HUS). The national registers cover the total population of Finland (5.4 million). The Helsinki-Vantaa-Espoo region will provide the EMR information of about 20% of the population, i.e. 1 million.

Approval of Ethical Review Board of Hospital District of Helsinki and Uusimaa will be requested to cover the nationwide study. Data permits will be requested from each registry holder based on the study protocol and ethical approval. If the ethical approval is not received EPID Research will not proceed with the permit process, and the study is considered to be ceased. Neither can the study be completed if one of the national register holders dismisses a permit application.

9.5 Study size

In preliminary analyses about 3,000 users were identified in the PHARMO GP Database up to December 2014, over 7,000 users in SIDIAP up to December 2014, 12,000 users in CPRD up to April 2016 and altogether 20,000 users in Finland during the year 2015, with about 4,000 in the Helsinki-Vantaa-Espoo area where blood pressure information from EMR data will be collected.

9.6 Data management

9.6.1 PHARMO Database Network (Netherlands)

The PHARMO Database Network combines data from different healthcare databases (pharmacy, hospital, GP etc.). These different databases are probabilistically linked through validated algorithms that do not invade the privacy of the patients. Before linkage of the different databases, patients for whom crucial information needed for linkage is missing (date of birth, gender, GP) are removed. When only one database is used, such as the GP Database in this study, these variables are required to be complete.

Healthcare databases are used as administration tools in patient care and have their limitations with regard to their use in scientific research. For example, the completeness of

data may differ per healthcare centre. Therefore, with each update of the database the completeness of registration per healthcare centre is evaluated (overall and within specific care areas, number of records, internal consistency and comparison of calendar years).

For each study, specific study checks on the data are performed. Per patient it is determined from which time point onwards the patient is registered in the database and from which time point the patient is lost to follow-up (due to for example death or moving out of the database catchment area). Patients are regarded eligible to be included in a study if they are registered and can be followed in the database.

Study data are processed and analysed using the utility SAS Enterprise Guide, an environment for SAS enabling the storage of syntaxes or codes belonging to a single study in one project file, subdivided into project flows for different aspects of a study.

9.6.2 SIDIAP database (Spain)

The SIDIAP Database contains data recorded in primary care electronic medical records from >300 practices around Catalonia. All these practices use the same EMR software (e-CAP), and participating staff (admin, GPs and nurses) receive similar training on the correct use of the software for optimal coding regarding clinical management of their patients.

For each study, the local investigator/s (DPA in this case) meet with the SIDIAP data managers in order to develop a data specification and extraction protocol based on the common (approved) protocol. Specific data quality checks are performed on a study per study basis. Patients are regarded eligible to be included in a study if they are registered and can be followed in the database.

Study data are processed using SQL and Python by the data management team, and analysed by the investigators, in this particular study using the SAS package.

9.6.3 CPRD database (United Kingdom)

Data from Vision and EMIS practices are collected and processed into separate databases. Patient and practice level quality checks are applied during the initial processing. Patients are flagged as ‘acceptable’ for use in research studies using an algorithm which excludes patients with ill-defined or non-continuous follow up, and missing or inconsistent registration information.

The main practice data quality metric is the ‘up to standard’ (UTS) date, defined as the date after which the practice is considered to have recorded continuous data of sufficiently high quality for use in research. The UTS date is based on two central concepts: assurance of continuity in data recording (gap analysis), and avoidance of use of data for which transferred out and dead patients have been removed (death recording).

Data is accessed using a suite of query and extraction tools developed in-house, or with commercially available software. Further data management and analysis are performed using Stata v14, with all scripts and programs stored to allow quality assurance checks and to ensure reproducibility of all tasks.

9.6.4 National registers and EMR data (Finland)

Data will be applied from national registers and from the data holders of the EMR data. Data holders will identify the study population and collect data based on the individual social security numbers (IDs) of patients. Non-nationwide patient data will be collected via the information service providers. IDs will be converted to study IDs by the data holders. They will then deliver the raw data (with study IDs) to EPID.

EPID Research will be the register holder for the study database and also responsible of destroying the data after the study. All study data and supporting documents will be retained for five years after the report finalization and then destroyed. As the register holder of the study register EPID Research is in charge of deleting the data. Secure archives will be maintained for the orderly storage and retrieval of all study-related material. An index shall be prepared to identify the archived contents and their location. Access to the archives will be controlled and limited to authorised personnel only. Access to the study data cannot be given to any third parties, nor can the study data be used for other purposes than described in this protocol. All requests to use the study data for other purposes than mentioned in this study protocol must be subjected to appropriate data permit processes.

9.7 Data analysis

Each investigator centre will extract the relevant data for the study and convert this to a study-specific common data model. Research file preparation and data analysis will be programmed in SAS by PHARMO and these programs will be shared for local analysis. Results tables will be sent back to PHARMO for incorporation into the study report.

9.7.1 Descriptive statistics

Patient characteristics and outcomes will be reported descriptively in tables and figures. Categorical data will be presented as counts (n) and proportions (%). Proportions of patients assigned to each hypertension status will be reported with 95% confidence intervals. Continuous data will be presented as means with standard deviation (SD) (age) or as medians with inter quartile range (IQR) (duration of follow-up after index date, duration of uninterrupted use of mirabegron).

Patient characteristics and hypertension status at index date of included and excluded mirabegron users (i.e. with less than 12 months history before the index date) will be listed in an appendix table.

Results on groups with less than 5 individuals will not be reported in order to protect the confidentiality and privacy of individuals.

9.7.2 Primary objective

The DHCP letter was disseminated on 7 September 2015. The analysis pre- and post dissemination will take this date as the intervention date. Besides a pre- and post dissemination analysis, incremental changes over time will be assessed using the aggregated data per quarter (January-March, April-June, July-September and October-December).

To estimate incremental changes in response to the DHPC letter in the proportion of mirabegron initiators with normal blood pressure, controlled hypertension, non-severe uncontrolled hypertension and severe uncontrolled hypertension at index date (primary objective), an interrupted time series approach [12, 13] (ITS) will be applied on the respective proportions in each quarter. A segmented linear regression model will be applied for ITS, which will indicate possible changes in the trend (slope) of the proportions of patients with specific hypertension status before and after DHPC dissemination, and whether or not there was a change in the proportion of these patients immediately after the DHPC letter.

In order to take into account temporal changes in the age and sex distribution of the population, we will model aggregated data points in the form of age and sex standardized quarterly proportions using segmented linear regression [14].For ease of interpretation, we will express regression coefficients for level and slope in the form of a single estimate of absolute change between estimated post-DHPC values and their counterfactual values [14, 15]; i.e., estimates for the same time point but based on pre-DHPC level and trend only.

The pre- DHPC period spans the period from start of mirabegron use up to September 2015, subdivided into quarters. No intervention period will be applied, so the post- DHPC period will span the period from October 2015 through December 2016.

Other covariates that might be considered explanatory for any possible trends, proportions or changes thereof (such as antihypertensive treatment) will not be included in the segmented regression model, as they are likely to diminish the statistical significance of any observed changes in trends before and after DHPC dissemination as well as any observed change in proportions at the time of DHPC dissemination.

Specific details of the modelling of the interrupted time series analysis depend on the granularity of the data: the number of pre-and post-DHPC aggregated data points will

depend on the uptake of the drug in each country, and whether the data suggest the first patients to receive mirabegron are selective severe patients that are not representative and might need to be excluded from the analysis. Also, categorization of the aggregated time points (in quarters, or shorter or longer time periods) may change depending on the number of subjects observed for each time point.

All assumptions for the ITS analyses will be checked to help interpretation of the results, but will not determine whether or not the analysis will be performed.

9.7.3 Secondary objective

The frequency of blood pressure recordings will be assessed before initiation of and during mirabegron treatment (see section 9.3.4). Blood pressure recordings at or before index date (up to 6 months) will be reported separately from the recordings during treatment. Treatment episodes including the DHPC dissemination will be split into pre- and post DHPC dissemination and the frequency of blood pressure recordings will be assessed accordingly.

The number of recordings will be assessed per person-month of treatment and the values before and after DHPC dissemination will be compared using a two sample t-test if the data are normally distributed according to the Kruskal-Wallis test or a Wilcoxon-Mann-Witney test if the data are not normally distributed.

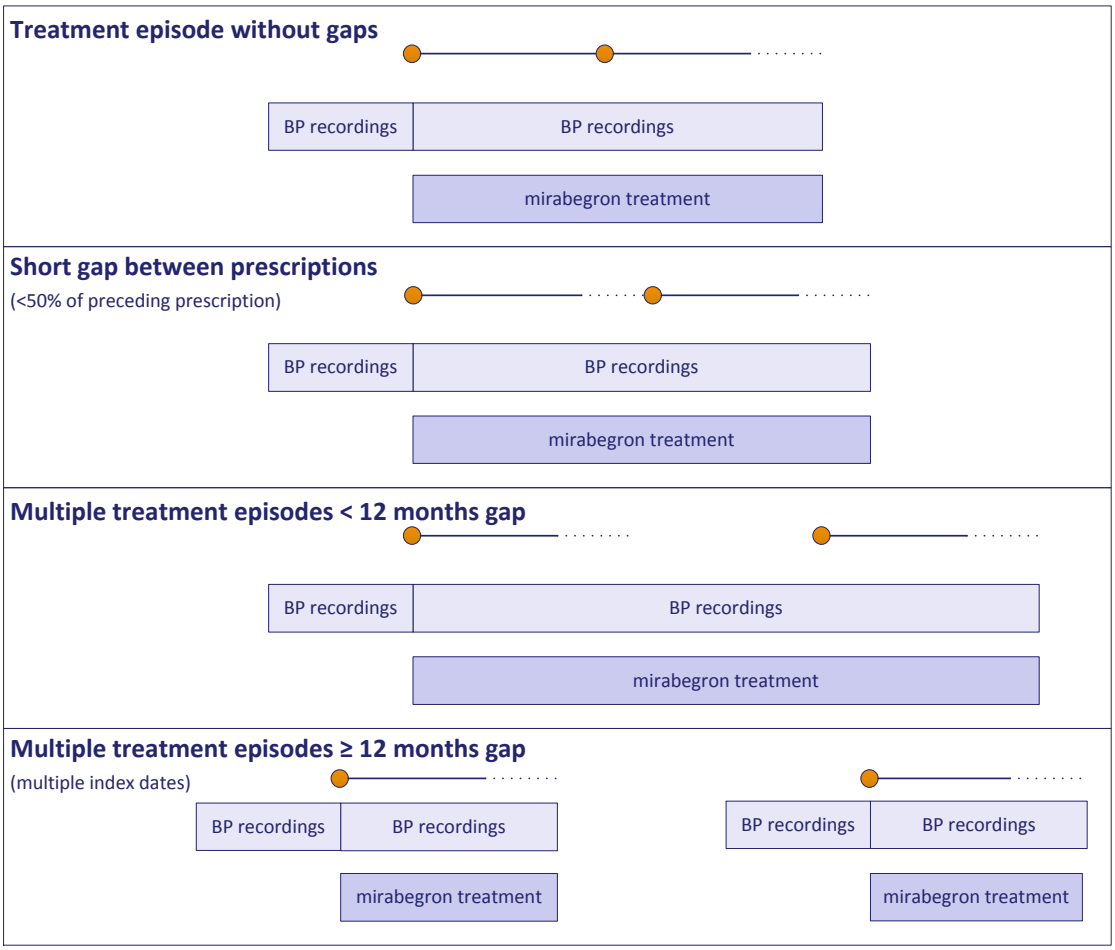

Figure 9.3: Assessment of blood pressure recordings before and during mirabegron treatment

9.7.4 Sensitivity analyses

Sensitivity analyses will be performed on the assumption that when no blood pressure was available the value was actually normal in the absence of a hypertension diagnosis and antihypertensive treatment. In these analyses, patients with no blood pressure value will be 1) categorized as hypertension status unknown or 2) removed from the analysis.

A sensitivity analysis will also be performed on potential differences between early users of mirabegron (shortly after launch) and later users. In this analysis, the time series analysis will exclude the earliest data points to see if this affects the observed trends in the proportions of each hypertension status. The choice of data points for exclusion will depend on the time between start of the study period (launch) and the first prescription record observed in the database.

For the assessment of the number of blood pressure recordings during mirabegron treatment, the time during treatment gaps (which are by definition <12 months) is included (see Figure 9.3). The assumption is that, as the discontinuation is temporary, patients are treated as if they were still exposed. To check this assumption, a sensitivity analysis will be performed ignoring time during gaps.

9.8 Quality control

9.8.1 PHARMO Database Network (Netherlands)

Standard operating procedures 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 and reporting, standards for writing analysis plans, programming and analysis, and requirements for senior scientific review.

All programming written by the executing researcher will be reviewed independently by a senior researcher. All key study documents, such as study reports, will undergo senior scientific review.

9.8.2 SIDIAP database (Spain)

Similar to Pharmo, locally implemented standard operating procedures will be used to guide secure and confidential data storage, as well as for data extraction and management. Data analyses will follow the provided (by Pharmo) analysis plans, programs and SAS analysis code.

All key study documents, including study protocol, data specification documentation, and study reports, will undergo senior scientific review.

9.8.3 CPRD database (United Kingdom)

The standard operating procedures of CPRD will guide the conduct of the study, and will include internal quality audits; following rules for secure storage and backup of confidential data and study documentation; quality control procedures for programming, and requirements for senior scientific review. All patients will be required to have data of acceptable research quality according to each database standards.

9.8.4 National registers and EMR data (Finland)

The study will be conducted as specified in this protocol. All revisions to the protocol must be approved by the sponsor, the principal investigator and the co-authors of the study. All changes to the protocol shall be properly documented as protocol amendments and when necessary such protocol amendments are delivered to register holders.

About storage of records and archiving of the statistical programming performed to generate the results, and possible audits, see section 9.6.4. Due to the study type (register study using administrative databases) on-site monitoring will not be performed.

Unless separately agreed with the client, EPID Research will work according to its internal standard operating procedures. All data management and data-analysis will be written by one statistician and will undergo a quality check by a second statistician. All quality control steps will be documented and written documentation of performed quality control steps will be maintained.

9.9 Limitations of the research methods

Electronic healthcare record information is not primarily collected for research purposes. Regarding the use of mirabegron, 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. Furthermore, databases often do not record the intended duration of use of each prescription (days of supply). This needs to be estimated from the interval between consecutive prescriptions and can result in misclassification of drug exposure.

Smoking and obesity are expected to be underreported in the databases. Diagnoses of other conditions or events may also be missing. When a characteristic is not recorded in the database, it cannot be determined whether it was not present or whether it was not recorded.

Regarding blood pressure and hypertension, missing data is to be expected. In studies focusing on diabetes, for which disease management programs including monitoring of blood pressure are in place, we have seen up to 50% of patients without blood pressure information in a pre-specified time window around prescriptions. For OAB, without a disease management program, at least this proportion of missing information may be expected especially before the DHPC dissemination. Assumptions are made regarding missing information on blood pressure in this study. When no blood pressure value, diagnosis or treatment is recorded, it is assumed that the value was normal, i.e. the patient was not hypertensive. The rationale for this assumption is that physicians tend to record the abnormal values rather that the normal values in daily practice. It may, however, result in misclassification of hypertension status and underestimation of the proportion of mirabegron users with hypertension. The proportion of missing information on blood pressure will be reported for each database and time period.

Because of the consideration above, the focus of the study will be on incremental changes in the data in response to the DHPC letter on a quarterly basis.

9.10 Other aspects

Table 2: Database characteristics

Country	**Netherlands**	**Spain**	**United Kingdom**	**Finland**
Database	PHARMO Database Network	Sistema d' Informació per al Desenvolupament de la Investigació en Atenció Primària	Clinical Practice Research Datalink	National registers and EMR data
Database name (short)	PHARMO	SIDIAP	CPRD	Finland
Source population (millions)	2.5	5.8	5.2	5.4 (1 with EMR data)
Preliminary study size, approximately	3,000 (≤ Dec 2014)	7,000 (≤ Dec 2014)	12,000 (≤ April 2016)	20,000 (≤ Dec 2015) (4,000 with EMR data)

10 Protection of human subjects

The study will be conducted in accordance with Good Pharmacoepidemiology Practices [16] and in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [17]. The ENCePP Checklist for Study Protocols [18] will be completed, and the study will be registered in the ENCePP EU PAS Register [10]. This is a retrospective, non-interventional study and does not pose any risks for patients. All data used for 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.

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

10.1 PHARMO Database Network (Netherlands)

The PHARMO Institute conducts research according to the latest directives regarding privacy and handling of data. The PHARMO Database Network combines data from different sources (pharmacy, hospital, laboratory etc.). Some of these databases are managed in-house and no permissions are required for access to data. For partnership databases, permissions are required for access to data. The various databases are probabilistically linked through validated algorithms that do not invade the privacy of the patients. Researchers only have access to data depleted of sensitive personal information (such as date of birth) that may be traced back to persons and study reports will contain aggregate data only. This approach is approved by the Dutch Data Protection Authority. Because of the use of de-identified data from existing databases without any direct enrolment of subjects, ethical approval or informed consent is not necessary according to the Dutch law regarding human medical scientific research (Wet medisch-wetenschappelijk onderzoek met mensen (WMO)), which is enforced by the Central Committee on Research involving Human Subjects (Centrale Commissie Mensgebonden Onderzoek, CCMO).

10.2 SIDIAP database (Spain)

SIDIAP conducts research according to the latest national and European directives regarding privacy and handling of data. Patient identifiers are removed by the data providers before any such data is merged with the SIDIAP database. In addition, a study-specific ID is assigned by SIDIAP data managers to each study participant. No re-identification of patients is needed for the proposed study, and data security and information governance policies are in place.

Approval by the SIDIAP Scientific Committee and the Idiap Jordi Gol Ethics committee will be obtained before any data is extracted for this study.

10.3 CPRD database (United Kingdom)

CPRD primary care research databases contain only de-identified patient data. All data held and processed by CPRD are done so in compliance with the relevant legal obligations including the Data Protection Act 1998.

All data is held on a secure computer network, with access restricted to authorised users.

CPRD's processes have been reviewed by the Confidentiality Advisory Group (CAG) and approved by the Health Research Authority (HRA) and Secretary of State to process patient identifiable information without consent under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002. This removes the obligation to obtain patient consent for the use of confidential patient information for conducting purely observational research using CPRD databases, including linked datasets. This approval is conditional on approval of a study protocol by the CPRD Independent Scientific Advisory Committee (ISAC - www.cprd.com/isac).

10.4 National registers and EMR data (Finland)

This is a fully register-based study and patients will not be contacted in any phase of the study. The study does not affect the treatment of the patients.

EPID Research will receive pseudonymized data including study identification numbers only. EPID Research employees have undertaken professional secrecy and are aware of their concern with the Finnish Act on the Openness of Government Activities 621/1999 (based on which the data can be received from the register holders). The study registers are formed on the basis mentioned in the Finnish Personal Data Act (523/1999) §12 and the data is handled as described in §14 therein.

The sponsor or any other third party will not have access to the patient level data. Being a member of the study scientific committee does not repeal this rule to benefit the sponsor employees.

The protocol will be subjected to Ethics Committee of Hospital District of Helsinki and Uusimaa for review and approval. Register notification of the forming study registers will be sent to the Finnish Office of the Data Protection Ombudsman.

11 Management and reporting of adverse events/adverse reactions

This study includes anonymized data from secondary data collection and is not designed to assess potential associations between drug use and outcomes. In these data sources and in particular the research files used for this study, it is not possible to identify a potential association between a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) were not available and adverse events will not be reportable as individual AE reports. See also the EMA Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products), for non-interventional study designs that are based on secondary use of data[19].

12 Plans for disseminating and communicating study results

An interim report will be delivered to Astellas in September 2017 including results from PHARMO up to 2015 and SIDIAP and CPRD up to 2016 (not EPID). The final report will include data up to 2016 for all databases and will be delivered in December 2017. See section 6 for the table of milestones.

Publication of study results in a (inter)national peer-reviewed journal or at a scientific conferences will be aimed for, see also the Guidelines for Good Pharmacoepidemiology Practices [16] and the ENCePP Code of Conduct [20]. With respect to the publication of study results, international ethical guidelines concerning academic publications (ICMJE guidelines [21]) and the RECORD statement [22] will be adhered to. A manuscript will be drafted shortly after approval of the final study report. Each author must have made a substantial contribution to (1) the concept and design, or acquisition of data, or analysis and interpretation of data; and (2) drafting the article/abstract/presentation or revising it critically, and contributing intellectual content. In addition, all authors must have approved the final version of the publication. The list of authors will include authors from each participating database and from Astellas. Following the above mentioned guidelines, the first author is the researcher who has made the greatest contribution to the research project, including its implementation, and the last author is the academic leader of the PHARMO research group.

13 References

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Annex 1. List of stand-alone documents

None.

Annex 2. ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

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 section number 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). 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:
Drug utilization study of mirabegron (Betmiga®) using real-world healthcare databases from the Netherlands, Spain, United Kingdom and Finland

Study reference number:
EUPAS15063

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☒	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
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)	☒	☐	☐	4,7
2.1.2 The objective(s) of the study?	☒	☐	☐	4,7,8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

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

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.3.4
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.7
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	11

Comments:

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2
4.2.2 Age and sex?	☒	☐	☐	9.2
4.2.3 Country of origin?	☒	☐	☐	9.4
4.2.4 Disease/indication?	☒	☐	☐	9.2
4.2.5 Duration of follow-up?	☒	☐	☐	9.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

The study population is defined by the use of mirabegron, this is what is assumed for the'disease/indication' question 4.2.4.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.9
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?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8, 9.3.4
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.4, 9.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.9

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☒	☐	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☐	☒	☐	
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☐	☒	☐	

Comments:

Study covariates only include age and gender

Section 8: Effect modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4
9.2 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)	☒	☐	☐	9.4
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	9.4 9.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4
9.3.3 Covariates?	☒	☐	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.6

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7
10.4 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.3.3, 9.9
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☒	☐	
12.1.2 Information bias?	☒	☐	☐	9.9

Section 12: Limitations	Yes	No	N/A	Section Number
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	

Comments:

Section 13: Ethical issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☐	☒	☐	

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Irene Bezemer, PHARMO Institute

Date: ../../….

Signature: _____

Annex 3. Codes for hypertension

	Coding system	Code
Hypertension uncomplicated	ICPC	K86
Hypertension complicated	ICPC	K87
Essential primary hypertension	ICD-10	I10
Hypertensive heart disease	ICD-10	I11
Hypertensive renal disease	ICD-10	I12
Hypertensive heart and renal disease	ICD-10	I13
Secondary hypertension	ICD-10	I15
Essential hypertension	Read V2	G20
Hypertensive heart disease	Read V2	G21
Hypertensive renal disease	Read V2	G22
Hypertensive heart and renal disease	Read V2	G23
Secondary hypertension	Read V2	G24
Stage 1 hypertension	Read V2	G25
Severe hypertension	Read V2	G26
Severe hypertension	Read V2	G26
Hypertension resistant to drug therapy	Read V2	G27
Stage 2 hypertension	Read V2	G28
Other specified hypertensive disease	Read V2	G2y
Hypertensive disease NOS	Read V2	G2z
[X] Hypertensive diseases	Read V2	Gyu2
Long-term monitoring of blood pressure	SPAT	SPAT1100
…	…	…
…	…	…
…	…	…
…	…	…

SPAT = Suomalainen perusterveydenhuollon avohoidon toimintaluokitus (a Finnish coding system for primary outpatient care procedures)

Annex 4. Drug codes for antihypertensives

	Coding system	Code
Antihypertensives	ATC	C02
Diuretics	ATC	C03
Beta blocking agents	ATC	C07
Calcium channel blockers	ATC	C08
Ace inhibitors, plain	ATC	C09A
Ace inhibitors, combinations	ATC	C09B
Angiotensin ii antagonists, plain	ATC	C09C
Angiotensin ii antagonists, combinations	ATC	C09D
Beta-adrenoceptor Blocking Drugs	BNF	2.4
Beta-adrenoceptor Blocking Drugs With Diuretic	BNF	2.4.1
Hypertension And Heart Failure	BNF	2.5
Vasodilator Antihypertensive Drugs	BNF	2.5.1
Centrally Acting Antihypertensive Drugs	BNF	2.5.2
Adrenergic Neurone Blocking Drugs	BNF	2.5.3
Alpha-adrenoceptor Blocking Drugs	BNF	2.5.4
Angiotensin-converting Enzyme Inhibitors	BNF	2.5.5.1
Angiotensin-ii Receptor Antagonists	BNF	2.5.5.2
Renin Inhibitors	BNF	2.5.5.3
Angiotensin-ii Receptor Antagonists With Diuretic	BNF	2.5.5.4

14 Signatures

ELECTRONIC SIGNATURE PAGE

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01/25/2017 07:42:38	Sofiane Agha	Qualified Person, EU-QPPV Officer
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