PASS INFORMATION

Title	Agomelatine Drug Utilisation Study in Selected European Countries: A Multinational, Observational Study to Assess Effectiveness of Risk-Minimisation Measures
Protocol version identifier	1.3 Final
Date of last version of protocol	10 November 2016
EU PAS Register number	The study will be registered following European Medicines Agency endorsement and prior to start of data collection
Active substance	Agomelatine (N06AX22)
Medicinal product	Valdoxan®/Thymanax®
Product reference	EU/1/08/499/001-008 (Valdoxan®) EU/1/08/498/001-008 (Thymanax®)
Procedure number	EMEA/H/C/915 (Valdoxan®) EMEA/H/C/916 (Thymanax®)
Marketing authorisation holder(s)	Les Laboratoires Servier 50 rue Carnot 92284 Suresnes Cedex - France
Joint PASS	No
Research question and objectives	The objective of this drug utilisation study is to evaluate the effectiveness of the newly implemented additional risk-minimisation measures for agomelatine (i.e., patient booklet and updated physician's guide) amongst prescribing physicians and their patients in relation to the following factors: - Adherence to the liver test monitoring regimen - Compliance with relevant contraindications - Patients' reasons for non-compliance with the liver test monitoring regimen
Country(ies) of study	France, Germany, Spain, and Denmark
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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

5-HT2C	A subtype of the 5-HT receptor that binds the endogenous neurotransmitter serotonin (5-hydroxytryptamine, 5-HT)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CHMP	Committee for Medicinal Products for Human Use (EMA)
CI	Confidence interval
CNIL	Commission nationale de l'informatique et des libertés [National Commission for Data Protection, France]
DHPC	Dear Health Professional Communication
DUS	Drug utilisation study
EC	Ethics committee
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS Register	European Union electronic register of post-authorisation studies
GP	General practitioner
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
I.R.I.S	Institut de Recherches Internationales Servier
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ISPE	International Society for Pharmacoepidemiology
MAH	Marketing authorisation holder
NA	Not applicable or not available (see table notes)
PAS	Post-authorisation study
PASS	Post-authorisation safety study
PBRER	Periodic Benefit-Risk Evaluation Report
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
RMMs	Risk-minimisation measures
RTI-HS	RTI Health Solutions
SmPC	Summary of Product Characteristics
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
ULN	Upper limit of the normal range

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title

Agomelatine Drug Utilisation Study in Selected European Countries: A Multinational, Observational Study to Assess Effectiveness of Risk-Minimisation Measures

Version 1.3, 10 November 2016

Lia Gutierrez, BScN, MPH; RTI Health Solutions

Rationale and background

In November 2014, within the context of the routine benefit-risk assessment of agomelatine performed by the Committee for Medicinal Products for Human Use (CHMP), the European Commission adopted a decision to amend the summary of product characteristics (SmPC) and package leaflet for agomelatine. The CHMP recommended clarifying the requirements for monitoring liver function. In particular, the recommendation mentioned the need for liver function tests to be performed before starting treatment. In addition, the following risk-minimisation measures (RMMs) were introduced to enhance adherence to the liver test monitoring regimen: (1) update of physician's guide to prescribing, (2) patient booklet with information regarding liver adverse reactions and liver monitoring requirements, (3) a post-authorisation safety category 3 study to evaluate adherence to the monitoring regimen and compliance with relevant contraindications.

Research question and objectives

The objective of this post-authorisation safety study (PASS) is to evaluate the effectiveness of the newly implemented additional RMMs for agomelatine recommended by the CHMP (i.e., patient booklet and updated physician's guide) amongst physicians prescribing agomelatine and their patients. The specific objectives of the study are to evaluate the following factors:

- Adherence to the liver test monitoring regimen
- Compliance with relevant contraindications
- Patients' reasons for non-compliance with the liver test monitoring regimen

The *medical record abstraction component* will evaluate adherence to the liver test monitoring regimen and compliance with relevant contraindications. The *patient survey component* will attempt to identify reasons for non-compliance with the liver test monitoring regimen from the patient perspective.

Study design

This will be a non-interventional, multinational cohort study of adult patients initiating agomelatine treatment in routine clinical practice in selected European countries. The study will comprise a retrospective "before" and "after" medical record data abstraction component (drug utilisation study component) and a cross-sectional patient survey component.

Medical record abstraction component

The retrospective medical record abstraction component of the study will comprise the following two periods:

- The before-RMM study period will capture information on patients initiating treatment with agomelatine from January 2013, the month after the implementation of prior RMMs (Dear Healthcare Professional Communication and physician's guide, distributed in October and December 2012, respectively), to November 2014 when the European Commission adopted the decision on the implementation of the latest additional RMMs (updated physician's guide and patient booklet).
- The after-RMM study period will collect information on patients initiating treatment with agomelatine beginning 1-2 months after the latest additional RMMs were fully disseminated in each country (i.e., the after-RMM study period starts in February 2015 in Denmark, April 2015 in Spain, May 2015 in Germany, and August 2015 in France) to the month prior to the initiation of study activities in each country.

At each centre, implementation of the retrospective medical record abstraction for the before and after study periods will be performed concurrently in time. The start of study data collection will vary across countries and will depend on the timing of the approval of national regulatory bodies and ethics committees required in each country. In addition, the start of data collection will be necessarily driven by the timing of the latest distribution of the additional RMMs in each country and is set to allow a minimum period of time for accrual of the target number of patients treated with agomelatine in the after-RMM period.

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

Patient survey component

The patient survey is a cross-sectional survey that will be performed after distribution of the patient booklet has taken place in each country. Patients will be recruited for this survey during the after-RMM period. At each centre, the patient survey will be implemented once the data collection for the retrospective medical record abstraction component has been initiated.

Population

The design of this PASS envisions the "physician prescriber" as the initial target for the subsequent sampling and identification of patients. Therefore, the source population for the study will consist of physician prescribers (i.e., psychiatrists and general practitioners [GPs]) practising in outpatient settings (hospital outpatient clinics, other outpatient clinics, or private practices) where outpatients treated with agomelatine are managed in Denmark, France, Germany, and Spain.

Variables

The study will collect the following data, listed by the mode of data collection.

Site/physician feasibility questionnaire

- Practice setting, patient volume, physician characteristics (age category, specialty, sex), site's resources and infrastructure for conducting the study, availability of laboratory test requests and results, reason for refusal to participate/reason site was not selected

Recruitment log for patient survey

- Patient age and sex, participation status (participant, non-participant), reason for refusal to participate (amongst patients refusing to participate)

Medical record abstraction component

For each period of the medical record review component, the following data will be abstracted from medical records of selected patients:

- Date of data abstraction.
- Characteristics of agomelatine users: patients' age and sex; date of diagnosis of the episode of major depression corresponding to the initiation of agomelatine; date, dose, and duration for the first and subsequent agomelatine prescriptions; and relevant medical conditions at the start of treatment (according to SmPC precautions for use), e.g., obesity/overweight, substantial alcohol intake, diabetes, and non-alcoholic fatty liver disease.
- Variables used to evaluate adherence to the liver test monitoring regimen: date of prescription of agomelatine treatment, agomelatine dose, date liver function tests were ordered, date of liver test results, results, and laboratory value of the upper limit of the normal range (ULN) for alanine aminotransferase [ALT] and aspartate aminotransferase [AST].
- Variables used to evaluate compliance with relevant contraindications: presence at the start of treatment and during treatment of conditions associated with hepatic impairment such as cirrhosis or active liver disease and concomitant prescription of fluvoxamine and/or ciprofloxacin at initiation of treatment or during treatment with agomelatine.

Patient survey

The patient survey component will collect the following data:

- Patient's age, sex, and educational level; time since initiation of agomelatine treatment; duration of agomelatine treatment; time since agomelatine discontinuation (if applicable); receipt of agomelatine patient booklet; knowledge of the key liver safety information (i.e., risk of hepatotoxicity and liver monitoring tests requirements); if liver tests were not performed, reasons for non-compliance with liver test monitoring.

Data sources

For the *medical record abstraction component*, data will be collected from medical records of patients initiating treatment with agomelatine during the defined study periods.

For the *patient survey component*, data will be collected from self-administered patient surveys.

Study size

The targeted number of patients for the *medical record abstraction component* is 600 patients in the before-RMM period and 600 patients in the after-RMM period, for a total of 1,200 patients across all countries. To the extent that it is feasible, the study size to be achieved in

each country will be proportional to the volume of prescriptions per country and prescriber specialty.

The *survey component* will target recruitment of a total of 400 patients across all countries.

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. The main analysis will estimate the prevalence of adherence to the recommended frequency of liver monitoring tests. To estimate the change in the main and secondary outcomes in the medical record abstraction component, the 95% confidence interval of the difference between the before-RMM and after-RMM study periods will be calculated. A chi-square test or a t-test will be used to test the differences in the main and secondary outcomes. Results will be presented overall, by country, and, if numbers allow, by physician specialty. If data are sufficient, overall analyses that include and exclude general practitioners will be conducted.

Milestones

- Distribution of the patient booklet: from December 2014 through March 2015
- Distribution of the updated physician's guide: from December 2014 through July 2015
- Endorsement of protocol version 1.1 by the EMA/PRAC: January 2016
- Endorsement of the amended protocol, version 1.2, by the EMA/PRAC: June 2016
- Registration in the EU PAS Register: prior to start of data collection
- Completion of the pilot phase: evaluation of site feasibility (i.e., estimate number of agomelatine-treated patients, centre/physician characteristics, and logistic aspects); pilot testing of medical record abstraction form and cognitive testing of patient survey questionnaire: November 2015
- Start of study implementation (i.e., preparation of study materials, submission documents for local regulatory bodies and ethics committee approvals, and training materials; set up of study processes; and other operational activities): May 2016
- Start of data collection: January 2017
- Interim study report for the medical record abstraction component based on available data: July 2017
- End of data collection: October 2017
- Final study report (including data from the patient survey): March 2018

5. AMENDMENTS AND UPDATES

Version number	Date	Section(s) of study protocol	Amendment or update	Reason
1.3	24 Oct 2016	Section 9.4, Data sources, and Section 10, Protection of human subjects	Anonymous/anonymised data were changed to de-identified since physicians will maintain a link between the ID number used in the EDC and the patient for the MRA	Patients must be allowed to access their study data, make changes or request that their data be deleted from the study, thus requiring a linkage
1.3	24 Oct 2016	Section 9.2.3, Patients, Inclusion criteria; Section 9.5.1, Medical record abstraction component; and Section 10, Protection of human subjects	Patients will provide written informed consent for the MRA in Demark, Germany, and Spain	Data will no longer be anonymized; therefore written consent is required in these countries
1.3	24 Oct 2016	Section 9.1, Study design	Text was changed for first local regulatory submission to July 2016	AEMPS submission package was submitted in July
1.3	24 Oct 2016	Section 9.1, Study design	Deleted text stating site recruitment will begin after CCTIRS approval is received	Based on CNIL Decision No: 2016-263, CCTIRS approval is no longer needed
1.3	24 Oct 2016	Section 9.1, Study design	Text was changed for start of physician contact to November 2016	Start of site recruitment will be delayed due to change in study design to active consent for MRA in Denmark, Germany, and Spain
1.3	24 Oct 2016	Section 9.1, Study design	Deleted text stating the start of data collection will occur after CNIL approval	Based on CNIL Decision No: 2016-263, CNIL approval is no longer needed
1.2	27 May 2016	Section 3, Responsible parties	Change in the principal investigator	To reflect the transfer of responsibilities to a new project leader
1.2	27 May 2016	Section 4 and Section 6, Milestones	Revised dates were added for the conduct of the full study	To reflect the revised timelines based on date of study implementation and January 2016 PRAC recommendations
1.2	27 May 2016	Section 6, Milestones; Footnote in Table 6	Text was added to clarify that data collection cannot begin in any country until CNIL approval is received in France	MAH is located in France
1.2	27 May 2016	Section 6, Milestones; Footnote in Table 6.	Text was changed to clarify that the end of data collection will occur in October 2017	End of data collection will be driven by the date and not by the number of completed medical record abstraction forms or surveys, to enable delivery of the study final report 1Q 2018.
1.2	27 May 2016	Section 9.1, Study design	Text was added to change the end date of the after-RMM period in all countries.	To reflect the revised timelines based on date of study implementation
1.2	27 May 2016	Section 9.1, Study design	Text was added to clarify that data collection cannot begin in any country until CNIL approval is received in France	MAH is located in France

Version number	Date	Section(s) of study protocol	Amendment or update	Reason
1.2	27 May 2016	Section 9.1, Study design	Text was added to clarify that data collection will not exceed 10 months overall	End of data collection will be driven by the date and not by the number of completed MRA forms or surveys to enable delivery of the study final report 1Q 2018.
1.2	27 May 2016	Section 9.1, Study design	Revised dates were added for the conduct of the full study	To reflect the revised timelines based on the date of study implementation
1.2	27 May 2016	Section 9.1, Study design	Text was added to clarify that the pilot phase has been completed	Completion of the pilot phase
1.2	27 May 2016	Section 9.2, Study setting	Deletion of text stating that lead investigators for the full study were identified during the pilot phase	Leading investigators in France and Denmark will need to be identified
1.2	27 May 2016	Section 9.2.3, Medical record abstraction	Date was changed to reflect the revised after-RMM study period	To reflect the revised timelines based on the date of study implementation
1.2	27 May 2016	Section 9.2.3, Study patients	Text was added to clarify that some centres in Spain and Germany may require informed consent to participate in the MRA portion of the study	To reflect requirements of some ethic committees in the countries participating; based on feedback from pilot phase
1.2	27 May 2016	Section 9.3.1, Collected data	Text was added to clarify that reasons for patient refusal to participate in the survey will be entered into the EDC system	To clarify the process for capturing information on the reasons for refusal to participate
1.2	27 May 2016	Section 9.4, Data sources	The word anonymised was changed to de-identified when describing the collection of patient survey data	A patient log will be kept by the site staff on patients participating in the patient survey; therefore, data will not be fully anonymized
1.2	27 May 2016	Section 9.6, Data management	Text was changed to clarify the MRA data entry process, and text was deleted to reflect that the patient survey data will not be queried	Typographical errors in previous version
1.2	27 May 2016	Section 9.9, Limitations of research method	Text was added to acknowledge that data may be limited as physicians who refuse to participate may not complete the key characteristic questions in the feasibility questionnaire	To account for physician refusal to provide answers to key questions on the feasibility questionnaire
1.2	27 May 2016	Section 10, Protection of human subjects	Text was changed to clarify that the MRA data will contain anonymized data and the patient survey data will be de-identified	A patient log will be kept by the site staff on patients participating in the patient survey; therefore, survey data will not be fully anonymized
1.2	27 May 2016	Appendix 3, Site feasibility questionnaire	Text was changed/added to streamline the questionnaire	To decrease the burden on potential investigators and to focus on those questions needed to identify sites
1.2	27 May 2016	Appendix 4, Medical record abstraction form	Text was changed/added to improve clarity of questions, reorder questions, and clarify instructions	Results from cognitive testing of the medical record abstraction form with physicians

Version number	Date	Section(s) of study protocol	Amendment or update	Reason
1.2	27 May 2016	Appendix 5, Patient Survey	Text was changed/added to clarify instructions	Results from cognitive testing of the patient survey during the pilot phase
1.1	3 Nov 2015	Section 9.1, Study design; Footnote in Figure 1	Text was added to clarify the underlying limitations of the timelines for the initiation of the after-RMM study period in relation to the timing of the latest distribution of the additional RMMs and the initiation of outreach to physicians	To highlight limitations for implementing a wider gap between the study periods (at the request of PRAC, 8 October 2015)
1.1	3 Nov 2015	Section 9.2.2, Physicians and sampling frame; Section 9.2.3, Patients, New Table 2, Revised Table 3	Text was added to describe in a more detailed manner the random sampling strategy for selection of physicians and patients and the minimum targeted and maximum allowed numbers of patients per site and period that will qualify a site for participation in the study. A new table (Table 2) was added, and Table 3 was revised.	To provide details on the process for random sampling of physicians and patients to achieve randomness (at the request of PRAC, 8 October 2015)
1.1	3 Nov 2015	Section 9.5, Study size, Section 9.5.1; Medical record abstraction component; Section 9.5.2 Patient survey component	Updated to clarify the underlying rationale for the assumption of 50% adherence to the liver monitoring regimen.	To justify the underlying assumption for evaluation of adherence to the liver monitoring regimen (at the request of the PRAC, 8 October 2015)
1.1	3 Nov 2015	Abstract, Section 9.3, Variables; Section 9.3.2, Outcomes; Section 9.7, Data analysis	Updated to add specific time windows for the liver function tests in relation to agomelatine treatment initiation and maintenance and new outcome variables for liver testing related to dose escalation. Updated specifications for main and secondary analysis.	To account for the timing of the liver function tests in relation to timing of treatment initiation, maintenance, and dose escalation (at the request of the PRAC, 8 October 2015)
1.1	3 Nov 2015	Section 9.7, Data Analysis	Updated to correct the approach for handling missing data.	Revised the approach for handing missing data (at the request of the PRAC, 8 October 2015)
1.1	3 Nov 2015	Section 9.6, Data Management	Text added to describe how data inconsistencies and errors will be handled.	To enable delivery of the study final report 2Q 2017 (response to PRAC assessment, 9 April 2015)

CNIL = Commission nationale de l'informatique et des libertés [National Commission for Data Protection, France]; EDC = electronic data collection; MAH = marketing authorisation holder; MRA = medical record abstraction; PRAC = Pharmacovigilance Risk Assessment Committee of the European Medicines Agency; RMM = risk minimisation measures.

6. MILESTONES

Milestone	Planned date
Distribution of the patient booklet	Dec 2014-Mar 2015
Distribution of updated physician's guide	Dec 2014-Jul 2015
Version 1.1 protocol endorsement by EMA/PRAC	January 2016
Version 1.2 amended protocol endorsement by EMA/PRAC	June 2016
Registration in the EU PAS Register	Prior to start of data collection
Completion of pilot phase: evaluate feasibility requirements of sites; explore local regulatory and ethics requirements; pilot test study materials; and conduct pilot and cognitive testing of data collection form	Nov 2015
Start of study implementation: preparation of study materials, submission documents for institutional review board/ethics committee approval, and training materials; set up of study processes; and other operational activities including site recruitment	May 2016
Start of data collection[a]	January 2017
Interim study report for the medical record abstraction component based on available data	July 2017
End of data collection[b,c]	October 2017
Final report of study results (including patient survey results)	March 2018

EMA = European Medicines Agency; EU PAS Register = European Union electronic register of post-authorisation studies PRAC = Pharmacovigilance Risk Assessment Committee.

[a] *Final timelines may be impacted by delays in obtaining regulatory and ethics committee approvals in the targeted countries and in establishing contracts with participant physicians, amongst others. Particularly, the comments received from the CCTIRS and the publication of a new French regulation has impacted the whole study. Timing of the start of data collection will depend on the timing of approvals by the national regulatory bodies and ethics committees in each country. Therefore, the timing of study initiation across countries might differ.*

[b] *Data collection will end on l October 2017, even if the target number of patients for each period has not been reached, in order to maintain the final report timeline (assuming that the final number of patients maintains a sufficient precision).*

[c] *Date from which the full study analytical data set is available.*

7. RATIONALE AND BACKGROUND

Agomelatine (Valdoxan/Thymanax) is a melatonergic agonist (MT_1 and MT_2 receptors) and a 5-HT2C antagonist indicated for major depressive episodes in adults. Based on the review of quality, safety, and efficacy data, the Committee for Medicinal Products for Human Use (CHMP) considered, by consensus, that the benefit-risk ratio of agomelatine was favourable for the treatment of major depressive episodes in adults. The marketing authorisation was granted in February 2009 and renewed in November 2013 in the European Union.[1] Valdoxan/Thymanax is marketed by les Laboratoires Servier.

Valdoxan/Thymanax is covered by a European risk management plan that includes hepatotoxic reactions as an identified important risk. The summary of product characteristics (SmPC) mentioned that 1.4% of patients treated with 25 mg of agomelatine and 2.5% of patients treated with 50 mg showed elevated transaminases.[2]

In November 2014, the European Commission adopted the decision to amend the SmPC and package leaflet within the context of the routine benefit-risk assessment of agomelatine performed by the CHMP. The CHMP recommended clarifying the requirements for monitoring liver function, in particular, regarding the need for liver function tests to be performed before starting treatment.[3] To enhance adherence to the liver test monitoring regimen, the CHMP also requested the introduction of the following additional risk-minimisation measures (RMMs) and pharmacovigilance activities in an updated version of the Risk Management Plan: (1) update physician's guide to prescribing, (2) patient booklet with information regarding liver adverse reactions and liver monitoring requirements, and (3) a post-authorisation safety category 3 study to evaluate adherence to the monitoring regimen and compliance with relevant contraindications.[4]

Servier initiated dissemination of both the physician's guide to prescribing and the patient booklet in December 2014 to the targeted audience through the distribution channels agreed upon with the European national competent authorities. End of distribution in the last country targeted for this post-authorisation safety study (PASS) occurred in July 2015.

To evaluate the effectiveness of the additional RMMs, a drug utilisation study (DUS) will be conducted in multiple European countries. This study will aim to assess how agomelatine is used in current clinical practice, with a focus on evaluating adherence to recommendations for monitoring liver function, compliance with relevant contraindications, and reasons for non-compliance with the liver function monitoring from the patient's perspective.

8. RESEARCH QUESTION AND OBJECTIVES

The overall objective of this DUS is to evaluate the effectiveness of the additional RMMs for agomelatine amongst physicians prescribing agomelatine and their patients during two periods: before and after implementation of the additional RMMs.

The specific objectives of the *medical record abstraction component* of the study are to evaluate (1) adherence to the liver test monitoring regimen and (2) compliance with relevant contraindications.

The specific objective of the *patient survey* is to evaluate patients' reasons for non-compliance with the liver test monitoring regimen.

9. RESEARCH METHODS

9.1. Study design

This will be a non-interventional, multinational PASS that will collect data from adult patients initiating agomelatine treatment in routine clinical practice in selected European countries, with a retrospective "before" and "after" medical record data abstraction component (DUS component) and a cross-sectional patient survey component. The targeted countries for the study are Denmark, France, Germany, and Spain.

Medical record abstraction component

The medical record abstraction component of the study will comprise two periods:

- The before-RMM period will collect information from January 2013, the month after the latest implementation of previous RMMs (Dear Healthcare Professional Communication [DHPC] and physician's guide, distributed in October and December 2012, respectively) to November 2014 (when European Commission adopted the latest additional RMMs)
- The after-RMM study period will capture information beginning 1-2 months after the latest implementation of the new additional RMMs in each country (i.e., the after-RMM study period starts in February 2015 in Denmark, April 2015 in Spain, May 2015 in Germany, and August 2015 in France) to the month prior to the initiation of study activities in each country.

At each site, the study data collection for the before-RMM and after-RMM periods of the medical record abstraction component will be performed concurrently in time.

Patient survey component

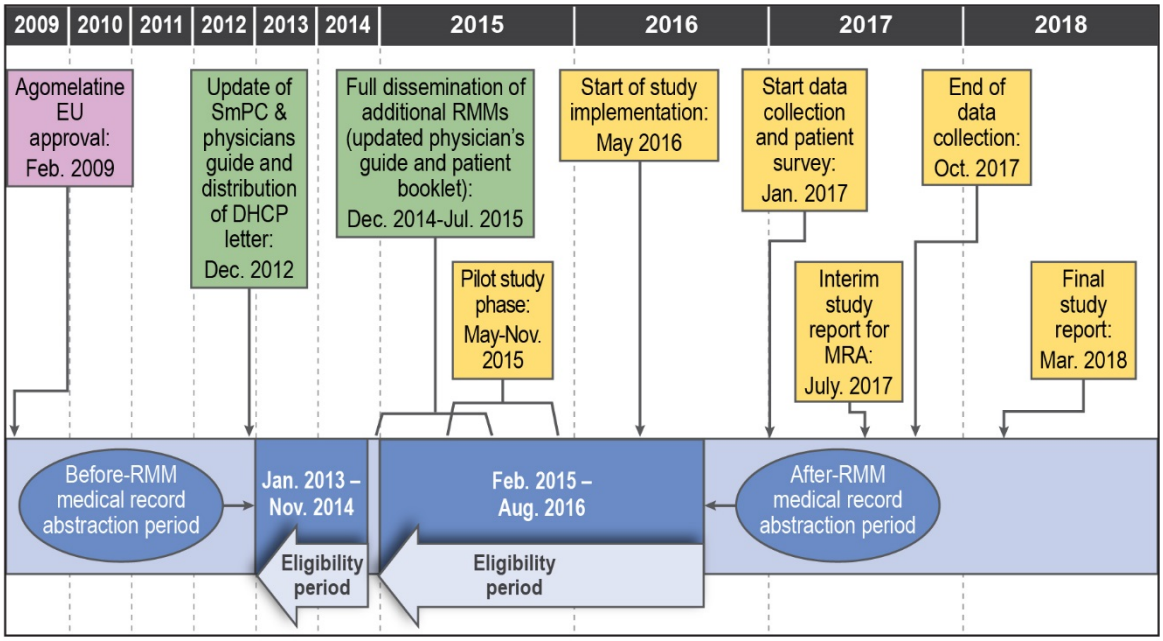
The cross-sectional patient survey will collect data from patients treated with agomelatine after the additional RMMs, including the patient booklet, have been fully distributed to the medical professionals in each country (i.e., December 2014 in the first country to July 2015 in the last country). In addition to educating patients, the patient booklet aims to enhance physician adherence to agomelatine prescription requirements. Recruitment of patients for participation in the patient survey component will be performed in a cross-sectional manner targeting patients treated with agomelatine during the after-RMM period.

At each site, the patient survey component will be conducted once data collection for the medical record abstraction component has been initiated.

The **full study** (comprising medical record abstraction and patient survey components) will be initiated in each country after implementation of the new additional RMMs adopted by the European Commission in November 2014. The full dissemination of the updated physician's guide and patient booklet was implemented in the targeted countries starting in December 2014 and was completed in the last country in July 2015. The after-RMM period will capture information from February 2015 through August 2016 in Denmark, April 2015 through August 2016 in Spain, May 2015 through August 2016 in Germany, and August 2015 through August 2016 in France, prior to the initiation of outreach study activities with physicians in each country. The start of study implementation activities is planned by May 2016. The date of the

start of the data collection is expected to vary across countries and will depend on the timing of local regulatory and ethics committee approvals in each country. To meet the timelines set for the finalization of the study, data collection must start in the first country no later than January 2017. In addition, the start of data collection will take into account the timing of the latest distribution of the additional RMMs in each country and will be set to allow a minimum time period for accrual of the targeted number of patients treated with agomelatine in the after-RMM period. Figure 1 provides a study overview and describes the planned overall study timelines.

Figure 1: Study overview



DHPC = Dear Health Professional Communication; EU = European Union; MRA = medical record abstraction; RMM = risk-minimisation measures; SmPC = summary of product characteristics.
Note: The after-RMM eligibility period will capture information from February 2015 through August 2016 in Denmark, April 2015 through August 2016 in Spain, May 2015 through August 2016 in Germany, and August 2015 through August 2016 in France, prior to the initiation of outreach study activities with physicians in each country. Early study implementation activities include preparation of documentation for ethics committee submission.

Initial study implementation activities will consist of preparing study materials and documentation for local regulatory and ethics committee (EC) submissions and setting up study processes. Contact with potential participating sites/physician investigators will not occur, other than with the lead investigator in each country, until November 2016. The first local regulatory/EC submission is targeted by July 2016. The start of data collection in each centre will occur after each local regulatory and ethics approval and the investigators' agreements are in place in the country. In some countries, set-up, including activities such as site recruitment and EC approval, is expected to require up to 6 months. Therefore, the timing of the start of data collection is expected to vary across countries, with data collection expected to start in the first country by January 2017. In each country, completion of data collection for the patient medical record abstraction component is anticipated to require approximately 6 months, but is not to exceed 10 months overall in order to maintain the final report timeline. The recruitment of patients for participation in the patient survey is expected to be completed in the same time frame. An interim study report will be provided in July 2017 describing the results of the medical record abstraction component based on data that will be available through the end of March 2017.

The end of study data collection is planned by October 2017 at the latest. We anticipate submitting the final report by the end of March 2018.

A **pilot phase** with 8 physicians and 19 patients was completed in four of the targeted countries. The goals of the pilot phase were to assess relevant aspects related to study design and study implementation (e.g., potential number of patients, shared care management practices, availability of key data, and frequency of follow-up visits) and to perform cognitive testing of the medical record abstraction form with physicians and of the patient questionnaire with patients. The pilot phase provided information on local ethics review requirements and timelines for ethics approvals. Results from the pilot phase informed the overall feasibility of the full study and uncovered operational and technical issues that required minor modifications in the full study implementation plan. The pilot phase was initiated in May 2015 and completed in November 2015. A country lead investigator for the full study will be identified in each country. Based on the pilot results, the protocol, the medical record abstraction form, and/or the patient questionnaire were amended.

9.2. Setting

The design of this PASS envisions the "physician prescriber" as the initial target for the subsequent sampling and identification of patients. Therefore, the source population for the study will consist of physician prescribers (i.e., psychiatrists and general practitioners [GPs]) practising in outpatient settings (in hospital outpatient clinics, freestanding clinics, or private practices) where outpatients treated with agomelatine are managed in each targeted country. 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 support the ethics committee submissions in each country and to provide input to define the strategy to approach and engage other potential physician investigators to participate in the study.

For both periods of the *medical record abstraction component*, patients initiating treatment with agomelatine will be identified by designated health care personnel at selected clinical centres, using the system available at each centre for tracking or scheduling patient visits and for identifying patients treated with agomelatine.

For the *patient survey component*, designated health care personnel at selected participating centres will identify and recruit eligible patients treated with agomelatine during routine visits and will keep a patient log with main demographic information (i.e., age and sex) on the patients approached about the study and the agreement or refusal of patients to participate in the survey.

9.2.1. Countries

The targeted countries for the study are Denmark, France, Germany and Spain. The selection of countries was driven by the volume of sales of agomelatine in Europe and the desire for a diverse geographic representation of European countries and their potential to represent current medical practices and specialty of prescribers for patients treated with agomelatine. The estimated patient-years of agomelatine exposure based on sales data since the marketing authorisation in the targeted countries is shown in Table 1.

Table 1: Estimated patient-years of agomelatine exposure based on sales data through January 2015

		Number of patient-years	
Countries	**Date of market authorisation**	**From market authorisation to Jan 2015**	**PSUR period, Feb 2014 to Jan 2015**
Denmark	June 2009	26,121	5,073
France	May 2010	239,210	57,649
Germany	March 2009	321,674	60,708
Spain	October 2009	249,277	46,591
Total in selected countries	NA	836,282	170,021
Total in EU countries	NA	1,197,957	244,296

EU = European Union; NA = not applicable; PSUR = Periodic Safety Update Report.
Source: Institut de Recherches Internationales Servier (I.R.I.S).

9.2.2. Physicians and sampling frame

Patients will be identified across targeted physician specialities, including general practitioners and psychiatrists (private offices and hospital outpatient clinics). Representation by each physician group will reflect, to the extent possible, prescribing patterns in each country.

In the absence of comprehensive lists of agomelatine prescribers, the initial sampling frame for the identification of participating physicians will use large lists of physician prescribers of agomelatine in each of the relevant specialties that are available for each of the targeted countries. The lists have been produced internally by Servier for France, obtained through IMS Health-Cegedim for Denmark and Spain, and obtained through Axciom for Germany. Table 2 summarizes the number of physician prescribers included in the available lists by specialty and country as of October 2015.

Table 2: Number of agomelatine prescribers included in the available prescriber lists per country and specialty as of October 2015

	Denmark	**France**	**Germany**	**Spain**
Physician specialty	**N of prescribers**	**N of prescribers**	**N of prescribers**	**N of prescribers**
General practitioners	3,676	18,132	3,766	10,357
Psychiatrists	616	4,655	2,116	3,878
Neurologists+ Internist	NA	NA	1,450	NA
Total	4,292	22,787	7,332	14,235

Source: agomelatine prescribers' lists available to Servier.

A sample of physicians in each country will be obtained from these lists of physician prescribers using random sampling. The sampling strategy will mimic the proportion of the volume of prescriptions by prescriber specialty in each country (see Table 3). The volume of prescriptions was also taken into account for the calculations on the study size (number of patients) required in each country for the medical record abstraction and the patient survey components, as summarised in Section 9.5, Table 4, and Table 5. The mean number of agomelatine-treated patients per specialty provided in Table 3 allows assessment of the potential of prescriptions to differ by specialty (e.g., lower for GPs than for psychiatrists), which will be considered to define the targeted number of patients by site, with the aim of achieving a sample of patients that will reflect current prescribing patterns.

Table 3: Agomelatine market experience and prescribing pattern in selected countries

	Agomelatine sales[a]		Percentage of prescriptions by type of setting and by physician specialty[b]			
Country	**n**	**%**	**Psychiatrist at a hospital[c]**	**Psychiatrist in private practice[c]**	**GP**	**Mean number of patients treated with agomelatine by prescriber each year[d]**
Denmark	53,834	4	15%	40%	45%	NA
France	568,636	34	19%[e]	22%	59%	GP: 0.7 Psychiatrist: 1.5
Germany	631,268	38	7%	52%	41%	GP: 0.5 Psychiatrist: 1.8
Spain	406,063	24	45%	19%	36%	GP: 0.5 Psychiatrist: 4.6
Total	1,659,801	100				

GP = general practitioner; NA = not available, could not be calculated because number of prescribers by specialty is not available for Denmark.
[a] Total Valdoxan sales, October 2014-June 2015 based on number of sold boxes.
[b] Data provided by Servier; percentages do not add to 100% for France and Spain.
[c] …or neurologist in Germany.
[d] Derived from Servier data (using agomelatine sales data from June-September 2013) on estimated patient-years of agomelatine exposure multiplied by the proportion of prescriptions by type of prescriber divided by the total number of physicians for each specialty in the country.
[e] Based on all hospital prescriptions irrespective of physicians' specialty.

To achieve the targeted number of patients per country (see Sections 9.5.1 and 9.5.2), a minimum number of agomelatine-treated patients in each study period per site/physician investigator have been set. Sites/physicians with low, moderate, and high volumes of prescriptions will be sampled. For GPs, because of their potential to write fewer prescriptions for agomelatine than psychiatrists or neurologists (assessed through the number of mean prescriptions), the minimum number of agomelatine-treated patients will be five per site per study period. For specialists, the minimum will be eight patients per site per study period. This will result in sampling more GPs than specialists in each country. In addition, with the aim to achieve a balanced representation of patients across different settings and specialties, the maximum number of patients per site and period should not exceed 10 for the GP sites and 15 for the specialist sites.

As an example, if a total of 206 patients are targeted in France for one period of the medical record abstraction component (see Table 4 in Section 9.5), in the scenario that most centres are only able to meet the targeted minimum number of patients per physician specialty and considering the prescribing patterns displayed in Table 3, the target number of sites/physician investigators in France will be as follows:

- 25 GPs with a minimum of 5 patients per site/physician investigator = 125 patients (approximately 60% of the total)
- 10 psychiatrists with a minimum of 8 patients per site/physician investigator = 80 patients (approximately 40% of the total)

The number of prescribers/physicians available in the lists (see Table 2) that will be used for sampling is expected to enable recruitment of such a targeted number of sites/physician investigators.

Sites/physicians will be eligible to participate if they treat this minimum number of potentially eligible patients and provide confirmation of capacity to perform chart abstraction.

Physicians will be approached and recruited in accordance with applicable data protection and confidentiality regulations.

In countries where, as a result of a longer set up phase, the period for data collection is shortened and 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. If the participation of sites/physicians is limited by the minimum number of patients by site/physician investigator, a reduction in the minimum number could be considered.

9.2.3. Patients

Medical record abstraction component

The source population will consist of "physician prescribers of agomelatine" as the initial target for the subsequent sampling and identification of all patients initiating treatment with agomelatine in routine clinical practice. If the number of eligible patients at a site is lower than the maximum number targeted for the medical record abstractions, the patient information and/or the informed consent will be sent to all these patients. Data of all patients who accept to participate will be abstracted. If the number of eligible patients at a site substantially exceeds the maximum number (i.e., more than 10 patients for GP sites and 15 patients for specialists sites and by period), the patient information and/or the informed consent will be sent to all these patients and the data of the first 10 or 15 (depending on the physician specialty) will be abstracted for the medical record abstraction component of the study.

A patient initiating agomelatine (new user) will be defined as a patient who receives a first prescription for agomelatine by their prescribing physician during the before-RMM study period (i.e., from January 2013 to November 2014) or during the after-RMM study period (i.e., from February 2015 to August 2016) and who does not have documented use of agomelatine during the 6 months prior to the first agomelatine prescription occurring during a study period. Patients will be approached by mail by the treating physicians or designated health care personnel for participation in the medical record abstraction component. Patients who agree to participate (return signed consent or do not object, as applicable by country) in the medical record abstraction will have their medical record abstracted.

Patient survey component

Patients initiating treatment with agomelatine from the latest time of implementation of the additional RMMs to the time of initiation of data collection will be approached by the treating physicians or designated health care personnel for participation in the patient survey in each centre. Patients who agree to participate in the survey will be asked to complete the survey during their visit at the site.

Inclusion criteria

- For the *medical record abstraction component*, (1) patients will provide written informed consent to participate in the medical record abstraction component of the study (exception: in France, the person does not object to the processing of his/her personal data for the purposes of this study) and (2) eligible patients will have documented initiation of treatment with agomelatine during one of the study periods.
- For the *patient survey component*, (1) patients will provide written informed consent to participate in the patient survey component of the study, (2) patients will be agomelatine users on current treatment or whose agomelatine treatment discontinued no longer than 3 months ago, and (3) patients will have initiated treatment with agomelatine after the dissemination of the patient booklet in each country.

Exclusion criteria

- For the *medical record abstraction component*, (1) patients with documented use of agomelatine in the 6 months prior to the first prescription of agomelatine in a study period, (2) patients who were participating in a clinical trial of agomelatine for the study period during which they would have contributed data, and (3) patients unable to provide a written informed consent when required or objecting to the processing of his/her personal data for the purposes of this study.
- For the *patient survey component*, (1) patients initiating treatment with agomelatine prior to the date of the latest dissemination of the additional RMMs in each country, (2) patients who were participating in a clinical trial of agomelatine during the time for which they would contribute data, (3) patients unable to provide a written informed consent, and (4) patients unable to understand and complete the patient questionnaire.

9.3. Variables

9.3.1. Collected data

The following data related to the centre and physician characteristics will be collected through a **site feasibility questionnaire** received from each centre:

- Physician characteristics: demographics, specialty, years in practice
- Practice setting
- Number of patients initiated with agomelatine during the each study period
- Receipt of the physician's guide and patient booklet
- Recording practices of laboratory test requests/orders and results

For patient recruitment efficiency and to avoid enrolling centres that are expected a priori to contribute limited information, centres will not qualify for participation, for example, because of a very low number of patients treated with agomelatine (e.g., less than 5) or if missing data in key variables is anticipated. The reasons for centres to not qualify and the number of centres not qualified for each reason will be listed in the study report to the extent that this information is available, and the potential impact of the process for selecting centres on generalisation of study results will be discussed in Section 11.4 of the study report.

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

Medical record abstraction component

For each study period of the *medical record abstraction component*, the following data will be abstracted from the medical records of selected patients by a designated health care professional at each centre:

At baseline:

- Date of data abstraction
- Demographics: age, sex
- Date of diagnosis of the current episode of depression
- Agomelatine prescription; start date, dose, and supply (i.e., number of boxes or number of months of drug supplied)

- Relevant (according to the SmPC) conditions at the start of treatment; conditions associated with hepatic impairment (cirrhosis, acute liver disease), relevant risk factors for hepatic injury (obesity/overweight, non-alcoholic fatty liver disease, diabetes, substantial alcohol intake), and concomitant prescription of fluvoxamine and/or ciprofloxacin
- Liver function tests (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]): date of liver test order, date of test results, results, and value of the upper limit of the normal range (ULN) according to the local laboratory

During treatment:
- Presence of conditions associated with hepatic impairment, concomitant use of fluvoxamine and/or ciprofloxacin
- Agomelatine prescriptions: dates, dose, and drug supply during follow-up
- Laboratory liver function tests (ALT and AST): dates tests were ordered, date of liver test results, results, and value of the ULN according to the local laboratory

Patient survey

The following data will be collected from patients treated with agomelatine who agree to participate in the *patient survey*:
- Demographics: age, sex, educational level
- Time since agomelatine initiation
- Agomelatine treatment duration
- Time since discontinuation (if applicable)
- Receipt of the patient booklet
- Knowledge of the key liver safety information (i.e., risk of liver problems and requirements for monitoring of liver function through laboratory tests)
- Reasons for patient non-compliance with liver test monitoring, if applicable (for example, refusal to have blood drawn for liver tests)

For patients who do not agree to participate in the patient survey, the reason for refusal will be obtained, if possible, and recorded by the site staff in the electronic data capture system.

9.3.2. Outcomes

For each study period of the *medical record abstraction component*, the following outcomes will be derived from the variables collected:
- Patient demographic characteristics, time of diagnosis of current episode of depression, targeted comorbidities associated with hepatic impairment or presence of relevant risk factors for hepatic injury, and concomitant prescription of fluvoxamine and/or ciprofloxacin at the start date
- Agomelatine prescription patterns: dose and drug supplied at start date and during follow-up
- Adherence to recommended frequency of liver function monitoring according to the revised SmPC:
  - Patients with liver testing performed prior to or at initiation of agomelatine
  - Patients with at least one liver test performed after treatment initiation
  - Patients with liver testing performed at dose escalation and following dose escalation
    The criteria to define adherence to liver function monitoring specifying the time windows to be considered for the analyses are detailed in Section 9.7.

- Liver test results:
  - Patients with at least one liver function parameter (AST or ALT) more than 3 times the ULN prior to or at initiation of agomelatine treatment

For the *patient survey component*, the following outcomes will be derived from the variables collected:

- Patient demographic characteristics
- Awareness of liver side effects and liver monitoring requirements:
  - Patients aware of liver problems as a side effect associated with agomelatine treatment
  - Patients aware of liver function monitoring requirement for agomelatine treatment
- Liver function monitoring:
  - Patients acknowledging having had a liver test performed prior to the start of agomelatine treatment
  - Patients acknowledging having had a liver test performed during treatment with agomelatine
- Patient's reasons for non-compliance with liver function monitoring
- Patient's booklet:
  - Patients acknowledging receipt of the patient booklet
  - Patients acknowledging that they read the patient booklet
- Distribution of main sources of information about agomelatine

9.4. Data sources

The source of information for the medical record abstraction component of the study will be the medical records of patients who initiated treatment with agomelatine in the periods before and after implementation of the 2014-2015 RMMs in the selected countries.

Medical records of patients initiating treatment with agomelatine will be identified by participating study physicians or designated centre support personnel in each country. If the number of eligible patients at the centre is large (e.g., more than 10 patients by period for a GP and 15 patients by period for a psychiatrist or a neurologist) and exceeds the study requirements, the patients to be abstracted will be randomly selected from the pool of eligible patients. De-identified data will be collected from the patients' records by designated centre 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.

For the patient survey component, the source of information will be the patient questionnaire that patients consenting to participate will complete during one of their regular clinic visits. The patient questionnaire will be self-administered (e.g., paper), and only de-identified data will be collected. As with the medical record abstraction component, if the pool of eligible patients exceeds the study requirements, the patients to be invited to participate in the survey will be selected randomly.

The medical record abstraction and the patient survey components will be performed independently (i.e., a patient can contribute information to the medical record abstraction component and to the survey component, but no linkage of individual patient data will be performed between the two components).

9.5. Study size

The initial sampling frame will be constructed from lists of physicians known to prescribe agomelatine in each country that are available to the MAH (see Section 9.2.2). Within the lists of prescriber physicians, prescribers will be selected randomly. Similarly, within the pool of eligible patients at each practice, for medical record abstraction or survey participation, if the number of eligible patients exceeds the targeted number (> 10 patients for GP practices and > 15 patients for specialty practices), patients will be selected randomly.

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

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

where *t* is the t-test value for a 95% confidence interval; *e* is the margin of error (absolute precision), and *p* the proportion to be measured. An assumption of a 50% proportion of patients compliant with SmPC recommendations results in the largest sample size (see Section 9.5.1). To correct for the difference in design, the sample size is multiplied by the design effect, assumed to be 1.4 for this study.[5,6] The targeted sample size is further increased by 10% to account for a number of contingencies (e.g., medical record not available, non-response).

9.5.1. Medical record abstraction component

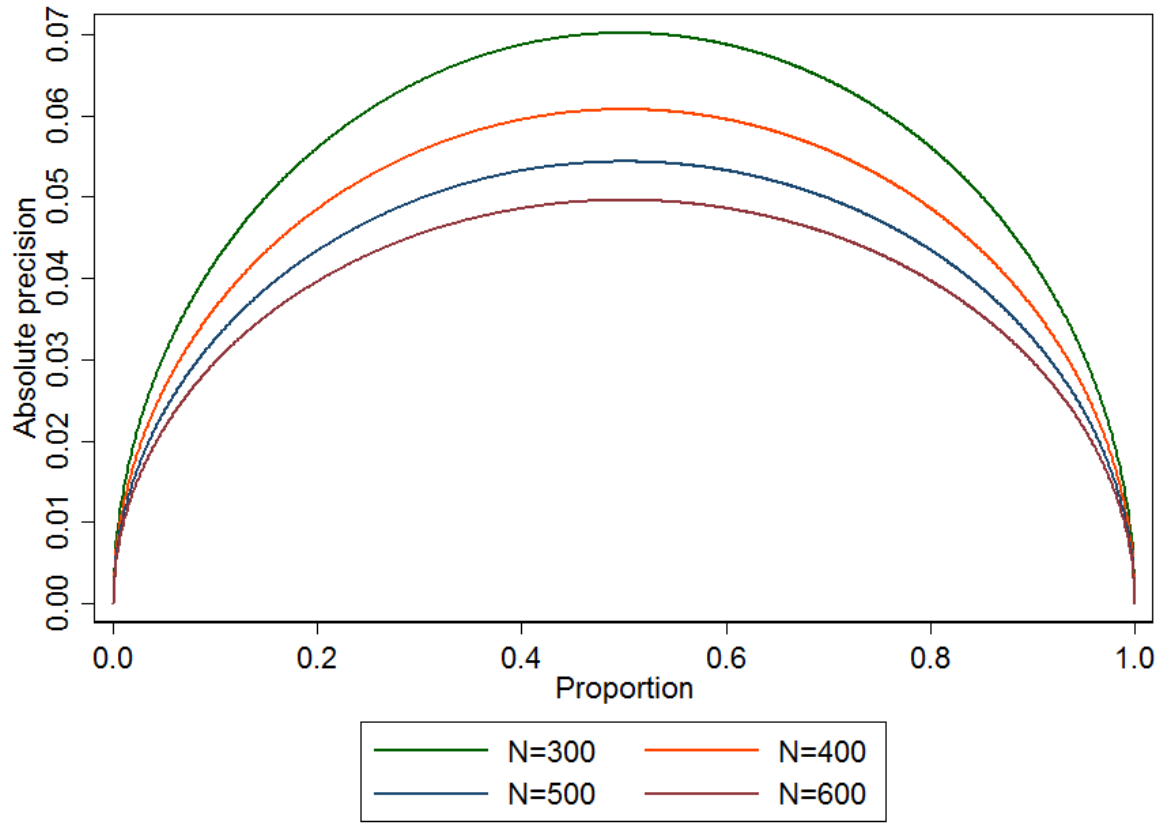
The study size planned for the medical record abstraction component is based on a total of 600 patients initiating treatment with agomelatine in each study period (600 patients before and 600 patients after implementation of the new RMMs) across all countries. The patients for the before-RMM and after-RMM periods will be different as patients will be identified by their first-time prescription of agomelatine. The probability that a patient will be selected for the medical record abstraction component depends on the practice or centre (cluster effect), the physician speciality, the availability of medical charts, and the patient's willingness to provide written consent for participation.

For the purpose of estimating the study size, the main variable of interest is adherence to the liver test monitoring regimen (defined as liver monitoring prior to or at treatment initiation and at least one liver test performed after treatment initiation), and an underlying assumption of 50% adherence to the testing regimen corresponds to the largest sample size. This assumption represents the worst-case scenario from the perspective of absolute precision for a target sample size (meaning it corresponds to the largest sample size). In addition, this worst-case scenario assumption (from a statistical perspective) is close to the 47% adherence observed in the CLE-20098-068 study (Servier study report, data on file). Using this assumption, for a confidence interval of 95% and an error margin of 5%, after applying the design effect factor, the required sample size would be 384 * 1.4 = 538. The further increase of 10% in the sample size to allow for contingencies results in a sample size of 538 + (538 * 10 / 100) = 592 (final target rounded to 600) across the four 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, assuming a proportion of 50% (worst hypothesis) in the measurement of the main outcome, the two-sided 95% confidence interval (CI) will be 45% to

55%. For this worst-case scenario, the absolute precision would be 5%. In the absence of evidence to support the expected proportion, a 50% adherence to liver testing recommendations is the worst-case scenario in terms of precision. Lower or higher point estimates will be associated with greater precision in the 95% CI.

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



Medical practices or centres, including hospital and private practices and physicians' specialties of interest (i.e., general practitioners and psychiatrists) will be targeted in each country. The total and per-country target patient numbers will take into account the volume of sales in each country. The distribution and rate of prescriptions by centre setting and type of prescriber varies between countries. Therefore, to achieve the target sample in each country, the number of centres and the number of patients per practice or centre will be adapted to account for the potential for recruitment, the setting, and the physician speciality.

All reasonable efforts will be made to reach the target sample size of 600 patients for the after-RMM study 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%.

Based on the sales volume per country, the theoretical number of patients for the scenarios with 600 patients and with 400 patients by country and for each period is presented in Table 4.

Table 4: Targeted sample size by country following prescribing pattern in selected countries

	Agomelatine sales[a]			
Country	**n**	**%**	**Targeted sample size for two scenarios**	
Denmark	53,834	3	19[b]	13[b]
France	568,636	34	206	137
Germany	631,268	38	228	152
Spain	406,063	24	147	98
Total	1,659,801	100	600	400

[a] *Total Valdoxan sales, October 2014-June 2015.*
[b] *A minimum of 30 patients for each period will be targeted in Denmark, where the sample size is too small to allow any statistical inference measure.*

A minimum target sample size of 30 patients for each period will be required in countries for which the theoretic sample size is too small to allow any statistical inference measure (e.g., 19 and 13 patients for Denmark).

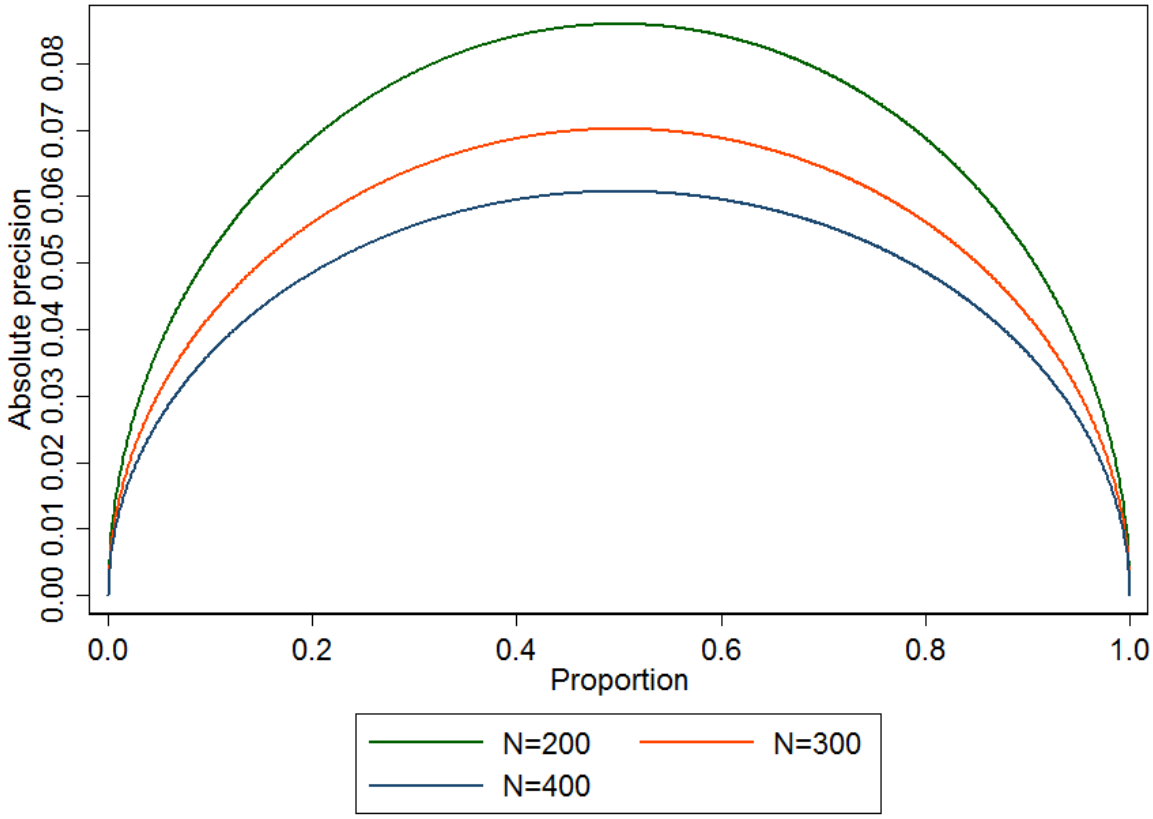
9.5.2. Patient survey component

For the patient survey component, the probability that a patient will be selected will depend directly on the patient's willingness to participate.

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 3. For the survey component of the study, a targeted study size of 400 patients, assuming that 50% of patients refuse to have blood liver tests performed, will have a two-sided 95% CI of 44% to 56%. The 50% assumption was selected because a proportion of 0.5 is the scenario requiring the largest study size. For a worst-case scenario (from a precision perspective) of a proportion of 50% and a targeted sample size of 400, the resulting precision would be 6%. The sample size would result from applying the design factor, 261 * 1.4 = 365 and increasing by 10% to allow for contingencies in attaining the required sample size, 365 + (365 * 10 / 100) = 401 (final target rounded to 400) for the overall selected countries. The lower number of patients targeted for the patient survey takes into account that survey participation is expected to be low in patients with underlying depression. The requirement of written informed consent may also influence patient participation. If the number of eligible patients is higher than the target sample size for each site, then instructions for random selection of eligible patients will be provided.

Efforts will be made to reach the target sample size of 400 patients for the patient survey. However, a target sample size of 300 patients will be considered acceptable to meet the study objective, as the absolute precision would be 7%.

Figure 3: Absolute precision for a 95% confidence interval and three sample size scenarios



The total and per-country target patient numbers will take into account the volume of sales in each country. The distribution and rate of prescriptions by type of prescriber varies between countries. Therefore, to the extent feasible, the distribution of centres will take into account the volume of sales and the pattern of agomelatine prescribers in each country (Table 5). However, a minimum target sample size of 30 patients will be required in countries for which the theoretic sample size is too small to allow any statistical inference measure (e.g., Denmark).

Table 5: Targeted sample size by country following volume of sales in selected countries

	Agomelatine sales[a]			
Country	**n**	**%**	**Targeted sample size, two scenarios**	
Denmark	53,834	3	13[b]	10[b]
France	568,636	34	137	103
Germany	631,268	38	152	114
Spain	406,063	24	98	73
Total	1,659,801	100	400	300

[a] *Total Valdoxan sales, October 2014-June 2015.*

[b] *A minimum of 30 patients in each study period will be targeted in Denmark where sample size is too small to allow any statistical inference measure.*

9.6. Data management

A data management plan will be developed to guide the handling of data, including the transfer of electronic files. The data management plan will include, if necessary, country-specific modifications due to local regulations or requirements.

Medical record abstraction

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 centre 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. The electronic data capture system will be designed with comprehensive logic, range, and edit checks that will allow for near–real-time feedback to the physician investigators and/or the site staff as they complete and submit the medical record abstraction form screens.

Data collection will be performed by physicians or designated centre support staff through the abstraction of data from the patients' medical records directly into the electronic data capture system after written informed consent is obtained (or in France, if the patient did not object to the processing of his/her personal data for health care research purposes). Before data collection begins in the study, formal training will be performed to instruct all study investigators/site support personnel on the study procedures and on procedures to be followed while entering data abstracted from medical records into the electronic data capture system or into a pen-and-paper abstraction form. The site staff will use single data entry when entering data from the patient's medical record into the electronic data capture system.

However, if some centres are found to have limited access to a computer, a pen-and-paper medical record abstraction form option could be considered, and double data entry will be performed by study staff at the data processing center for medical record data collected on paper forms.

Patient survey

Patients will complete the patient survey on paper forms after informed consent is obtained. Patients will be instructed to seal their completed questionnaire in an envelope and return it to the site staff during their visit to the site. Data from complete patient questionnaires will be sent by sites to the data processing centre, located in a central location, for double data entry into the electronic data capture system by the designated study team member responsible for patient data entry.

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, analyses planned, and planned tables and figures.

The analyses will be descriptive and will be performed separately for each study period, country, and, if numbers allow, physician specialty. Description of patient and physician characteristics will be presented as frequency distributions and summary statistics (median, mean, standard deviation, and range).

The main results will be presented as a single estimate of the prevalence of adherence to the frequency of liver monitoring recommendations, defined as the proportion of patients with at least one liver test performed between 4 weeks prior to and 3 days after treatment initiation and at least one test performed during treatment (from 2 weeks to 28 weeks after treatment initiation). This adherence definition will be applicable for both the before-RMM and after-

RMM periods. Prevalence of adherence will be provided with 95% CIs around the point estimate.

In defining the main analysis, we have taken into account that is likely that, due to the shared care management between GPs and specialists, liver function test results and/or dates of tests may not be available in the medical records for all patients. However, a secondary analysis (see below) with a stricter definition of adherence will be conducted with the patients for which testing dates are available. The difference between the calculated prevalence for the main and secondary analyses of the medical record abstraction component before and after implementation of the additional RMMs 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.[7] A chi-square test or a t-test will be used to test the differences for the main and secondary variables between the two study periods.[8]

Regarding missing data, a specific section describing the procedures to study the impact of missing data will be included in the statistical analysis plan. Missing data are expected to be insubstantial and distributed at random. The reason for non-response will be sought, ensuring that missing data will be reported with enough detail to strengthen the validity of the results.

The extent of missing data will be evaluated and described in the final report. The number of subjects with missing data for each variable in the medical record abstraction form and patient questionnaire will be reported in the descriptive tables. Variables found to be recorded only partially or inconsistently in the medical record abstraction form will not be included in the estimation of overall adherence to liver monitoring recommendations and compliance with contraindications. The main analyses will be based on recorded data. Descriptive analysis comparing patients with and without missing data will be conducted. To assess the potential impact of a non-random missing data pattern for adherence/compliance, a sensitivity analysis assuming different percentages of adherence/compliance among patients with missing data will be conducted.

The following analyses are of interest for the data collected through the *site/physician feasibility questionnaire*:

- Distribution of physician characteristics and types of practice settings (for participants and non-participants)
- Proportion of physicians refusing to participate in the study and reasons for refusal
- Reasons for non-qualification of centres

The following analyses are of special interest for each period of the *medical record abstraction component* of the study:

- Distribution of patient demographic characteristics and relevant comorbidities at agomelatine initiation
- Distribution of agomelatine prescription dose at treatment initiation and during follow-up
- Treatment duration based on a Kaplan-Meier curve
- Proportion of patients with liver test (i.e., ALT and/or AST) results more than 3 times the ULN at initiation
- Prevalence of conditions associated with hepatic impairment such as cirrhosis or active liver disease at treatment initiation and occurrence of these conditions during follow-up

- Proportion of patients with concomitant prescriptions of fluvoxamine or ciprofloxacin at treatment initiation or during follow-up
- Proportion of patients with varying levels of adherence to the recommended liver test monitoring regimen—before or at initiation of agomelatine treatment and at 3, 6, 12, and 24 weeks after treatment initiation—accounting for "duration of treatment" and dose escalation.
  - *Main analysis*:
    - The proportion of patients who meet all the following adherence criteria:
      - Criterion 1: Before or at initiation of agomelatine treatment, the proportion of patients with a liver test performed between 4 weeks prior to and 3 days after initiation of treatment

        Criterion 2: After treatment initiation (follow-up), at least one test has been performed during treatment (from 2 weeks to 28 weeks after treatment initiation).

        The frequency of each individual adherence criterion will be estimated. However, in the main analysis, in order to be classified as adherent, patients will have to meet both criteria 1 and 2.
  - *Secondary analyses*:
    - The proportion of patients who meet all the following adherence criteria:
      - Criterion 1: Before or at initiation of agomelatine treatment; a liver test has been performed between 4 weeks prior to and 3 days after initiation of treatment
      - Criterion 2: All required tests during follow-up have been performed according to the duration of treatment and to the following timings as defined in the SmPC recommendations :
        - For the test to be performed 3 weeks after treatment initiation, tests performed in the time period from 2 weeks to 4 weeks after treatment initiation will be acceptable.
        - For the test to be performed 6 weeks after treatment initiation, tests performed in the time period from 5 weeks to 8 weeks after treatment initiation will be acceptable.
        - For the test to be performed 12 weeks after treatment initiation, tests performed in the time period from 9 weeks to 16 weeks after treatment initiation will be acceptable.
        - For the test to be performed 24 weeks after treatment initiation, tests performed in the time period from 17 weeks to 28 weeks after treatment initiation will be acceptable.

        The frequency of each individual adherence criterion will be estimated. However, as in the main analysis, in order to be classified as adherent patients will have to meet both criteria 1 and 2.

        Regarding treatment duration, only the time that the patient has been under treatment will be relevant for timing definition purposes. As an example, if a patient stopped treatment after 1 month, only the test at 3 weeks will have to be documented to consider the patient/physician adherent to the recommended liver test monitoring regimen.

- For those patients who received dose escalation, adherence will be defined as follows:
  - Criterion 1: Before or at dose escalation, a liver test has been performed within 1 week before or after dose escalation
  - Criterion 2: After dose escalation, at least one test has been performed from 2 weeks to 28 weeks after dose escalation.

  The frequency of each individual adherence criterion will be estimated. However, as in the main analysis, in order to be classified as adherent, patients will have to meet both criteria 1 and 2. These criteria will be applicable only to patients who received dose escalation.

- The proportion of patients with the following liver function tests performed:
  - A liver test performed between 4 weeks prior to and 3 days after initiation of treatment
  - One liver function test performed after treatment initiation and while on treatment
  - Two liver function tests performed after treatment initiation and while on treatment
  - Three liver function tests performed after treatment initiation and while on treatment
  - Four liver function tests performed after treatment initiation and while on treatment
  - A liver function test performed between 4 weeks prior to and 3 days after initiation of treatment AND one (or two or three or four) tests performed after treatment initiation and while on treatment.

  For this analysis, as well, only the time that the patient has been under treatment will be relevant for timing definition purposes.

  Sensitivity analyses on varying time-windows will be provided.

The following analyses are of interest for the data collected through the *patient survey*:

- Proportion of patients acknowledging receipt of the patient booklet
- Distribution of patient demographic characteristics (age and sex) for participants and non-participants
- Proportion of patients aware of the risk of liver side effects
- Proportion of patients aware of the liver test monitoring requirement
- Distribution of reasons for refusal to participate in the survey
- Description of the reasons for non-compliance with the liver test monitoring regimen from the patient's perspective

The *main analysis for the patient survey* component will focus on the following:

- Proportion of patients acknowledging receipt of the patient booklet
- Description of the reasons for non-compliance to the liver test monitoring regimen from the patient's perspective; reasons for non-compliance will be categorised and proportions estimated

All analyses will be conducted using SAS statistical software for Windows (version 9.3 or higher) (SAS Institute, Inc., 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, medical record abstraction form, patient questionnaire 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

As with all voluntary studies, some limitations are inherent. The strategy for the selection of centres/physicians is designed to take into account the observed patterns of agomelatine use in each country in relation to the type of centre (e.g., hospital clinic, private clinic) and the proportion of physicians by specialty (e.g., psychiatrists, general practitioners). This approach will aim to ensure selection of a diverse and generally representative sample of centres/physicians and their treated patients to participate in this study. However, there exists no exhaustive list of all agomelatine prescribers and patients from which to draw a sample; hence, it is impossible to select a random sample of all centres/patients. Therefore, the study participants may not necessarily represent all users of agomelatine. All efforts will be made to minimise this bias by accessing large lists of prescribers of agomelatine in each country and by contacting all physicians whose names are randomly selected from the lists for participation in the study. In addition, for recruitment efficiency and to ensure that the target patient numbers are reached, the study will focus on recruitment of sites that have an adequate number of agomelatine-treated patients and sites where data on key variables are available. The number and reasons for excluding sites will be summarized in the study report (Section 11.4, Generalisability). Main characteristics of physicians from the responses to the feasibility questionnaire will help assess potential differences between physicians agreeing to participate

and those refusing to participate. However, these data may be limited as physicians who refuse to participate may not complete the key characteristic questions in the feasibility questionnaire.

In addition, as is true with most surveys, it is possible that patients who participate will differ from those who do not participate in characteristics measured by the study (e.g., knowledge and compliance regarding liver risk and liver test monitoring requirements). The direction and magnitude of such potential respondent bias is not known. Information on main characteristics of participating and non-participating patients (e.g., age, sex) will be collected to help gain further insight into the potential differences between patient participants and non-participants.

Additional challenges and limitations are those related to studies based on data abstracted retrospectively by health care professionals from patient medical records. The study will rely on health care professionals at each participating centre to abstract 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 favour the selection of patients with potentially better information recorded in the medical records or with better adherence to the recommendations for monitoring of liver function. This can be minimised by using selection strategies such random selection of new users of agomelatine, if the available number of eligible patients is large, by providing only limited information about the study to personnel responsible for abstracting the medical record data, and by requesting that patients complete the survey questionnaire at the centre prior to receiving any additional counselling about treatment. Having health care professionals at each centre perform the medical record abstraction also has some advantages. The clinical experience and knowledge about the medical records and centre-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. The probability of missing or underrecording of data for key study variables (e.g., liver function tests results, relevant comorbid conditions) also must be considered. We will investigate the degree of missingness in the data by examining the frequency of missing values for key variables that if found to exceed the established threshold will have an effect on the final number of participants with useful data. The potential for missing data is particularly relevant in the context of the expected shared care management of patients between physicians of different specialties (GPs, psychiatrists).

This study will be based on the information collected in routine medical records, the completeness of which will vary. A potential challenge for study implementation is those countries where patient management is shared by specialists and primary care doctors. In those situations, initial prescriptions might be written by specialists but maintenance prescriptions might be written by GPs. For example, if the specialist was in charge of only the first visit and could not follow the patient for the whole period of treatment, liver test results might have been requested by the specialist and the results were available in the GP's medical records but not in the specialist's medical records. The potential for shared patient management to impact the amount of missing data was evaluated during the pilot phase. Likewise, patient recollection will impact the information collected in the patient survey. Recollection of liver monitoring tests is likely to be higher amongst patients who experienced liver-related adverse events and/or were informed by their physician of abnormal test results.

It is expected that the same physicians will contribute data on new users of agomelatine from both the before-RMM and after-RMM study periods. Pilot 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).[9] However, this effect is expected to be minimal, and to a large extent will be neutralised by the retrospective nature of the study, that is, by timing the start of centre and physician recruitment activities to occur only after dissemination of the new RMMs has been completed and timing the start of data collection to be performed concurrently for both study periods.

10. PROTECTION OF HUMAN SUBJECTS

The study is a non-interventional study that will collect de-identified information from patient medical records and de-identified information through a survey of patients. Only de-identified data will be made available to the research staff and the study sponsor. Thus, any reports that are generated will not contain any patient identifiers. Data will be linked to individual patients and participating physician investigators; however, the linkage will remain with the participating physician investigators and will not be shared with the research staff or the study sponsor.

Local regulations concerning the provision of patient informed consent/patient approval for the retrospective collection of medical record data will be followed. Written informed consent will be required in Denmark, Germany, and Spain. In France, patients will be given the opportunity to object to the processing of his/her personal data for health care research purposes. For the survey component, all patients will provide a written informed consent prior to their participation.

The study protocol and consent forms will be submitted to the required independent ethics committee for review and approval (as required) according to the guidance of each country's research ethics requirements. In addition, applicable national regulations concerning data protection and privacy of individuals that require physicians' authorisation prior to contacting patients for participation in research will be followed.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS / ADVERSE REACTIONS

Based on current guidelines from the International Society for Pharmacoepidemiology (ISPE) [10, Section VI] and the European Medicines Agency (EMA) *Guideline on Good Pharmacovigilance Practices (GVP): Module VI – Management and Reporting of Adverse Reactions to Medicinal Products,*[11, Section VI:C.1.2.1] non-interventional studies such as the one described in this protocol, conducted using medical record reviews or electronic claims and health care records, do not require expedited reporting of adverse events/reactions.

However, adverse events may be reported by patients through the patient survey component of the study. Therefore, any adverse event reported by the patient through the patient questionnaire regardless of its relation to agomelatine treatment will be reported to the Servier pharmacovigilance department, which will be responsible for compliance with applicable

regulatory reporting requirements. The process for safety reporting will be described in detail in the safety reporting plan.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study protocol and interim and final study reports 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.[12]

Study results will be published according to the guidelines, including those for authorship, established by the International Committee of Medical Journal Editors.[13] 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.[14]

13. OTHER GOOD RESEARCH PRACTICE

This study adheres to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)*[10] and has been designed in line with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology*.[15] The *ENCePP Checklist for Study Protocols*[16] has been completed (see Annex 2).

The study is a PASS and will comply with the definition of the non-interventional (observational) study referred to in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) tripartite guideline *Pharmacovigilance Planning E2E*[17] and provided in the EMA *Guideline on Good Pharmacovigilance Practices (GVP): Module VIII: Post-Authorisation Safety Studies*,[12] and with the 2012 European Union pharmacovigilance legislation, adopted June 19, 2012.[18] The study will comply with the study-reporting requirements specified in Module VIII, Section VIII.B.6.3.2, Final Study Report, of the *Guideline on Good Pharmacovigilance Practices*.[12]

The study will be registered in the EU PAS Register[19] before the start of data collection.

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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:
Agomelatine Drug Utilisation Study in Selected European Countries: A Multinational, Observational Study to Assess Effectiveness of Risk-Minimisation Measures

Study reference number:
EU/1/08/499/001-008 (Valdoxan®)
EU/1/08/498/001-008 (Thymanax®)

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[1]	☒	☐	☐	15
1.1.2 End of data collection[2]	☒	☐	☐	15
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☒	☐	☐	15
1.1.5 Registration in the EU PAS Register	☒	☐	☐	15
1.1.6 Final report of study results	☒	☐	☐	15

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)	☒	☐	☐	16
2.1.2 The objectives of the study?	☒	☐	☐	16
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	17
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)	☒	☐	☐	17-19
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	24-25
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.

[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 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	19-23
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	19-23
4.2.2 Age and sex?	☒	☐	☐	19-23
4.2.3 Country of origin?	☒	☐	☐	19-23
4.2.4 Disease/indication?	☒	☐	☐	19-23
4.2.5 Co-morbidity?	☒	☐	☐	19-23
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)	☒	☐	☐	19-22

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)	☒	☐	☐	23-25
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
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.)	☒	☐	☐	19-25
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)	☒	☐	☐	19-25
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?	☒	☐	☐	26-29

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?	☒	☐	☐	30-34
10.3 Are descriptive analyses included?	☒	☐	☐	30-34
10.4 Are stratified analyses included?	☒	☐	☐	30-34
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?	☒	☐	☐	30
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	29-34
11.3 Are methods of quality assurance described?	☒	☐	☐	34
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	34-36
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	34

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	34-36
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)	☒	☐	☐	34-36
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	19-29
12.3 Does the protocol address other limitations?	☒	☐	☐	34-36

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?	☒	☐	☐	36

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	36
13.3 Have data protection requirements been described?	☒	☐	☐	36

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?	☒	☐	☐	12

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)?	☒	☐	☐	37
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	37

Comments:

Name of the main author of the protocol: Lia Gutierrez

Date: 10/November/2016

Signature: ___

Appendix 3: Site Feasibility Questionnaire

Agomelatine Risk Minimisation Evaluation Study

Site Feasibility Questionnaire

Country and City: _____

Clinic/Institution Name: _____

Clinic/Institution Address: _____

_____

Introduction

This site feasibility questionnaire is intended to determine your centre's eligibility and interest in participating as a study site in a post-authorisation observational study that will be conducted in several European countries to assess effectiveness of risk minimization measures for agomelatine in routine clinical practice.

We would be grateful if you would take a moment to read and complete this questionnaire.

Section 1 presents the statement of interest to participate

Section 2 collects information on centre characteristics

Section 3 contains questions to determine your centre's eligibility and the feasibility of implementing data collection at your centre

Section 4 collects the investigator and centre contact details

If you **do not** wish to participate, we would appreciate if you would still complete **Questions 1 through 5** and return a copy to us, because information about both participating and non-participating sites is important to the quality of our study.

For managing purposes of the study, your personal data will be coded and transferred to RTI-HS in the US. You agree to the processing and transfer outside EU of such data.

In accordance with the French Law n°78-17 of January 6th, 1978 called "Loi Informatique et Libertés", you have a right to access or rectify your personal data that you can exercise by sending an email at: dataprivacy@servier.com.

Please return your completed questionnaire to Kantar Health by e-mail or fax by [*insert date*].

Scan and e-mail to: [*e-mail address*]

Fax: [*add number*]

If you have questions about the study, you may contact [*insert name at Kantar Health*] by telephone [*add number*] or e-mail [*add contact e-mail addresses*].

Section 1: Statement of Interest to Participate

1. Please tick one of the following choices to indicate whether you are interested in participating:
   - ☐ Yes. I am interested.
   - ☐ Maybe. I might be interested, but I want to know more. Please telephone me to discuss.
   - ☐ No. I am not interested. Please tick the reason below:
     - ○ I do not have the time and/or staff resources to participate.
     - ○ This study does not apply to me. Neither I nor other physicians at the centre treat patients with agomelatine.
     - ○ Other (please specify)

       _____

It is important for the quality of our study that we are able to compare the characteristics of the participating centres with all centres originally contacted in order to examine potential biases. We would therefore be grateful if you would complete the questions in Section 2 (centre and lead investigator characteristics), even if you indicated that you are not interested in participating in the study.

Section 2: Centre and Physician Characteristics

Questions 2 - 4 ask about the treating physician.

2. What is your medical specialty?
   - ☐ General medicine
   - ☐ Internal medicine
   - ☐ Psychiatry
   - ☐ Neurology
   - ☐ Other, please specify: _____

3. What is your gender?
   - ☐ Male
   - ☐ Female

4. What is your age?
   - ☐ Under 40 years old
   - ☐ 41 to 60 years old

☐ 61 years or older

Question 5 asks about the centre where the study would be conducted.

5. How would you characterise your centre? Check all that apply.

☐ Private practice

☐ Public primary care centre

☐ Hospital-based clinic

☐ Other, please specify: _____

_____

If you are interested in participating in the study or would like additional information, please complete all of the remaining sections.

If you **are not interested** in participating in the study, there is no need to complete the remaining sections. We would be most grateful if you would send your completed form back to Kantar Health according to the instructions on page 1.

Section 3: Centre Eligibility and Data Collection Feasibility

6. Does your site have a systematic way to identify **all** patients treated with agomelatine from January 2013 to the present?

   ☐ Yes ☐ No

7. Over the past 4 years, approximately how many ***unique*** adult patients started treatment with agomelatine at your centre **each year**? Do not include patients who started treatment as part of a clinical trial.

Year	Approximate number of unique adult patients who started agomelatine treatment
2013	
2014	
2015	
2016	

8. Approximately how many ***unique*** adult patients would your site be able to recruit to complete a patient self-administered questionnaire **during a 6-month period** considering the following criteria?

   - Include patients who are currently being treated with agomelatine or who discontinued treatment less than 3 months ago
   - Exclude patients who received agomelatine as part of a clinical trial

   ☐ 1 to 2 patients
   ☐ 3 to 4 patients
   ☐ 5 to 10 patients
   ☐ 10 to 20 patients
   ☐ More than 20 patients

9. Do you or your staff have the resources/time to coordinate study activities at your centre? These activities would include (1) identifying medical records and performing a simple 20- to 30-minute abstraction into an electronic data capture system for approximately 10-30 patients and (2) recruiting 5-10 eligible patients, obtaining informed consent, and enrolling them into the study to complete a patient self-administered questionnaire during their regularly scheduled visit and subsequently mailing the questionnaire to a central location for data entry.

   ☐ Yes, the centre has staff resources available to support these activities.

   ☐ No, the centre does not have any staff resources available.

10. Are details related to **liver function testing (e.g., dates, results)** likely to be available in your centre's medical records for patients treated with agomelatine?

    ☐ Yes

    ☐ No

    Please comment as needed (e.g., if information is partially available or not available):

    _____

11. Does your site have an Internet browser (e.g., Internet Explorer, Google Chrome) that allows access to external web page?

    ☐ Yes ☐ No

Section 4: Investigator and Centre Contact Details

Please provide the following information about the principal investigator.

Principal Investigator	
Title, first and last name	
Telephone number	
Fax number	
E-mail address	

12. Please designate a person who would coordinate study activities at your centre (e.g., study nurse, site coordinator, physician assistant), and provide their contact information below.

    ☐ Please check this box if the principal investigator will coordinate study activities.

Study Coordinator (leave blank if the principal investigator will coordinate study activities)	
First and last name	
Job title	
Telephone number	
Fax number	
E-mail address	

Thank you very much for your interest in this study!

Once we have confirmed your site's eligibility and interest, we will send the site agreement.

If you have any questions, please contact [*insert name*] from Kantar Health at [*e-mail address*] or [*phone number*].

Appendix 4: Medical Record Abstraction Form

Medical Record Abstraction Form

Site ID: ☐☐☐ **Abstractor's Initials:** ☐☐ **Patient ID**: ☐☐☐☐☐☐☐

Patient Demographics and Characteristics

1. Date of abstraction: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)

2. Patient's age at agomelatine treatment initiation:
   - ☐ 18-30 years
   - ☐ 31-45 years
   - ☐ 46-65 years
   - ☐ 66-74 years
   - ☐ ≥ 75 years

3. Patient's sex:
   - ☐ Male
   - ☐ Female

4. **Weight:** ☐☐☐ kg
   - ☐ Unknown

5. **Height:** ☐☐☐ cm
   - ☐ Unknown

6. Date of diagnosis for the episode of major depression associated with initiation of agomelatine treatment: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)

Medical Record Abstraction Form

Site ID: ☐☐☐ **Abstractor's Initials:** ☐☐ **Patient ID**: ☐☐☐☐☐☐☐

Relevant Conditions

7. For each medical condition, please indicate whether or not the condition was present at the initial agomelatine prescription and/or occurred while the patient was taking agomelatine.

Condition:	Present at agomelatine initiation and/or during treatment?	If yes, date of diagnosis:
a. Active liver disease (either acute or chronic) Specify: _____	☐ Yes ☐ No	☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) ☐ Date unknown
b. Non-alcoholic fatty liver disease	☐ Yes ☐ No	☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) ☐ Date unknown
c. Cirrhosis	☐ Yes ☐ No	☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) ☐ Date unknown
d. Alcohol use disorder	☐ Yes ☐ No	☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) ☐ Date unknown
e. Obesity/overweight	☐ Yes ☐ No	☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) ☐ Date unknown
f. Diabetes mellitus (either type 1 or type 2)	☐ Yes ☐ No	☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) ☐ Date unknown

Medical Record Abstraction Form

Site ID: ☐☐☐ **Abstractor's Initials:** ☐☐ **Patient ID**: ☐☐☐☐☐☐☐

Concomitant Medications

8. For each medication, please indicate whether or not the patient was taking the medication at any time while receiving treatment with agomelatine.

Medication:	**Taken by patient?**	**If yes, date medication was started:**
a. Fluvoxamine (add national trade names)	☐ Yes ☐ No	☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) ☐ Date unknown
b. Ciprofloxacin (add national trade names)	☐ Yes ☐ No	☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) ☐ Date unknown

Medical Record Abstraction Form

Site ID: ☐☐☐ **Abstractor's Initials:** ☐☐ **Patient ID**: ☐☐☐☐☐☐☐

Agomelatine Treatment Information

9. Agomelatine prescription dates and doses

Initial prescription

a. Please choose one option to indicate the status of the initial agomelatine prescription:

- ☐ Initial prescription written by physician at recruiting practice → Go to 9b
- ☐ Initial prescription written by a physician outside of recruiting practice → Go to 9b

b. Please enter the agomelatine prescription details:

Date of initial prescription:	Prescribed daily dose:	Prescribed supply:
☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)	☐☐ mg	☐☐ # of boxes → ☐☐ # of pills per box
		OR
☐ Date unknown	☐ Dose unknown	☐☐ # of months
		☐ Supply unknown

Subsequent agomelatine prescription(s)[3]

c. Please choose one option to indicate the status of subsequent agomelatine prescription(s):

- ☐ Subsequent prescription(s) written by physician at recruiting practice → Go to 9d
- ☐ Subsequent prescription(s) written by physician outside of recruiting practice Are details available?
  - ☐ Yes → Go to 9d
  - ☐ No → Go to 9f
- ☐ There is no information available on subsequent prescription(s) → Go to 9f

[3] In the electronic data collection system, the person conducting the medical record abstraction will be able to tick an option to open another screen to record a subsequent prescription. If this option or the next option is ticked, the electronic data collection system will present the next item.

Medical Record Abstraction Form

Site ID: ☐☐☐ **Abstractor's Initials:** ☐☐ **Patient ID**: ☐☐☐☐☐☐☐

d. Please enter the agomelatine prescription details:

Date of renewal or dose change:	Prescribed daily dose:	Prescribed supply:
☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) ☐ Date unknown	☐☐ mg ☐ Dose unknown	☐☐ # of boxes → ☐☐ # of pills per box **OR** ☐☐ # of months ☐ Supply unknown

e. Is there another agomelatine prescription to enter?[4]

☐ Yes → Go to 9d

☐ No → Go to 9f

Discontinuation of treatment☐

f. Please choose one option to indicate the status of treatment discontinuation:

☐ The patient is known to have discontinued treatment → Go to 9g

☐ Prescription information in the medical record indicated that treatment with agomelatine was ongoing at the time of medical record review → Go to 10

☐ It is not known whether treatment has continued or has been discontinued; management of patient's treatment is shared with another physician → Go to 10

g. Please enter the date of treatment discontinuation:

Date of discontinuation: ☐ Date unknown

☐☐/☐☐/☐☐☐☐

(dd/mm/yyyy)

[4] In the electronic data collection system, the person conducting the medical record abstraction will be able to tick an option to open another screen to record a subsequent prescription. If this option or the next option is ticked, the electronic data collection system will present the next item.

Medical Record Abstraction Form

Site ID: ☐☐☐ **Abstractor's Initials:** ☐☐ **Patient ID**: ☐☐☐☐☐☐☐

Liver Function Test Information

10. Liver function test results

a. Please choose one option to indicate the status of liver function test(s):

- ☐ Test(s) performed by physician at recruiting practice → Go to 10b
- ☐ Test(s) performed by physician outside of recruiting practice
  Are details available?
  - ☐ Yes → Go to 10b
  - ☐ No → Stop here you have completed the form
- ☐ Test(s) were ordered but were not performed → Go to 10b
- ☐ Test(s) were not ordered and were not performed → Stop here you have completed the form
- ☐ Unknown whether test(s) were performed; management of patient's treatment is shared with another physician – Stop here you have completed the form

b. Please enter the liver function test details:[5]

Date test was ordered:	Date of test results:
☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)	☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)
☐ Date unknown	☐ Test not completed ☐ Date unknown
ALT (SGPT) – patient's test result:	ALT – lab's upper limit of normal:
☐☐☐☐ U/L	☐☐☐☐ U/L
☐ Normal ☐ Abnormal ☐ Result unknown ☐ Not tested	☐ ULN unknown

[5] Entry fields for liver function test results will be repeated in the electronic data capture system for every blood test that was ordered.

Medical Record Abstraction Form

Site ID: ☐☐☐ **Abstractor's Initials:** ☐☐ **Patient ID**: ☐☐☐☐☐☐☐

AST (SGOT) – patient's test result: ☐☐☐☐ U/L ☐ Normal ☐ Abnormal ☐ Result unknown ☐ Not tested	AST – lab's upper limit of normal: ☐☐☐☐ U/L ☐ ULN unknown

c. Is there another liver function test to enter?

☐ Yes → Go to 10b

☐ No → Stop here you have completed the form

Appendix 5: Patient Survey

Thank you for agreeing to participate in this study!

Questionnaire Instructions

Answer all of the questions by checking the box to the left of your answer.

Select only one answer to each question unless otherwise instructed.

You are sometimes told to skip over some questions in this questionnaire. When this happens, you will see an arrow with a note that tells you what question to answer next; like this:

- ☐ Yes → Go to Question 2.
- ☐ No

If you have any questions or concerns about the information in the questionnaire, please talk with your health care professional.

Patient ID: ☐☐☐☐☐☐☐

Patient Questionnaire

Before you start the questionnaire, we need to confirm that you have signed the informed consent form.

Q1. Did you sign the informed consent form for the study?

- ☐ Yes → Go to Question 2
- ☐ If you have not signed the consent form, please stop here. You must sign the consent form before completing the questionnaire. Please ask the doctor, nurse, or study coordinator for help.

Q2. Please enter today's date: ☐☐/☐☐/☐☐☐☐ (dd/mon/yyyy)

The first few questions ask about your Valdoxan/Thymanax[1] use.

Q3. When did you start your most recent treatment with Valdoxan/Thymanax (also known as agomelatine)? If you do not know or do not remember, please stop here and ask the doctor, nurse, or study coordinator for help in answering this question.

Select the one answer that best applies.

- ☐ Less than 1 month ago
- ☐ Between 1 and 3 months ago
- ☐ More than 3 months ago but less than 6 months ago
- ☐ More than 6 months ago

Q4. Are you currently taking Valdoxan/Thymanax?

- ☐ Yes → Go to the instructions **after** Question 5
- ☐ No → Go directly to Question 5

Q5. How long ago did you **stop** taking Valdoxan/Thymanax? If you do not know or do not remember, please stop here and ask the doctor, nurse, or study coordinator for help in answering this question.

Select the one answer that best applies.

- ☐ Less than 1 month
- ☐ Between 1 and 3 months
- ☐ More than 3 months (please stop and speak with the study coordinator to confirm your eligibility to finish this questionnaire)

[1] Prior to finalizing the questionnaire, separate versions of the questionnaire will be created for each brand name that is used in each country.

Patient ID: ☐☐☐☐☐☐☐

Patient Questionnaire

The next two questions ask about your knowledge of the safety information for Valdoxan/Thymanax (agomelatine). Please note that for these questions, we are interested in your knowledge in general and not about your own experiences with Valdoxan/Thymanax.

Q6. Which of the following side effects can potentially happen from taking Valdoxan/Thymanax?
(Please remember that this question is asking about what you know about possible side effects with Valdoxan/Thymanax and not about side effects that you may have personally experienced.)

Select all that apply.

- ☐ Urinary infections
- ☐ Liver problems
- ☐ Tremors
- ☐ I do not know

Q7. Should patients taking Valdoxan/Thymanax have their liver checked through blood tests?

(Please remember that this question is asking about your knowledge in general and not about liver tests you may have personally had.)

- ☐ Yes
- ☐ No
- ☐ I do not know

The new few questions ask about blood tests you may have had as part of your treatment with Valdoxan/Thymanax.

Q8. Did you have a blood test **before you started taking** Valdoxan/Thymanax?

- ☐ Yes → Go to Question 8a

  Q8a. Was one of the purposes of your blood tests to check your liver function?

  - ○ Yes
  - ○ No
  - ○ I do not know or I do not remember

No → Go to Question 8b

Patient ID: ☐☐☐☐☐☐☐

Patient Questionnaire

Q8b. We are interested in understanding your reason for **not** having blood tests to check your liver function.
Select all that apply.

- ○ I am afraid of needles or having my blood drawn
- ○ I am not able to travel to have my blood drawn
- ○ I do not have the time to have my blood drawn
- ○ I have a blood test planned/scheduled, but I have not had the blood test yet
- ○ My physician did not talk with me about having blood tests
- ○ My physician told me that a blood test is not necessary at this time
- ○ Other, please specify:
  _____
- ○ I do not know or I do not remember → Go to Question 9

Q9. Have you had blood tests **while taking** Valdoxan/Thymanax?

☐ Yes → Go to Question 9a

Q9a. Was one of the purposes of your blood tests to check your liver function?

- ○ Yes
- ○ No
- ○ I do not know or I do not remember

☐ No → Go to Question 9b

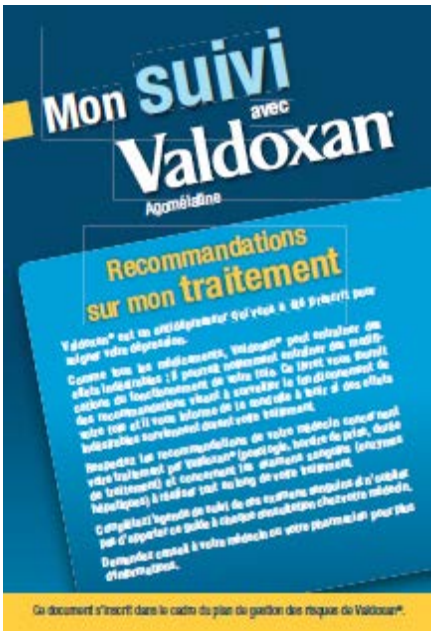
Q9b. We are interested in understanding your reason for **not** having blood tests to check your liver function.
Select all that apply.

- ○ I am afraid of needles or having my blood drawn
- ○ I am not able to travel to have my blood drawn
- ○ I do not have the time to have my blood drawn
- ○ I have a blood test planned/scheduled, but I have not had the blood test yet
- ○ My physician did not talk with me about having blood tests
- ○ My physician told me that a blood test is not necessary at this time
- ○ Other, please specify:
  _____
- ○ I do not know or I do not remember

Patient ID: ☐☐☐☐☐☐☐

Patient Questionnaire

Now we are going to ask you some questions about the Patient Booklet that you may have received from your doctor or other health care professional. The Patient Booklet contains important safety information about Valdoxan/Thymanax. A picture of the Patient Booklet is provided below.[1]



Q10. Have you ever received or been given a Patient Booklet for Valdoxan/Thymanax?

- ☐ Yes → Go to Question 11
- ☐ No → Go to Question 13
- ☐ I do not know or I do not remember → Go to Question 13

Q11. Have you ever read the Patient Booklet for Valdoxan?

- ☐ Yes
- ☐ No
- ☐ I do not know or I do not remember

[1] The patient questionnaire for each country will have a picture of the cover of that country's patient booklet.

Patient ID: ☐☐☐☐☐☐☐

Patient Questionnaire

Q12. Did you look at the Patient Booklet for Valdoxan just before or while you were completing this questionnaire?

- ☐ Yes
- ☐ No

Q13. Where do you get most of your information about Valdoxan/Thymanax?

Select the one answer that best applies.

- ☐ From my general practitioner
- ☐ From my psychiatrist
- ☐ From my pharmacist
- ☐ From a friend or family member
- ☐ From my caregiver
- ☐ From the Valdoxan/Thymanax Patient Booklet
- ☐ From the Valdoxan/Thymanax Patient Information Leaflet provided inside the medication box
- ☐ From articles in newspapers or magazines
- ☐ From the Internet
- ☐ Other, please specify: _____
- ☐ I have not received information about Valdoxan/Thymanax

Patient ID: ☐☐☐☐☐☐☐

Patient Questionnaire

In this last section, please tell us a little information about yourself to help us describe the participants completing this questionnaire.

Q14. How old are you?

- ☐ 18-30 years
- ☐ 31-45 years
- ☐ 46-65 years
- ☐ 66-74 years
- ☐ ≥ 75 years

Q15. Are you …?

- ☐ Male
- ☐ Female

Q16. What is the highest level of education you have completed?[1]
Select the <u>one</u> answer that best applies.

- ☐ Primary school education or less
- ☐ Secondary school education
- ☐ Professional or work-related college qualifications (for example, Certificate of Higher Education, Diploma of Higher Education, foundation degree)
- ☐ Undergraduate university degree (for example, BSc/BA)
- ☐ Postgraduate university degree (for example, MSc/MA, MPhil, PhD)

You have now reached the end of the questionnaire. Thank you for your participation. Please place your completed questionnaire back into the envelope and seal the envelope.

[1] Response choices for this question will be specific for each country.