PASS Information

Document title	Post-Authorisation Safety Study of Agomelatine and the Risk of Hospitalisation for Acute Liver Injury
Protocol version identifier	2.1
Date of last version of protocol	22 July 2015
EU PAS Register number	Will be registered following European Medicines Agency endorsement and prior to start of data collection
Active substance (ATC code)	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
Joint PASS	No
Research question and objectives	The objective is to compare the risk of hospitalisation for acute liver injury in patients initiating treatment with agomelatine and other antidepressants with the risk in patients initiating treatment with citalopram
Country(-ies) of study	Spain, Germany, Denmark, and Sweden
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CONFIDENTIAL

Approval Page: RTI Health Solutions

Project Title: Post-Authorisation Safety Study of Agomelatine and the Risk of Hospitalisation for Acute Liver Injury

IRIS Protocol ID Number: CLE-20098-94

Effective Date:

Authors	Manel Pladevall, MD, MS; Cristina Rebordosa, MD, PhD; Jordi Castellsague, MD, MPH; Susana Perez-Gutthann, MD, MPH, PhD (RTI Health Solutions)
Version:	2.1
Version Date:	22 July 2015

The following person has reviewed the protocol and gives approval:

[redacted]

Susana Perez-Gutthann, MD, MPH, PhD, FISPE, FRCP
Vice President and Global Head of Epidemiology

22 JULY 2015
Date

Approval Page: Les Laboratoires Servier (IRIS)

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Version:	2.1
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The following people have reviewed the protocol and give their approval:

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Approval Page: Scientific Advisers

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Version:	2.1
Version Date:	22 July 2015

The following people have reviewed the protocol

Prof. Bruno Falissard
Professor in Public Health; Head of INSERM Research Unit U669 (Public Health and Mental Health); Child & Adolescent Psychiatrist

Prof. Gabriel Perlemuter
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Note: The final version of the protocol will be signed by a representative of each research partner: IACS, SIDIAP, BIPS GmbH, University of Southern Denmark (Institute of Public Health), and Karolinska Institutet

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2. LIST OF ABBREVIATIONS

ALI	acute liver injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BIPS GmbH	Leibniz Institute for Prevention Research and Epidemiology
CI	confidence interval
CMBD-AH	database of hospital admissions (Spain)
COPD	chronic obstructive pulmonary disease
CPN	central pharmaceutical number
DILI	drug-induced liver injury
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EpiChron	EpiChron Research Group on Chronic Diseases (Spain)
EU	European Union
GePaRD	German Pharmacoepidemiological Research Database
GP	general practitioner
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
IACS	Aragón Institute of Health Sciences (Instituto Aragonés de Ciencias de la Salud)
ICD-10	*International Statistical Classification of Diseases and Related Health Problems, 10th Revision*
ICD-10-CM	*International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification*
ICD-9-CM	*International Classification of Diseases, 9th Revision, Clinical Modification*
ICPC	International Classification of Primary Care
IPR	Swedish National Inpatient Register
IRB	institutional review board
IRIS	Institut de Recherches Internationales Servier
ISPE	International Society for Pharmacoepidemiology
NSAID	non-steroidal anti-inflammatory drug
OQA	Office of Quality Assurance (RTI-HS)
PASS	post-authorisation safety study
RR	rate ratio (or risk ratio)
RTI-HS	RTI Health Solutions

SHI	statutory health insurance agency (Germany)
SIDIAP	Information System for the Advancement of Research in Primary Care (Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària)
TB	total bilirubin
ULN	upper limit of the normal range

3. RESPONSIBLE PARTIES

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Manel Pladevall, MD, MS; Director of Epidemiology

Jordi Castellsague, MD, MPH; Director of Epidemiology

Cristina Rebordosa, MD, PhD; Senior Research Epidemiologist

Collaborating Institutions	Study Sites
EpiChron Research Group on Chronic Diseases[a] at the Aragón Institute of Health Sciences (IACS),[b] Spain	EpiChron database, Spain
Research Institute in Primary Care (IDIAP), Jordi Gol (IDIAP),[c] Spain	The Information System for the Advancement of Research in Primary Care (SIDIAP)[d] database, Spain
Department of Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology (BIPS GmbH), Bremen, Germany	The German Pharmacoepidemiological Research Database (GePaRD), Germany[e]
University of Southern Denmark (Institute of Public Health)	Danish National Patient Register + Danish National Prescription Registry + Danish National Database of Reimbursed Prescriptions
Karolinska Institutet, Sweden	National Registers, Sweden

[a] *Grupo EpiChron de Investigación en Enfermedades Crónicas.*
[b] *Instituto Aragonés de Ciencias de la Salud.*
[c] *Institute d'Investigació en Atenció Primària.*
[d] *Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària.*
[e] *Pending approval by the statutory health insurance providers.*

4. ABSTRACT

Title: Post-Authorisation Safety Study of Agomelatine and the Risk of Hospitalisation for Acute Liver Injury.
Version 2.1, 22 July 2015
Manel Pladevall, MD, MS; RTI Health Solutions

Rationale and background: Agomelatine (Valdoxan, Thymanax) is a melatonergic agonist and 5-HT2C antagonist indicated for major depressive episodes in adults. Hepatotoxic reactions are an identified risk of agomelatine included in the European risk management plan. The goal of this post-authorisation safety study (PASS) is to evaluate the risk of acute liver injury (ALI) associated with agomelatine as used in current medical practice in comparison with other antidepressant drugs. This protocol describes the design and main characteristics of the agomelatine PASS planned to be conducted in automated health databases in Spain, Germany, Denmark, and Sweden. The selection of these databases was based on a feasibility study showing they had a reasonable number of patients exposed to agomelatine.

Research question and objectives: The primary objective will be to estimate, with the nested case-control analysis, the fully adjusted odds ratio of hospitalisation for ALI comparing new users of agomelatine and other antidepressants with new users of citalopram. The secondary objective will be to estimate the age- and sex-adjusted incidence rate ratio of hospitalisation for ALI comparing new users of agomelatine and other antidepressants with new users of citalopram.

Study design: This is a large, multinational, retrospective longitudinal cohort and nested case-control study of new users of agomelatine (main exposure of interest) and new users of citalopram (common reference group), fluoxetine, paroxetine, sertraline, escitalopram, mirtazapine, venlafaxine, duloxetine, and amitriptyline.

Population: The study cohort includes adults from the source populations with at least 12 months of continuous enrolment in the data source who have a first-recorded prescription of agomelatine or one of the other study antidepressants during the study period and had not received a prescription for the same study antidepressant within the prior 12 months. Patients with history of liver disease or risk factors for liver disease, chronic biliary or pancreatic disease; malignancy or other life-threating conditions; and women during pregnancy will be excluded from the study cohort.

Variables: The main exposures of interest will be current use of agomelatine and other selected antidepressants. The primary endpoint, common in all the study data sources, is defined as any patient with a hospital diagnosis for ALI identified with specific ICD-9-CM or ICD-10-CM1 diagnosis codes. The secondary endpoint is defined by specific and non-specific diagnoses and will be evaluated only in selected study databases (Spain and Denmark) in which validation of this less specific outcome by review of medical records and/or results from liver tests will be implemented. The tertiary endpoint will be assessed using specific and non-specific codes identified in both hospital and ambulatory settings, and the endpoint will be evaluated in all data sources whether or not validation is feasible.

1 *International Classification of Diseases, 9th Revision, Clinical Modification* and *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification.*

Data sources: Based on the results of a feasibility evaluation in 2013, the EpiChron and SIDIAP databases in Spain, the German Pharmacoepidemiological Database (GePaRD) in Germany, the national registries in Denmark, and the national registers in Sweden have been identified as the best candidate data sources in which to implement the study. All the research institutions have confirmed interest in participating in the study.

Study size: The study size is driven by the uptake of agomelatine in the populations from which the automated data sources obtain data. We have estimated that approximately 65,000 to 92,000 users of agomelatine might be available for analysis during the study period. With this study size, and depending on the incidence of hospitalisation for ALI in the study populations, the minimum odds ratio to be detected in the nested case-control study with an 80% power ranges from 2.1 to 6.8 for the scenario with the lowest number of users of agomelatine and from 1.9 to 5.6 for the scenario with the highest number of users of agomelatine.

Data analysis: In the cohort analysis, crude and age- and sex-standardised incidence rates of hospitalisation for ALI will be estimated for current use of agomelatine and each study antidepressant. The Kaplan-Meier method will be used to estimate the crude cumulative incidence of ALI at monthly intervals after the first dispensing of agomelatine and each study antidepressant. Age- and sex-adjusted incidence rate ratios will be estimated for agomelatine and each study antidepressant during current use, compared with citalopram current use.

In the nested case-control analysis, cases and controls will be matched on age, sex, index date, and calendar year of start date. By using density-based sampling, controls will have a duration of follow-up proportionate to that of cases, and the index date of the case will be assigned to the matched controls. For all study endpoints, the risk of ALI in current users of agomelatine and current users of the other study antidepressants will be compared with the risk in current users of citalopram, adjusting for confounders using conditional logistic regression. A secondary analysis will be conducted to estimate the effect in current single users of the study antidepressants. Sensitivity analyses will include, among others, the assessment of recent and past use of the study antidepressants, as well as the impact of validation.

Milestones:[1]

- October 2014: Submission to the European Medicines Agency Pharmacovigilance Risk Assessment Committee
- 23 April 2015: Final PRAC and CHMP endorsement of the study protocol
- 31 July 2015: Contracts and registration in the EU PAS Register
- Between 1 August 2015 and 31 March 2016: Data collection
- 30 June 2016: Interim data analysis (SIDIAP, EpiChron, Denmark)
- 30 September 2016: Interim report (SIDIAP, EpiChron, Denmark)
- 30 November 2016: Final data analysis completed (SIDIAP, EpiChron, Denmark, Sweden, and Germany)
- 31 January 2017: First draft study report (SIDIAP, EpiChron, Denmark, Germany, and Sweden)
- 30 April 2017: Final study report (SIDIAP, EpiChron, Denmark, Germany, and Sweden)

1 Contracts between the sponsor and research organization(s) and approvals by data protection, data custodian, ethics, and scientific and regulatory (e.g., Pharmacovigilance Risk Assessment Committee) review bodies are pending. Timelines may be impacted by approvals of these bodies, duration of contract reviews, and availability of data and staff at research institutions once contracts and approvals are finalized.

5. AMENDMENTS AND UPDATES

Protocol version 2.0 is a revision of version 1.0.

Version Number	Date	Section(s) of Study Protocol	Amendment or Update	Reason
2.1	22 July 2015	Section 6, Milestones and Timeline	Timeline was updated	To reflect actual anticipated dates of completion
2.1	22 July 2015	Sections 8.1, Specific Aims; 9.2.1, Source Population; 9.2.2, Study Period; 9.2.3.5, Exclusion Criteria; 9.2.4.2, Selection of Controls; 9.3.1; Endpoint Definition and Ascertainment; 9.3.2, Exposure Assessment; 9.3.3, Risk Factors and Confounding; 9.4, Data Sources; 9.5, Study Size 9.7.1.3, Estimation of Cumulative Incidences; 9.7.3, Interim Analysis (new); 9.7.4, Sensitivity Analyses; 9.7.5, Meta-analysis; 9.9, Limitations of the Research Methods; and 10, Protection of Human Subjects; Table (14.6) 4 - Key Features of the Swedish Databases	Text was edited	To clarify unclear statements identified in additional reviews by the research team, correct identified typos, and update the text with the most recent information available after review of the protocol by research partners.

Version Number	Date	Section(s) of Study Protocol	Amendment or Update	Reason
2.1	22 July 2015	Section 9.4, Data Sources, and across the protocol	The name of the Aragón Institute of Health Sciences (Instituto Aragonés de Ciencias de la Salud [IACS]) database was changed to the EpiChron Database	Requested by research partners from the EpiChron Research Group on Chronic Diseases at IACS
2.1	22 July 2015	Section 9.7.2.1, Description of the cases and controls	A subsection explicitly specifying that description of the cases and controls will be performed was added	It was planned but not explicit in the protocol that cases and controls would also be described
2.1	22 July 2015	Section 9.7.4.3, Switching and Multiple Current Use	Additional sensitivity analysis was added	To explore the impact of switching and multiple use
2.1	22 July 2015	Section 9.2.3.5, Exclusion Criteria	History of paracetamol intoxication has been added as an exclusion criterion	The condition is a potential confounder of the association between the exposures of interest and the study endpoints
2.1	22 July 2015	Table (14.5) 3 - Exclusion Codes for Drug Abuse and Dependence	Codes for other stimulant-related disorders were added	The conditions are potential confounders of the association between the exposures of interest and the study endpoints

Version Number	Date	Section(s) of Study Protocol	Amendment or Update	Reason
2.0	13 Feb 2015	Section 8, Research Question and Objectives; Section 9.7, Data Analysis; Section 9.7.1, Cohort Analysis (Secondary Analysis); Section 9.7.2, Case-Control Analysis (Primary Analysis).	Aims have been re-written to clarify that the primary objective is to estimate the odds ratio of hospitalisation for ALI comparing new users of agomelatine and the other study antidepressants with new users of citalopram. The primary objective and primary analysis have been aligned. The nested case-control analysis, in which complete confounder adjustment will be implemented, is the primary analysis. The cohort analysis with adjustment limited to age and sex is the secondary analysis.	To clarify and align primary and secondary goals with primary and secondary analysis (PRAC request)
2.0	13 Feb 2015	Section 9.1, Study Design; Section 9.7.1, Cohort Analysis (Secondary Analysis)	Age- and sex-standardised incidence rates of ALI for agomelatine and each study antidepressant will be estimated. Moreover, age- and sex-adjusted incidence ratio ratios will be estimated for agomelatine and each study antidepressant versus citalopram (common reference group).	To gain efficiency by including estimates, although not fully adjusted, from the cohort analysis that should have better precision than the nested case-control analysis estimates (PRAC request)
2.0	13 Feb 2015	Section 9.1, Study Design; Section 9.4.1, Status of Contacts With the Study Data Sources; Section 9.4.2, Description of the Data Sources; Section 9.4.2.3.3, The Danish National Database of Reimbursed Prescriptions	Participation in the study of the investigators at The Karolinska Institutet (Sweden) and Swedish data sources was confirmed. Clarification that the whole SIDIAP database will be used and not just SIDIAP-Q, which will allow a larger number of patients.	In the previous protocol version, Swedish participation was pending After discussions between RTI-HS and SIDIAP, it was decided that given the study goals and variables needed, restriction to SIDIAP-Q was not necessary

Version Number	Date	Section(s) of Study Protocol	Amendment or Update	Reason
			Description of data source characteristics was updated after review and additional information were provided by research partners. Text describing the finally selected prescription data source in Denmark has been added.	New database in Denmark selected for logistic and efficiency reasons
2.0	13 Feb 2015	Section 9.1, Study Design; Section 9.3.1.1, Endpoint Definition; Section 9.3.1.1.2, Secondary Endpoint (Selected Databases); Section 9.3.1.1.3, Tertiary Endpoint (All Databases); Section 9.3.1.1.4, Validation of Secondary and Tertiary Endpoints	A new tertiary endpoint, including both hospitalised and outpatient cases of ALI, has been added. This outcome will be ascertained in all data sources. Additional codes have been added to the list of codes used to identify secondary endpoint cases.	To capture additional cases of ALI and to increase the study power (PRAC request)
			Text has been added in the validation section to describe how and in which data sources validation of the tertiary endpoint will be implemented. A New table, which display the information availability for case validation for the hospitalised endpoints (primary and secondary) and the hospitalised and outpatient endpoint (tertiary), have been added in Section 9.3.1.1. Text describing the process of validating outpatient records has been added.	To provide detailed description of the validation process for the three study endpoints
2.0	13 Feb 2015	Section 9.2.3.2, New Users; Section 9.2.3.6, Follow-up	Text clarifying that cohort members can be included in more than one study antidepressant cohort if they met criteria for inclusion and that follow-up will not be censored if a cohort member switches to a new study antidepressant.	To add clarity to the text (PRAC request)

Version Number	Date	Section(s) of Study Protocol	Amendment or Update	Reason
2.0	13 Feb 2015	Section 9.2.3.5, Exclusion Criteria; Section 9.3.3.2, Nested Case-Control Study; Section 9.3.3.2.3, Liver Disease and Risk Factors; Section 9.7, Data Analysis	A detailed differentiation between acute/subacute liver diseases and chronic liver diseases as exclusion criteria has been added. Text has been added to specify that both time before the start date and time before the index date will be assessed for the presence of comorbidities and potential confounders. Occupational exposures related to liver diseases have been added.	To add clarity and detail to the list of exclusion criteria conditions and to the description of the time window for evaluation of potential confounders (PRAC request)
2.0	13 Feb 2015	Section 9.2.4.2, Selection of Controls	Text specifying that no cases will be lost during the matching process was added.	To add clarity to the text (PRAC request)
2.0	13 Feb 2015	Section 9.3.3.2.11, Number of Liver Tests Performed	Text to indicate that liver function test results will be available not only in SIDIAP but also in EpiChron was added.	New information added
2.0	13 Feb 2015	Section 9.5, Study Size	The number of potential users of agomelatine was updated by adding 2013 data for SIDIAP and GePaRD.	To update the information previously provided
2.0	13 Feb 2015	Section 9.7, Data Analysis; Section 9.7.4.5, Confirmed Cases Versus Unconfirmed Cases)	Description of the software that will be used to perform the statistical analysis has been added. A sensitivity analysis for the tertiary endpoint, comparing results of analysis including only validated cases with results of analysis including all cases, has been added.	To provide more detailed information (PRAC request) To evaluate the potential impact of detection bias
2.0	13 Feb 2015	Section 9.9, Limitations of the Research Methods	Text has been added to comment on the potential for detection bias associated with the tertiary endpoint that includes both hospitalised and outpatient cases.	To comment on the limitations of the newly added tertiary endpoint

6. MILESTONES AND TIMELINE

Milestone	Anticipated Date
Protocol V1.0 submission to PRAC	October 2014
Protocol V2.0 submission to PRAC	February 2015
EMA protocol endorsement	23 April 2015
Contracts finalised	31 July 2015
Registration in the EU PAS Register	31 July 2015
Start of data collection (first data source)[a]	1 August 2015
End of data collection (last data source)[b]	31 March 2016
Interim data analysis and report: SIDIAP, EpiChron, Denmark, primary endpoint[c]	
Interim analysis completed	30 June 2016
Interim report	30 September 2016
Final data analysis and report: SIDIAP, EpiChron, Denmark, Sweden, and Germany	
Final data analysis completed	30 November 2016
First draft report	31 January 2017
Final report	30 April 2017

EpiChron = EpiChron Research Group on Chronic Diseases at the Aragón Institute of Health Sciences; PRAC = Pharmacovigilance Risk Assessment Committee; PSURs = Periodic Safety Update Reports; SIDIAP = Information System for the Advancement of Research in Primary Care.

Note: Contracts between the sponsor and research organisation(s) and approvals by data protection, data custodian, ethics, and scientific and regulatory review bodies (e.g., PRAC) are pending. Timelines may be impacted by approvals of these bodies, duration of contract reviews, and availability of data and staff at research institutions once contracts and approvals are finalised. Above timeline are based on contracts signed by April 2015.

[a] Start of data collection is "the date from which information on the first study subject is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts." (EMA, 2012a, Section VIII.B.2)
[b] End of data collection is "the date from which the analytical data set is completely available." (EMA, 2012a, Section VIII.B.2)
[c] It was not possible to complete the validation process for this date, so the interim analysis will be limited to the primary endpoint as no validation is needed for this endpoint.

7. RATIONALE AND BACKGROUND

Agomelatine (Valdoxan, Thymanax) is a melatonergic agonist and 5-HT2C antagonist indicated for major depressive episodes in adults (EMA, 2013a). 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 (Valdoxan/Thymanax) was favourable in the treatment of major depressive episodes. The marketing authorisation was granted in February 2009 and renewed in November 2013 in the European Union. 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 mentioned that 1.4% of patients treated with 25 mg of agomelatine and 2.5% of patients treated with 50 mg showed elevated transaminases. In addition, as a risk-minimisation measure, the summary of product characteristics recommends that transaminase levels be checked before treatment initiation and then after 3, 6, 12, and 24 weeks and also following a dose increase.

To completely characterise the hepatic risk with agomelatine, the European risk management plan included as an additional pharmacovigilance activity a post-authorisation safety study (PASS) assessing and investigating this risk in current medical practice in patients newly treated with agomelatine and major antidepressants. In February 2014, the Pharmacovigilance Risk Assessment Committee invited the marketing authorisation holder to comment on whether it would be advisable to perform the database cohort study, at that time proposed to be performed in the Clinical Practice Research Database in the United Kingdom, in a different or additional data sources to provide results from the study earlier than currently estimated. At the request of the Institut de Recherches Internationales Servier (IRIS), RTI Health Solutions (RTI-HS) conducted a feasibility evaluation of European data sources (Pladevall et al., 2013a) and developed a protocol synopsis outline (Pladevall et al., 2013b) for conducting the study. The feasibility evaluation revealed that given the very low incidence of acute liver injury (ALI) (Andrade et al., 2005; Ibanez et al., 2002; Sgro et al., 2002), a study using multiple data sources was necessary to estimate the associated risk with a minimum level of precision. As reflected in the feasibility evaluation results, the number of users in the United Kingdom (UK) and Italy was too low to use data sources available in those countries, and the authors of the feasibility evaluation proposed using available data sources in Spain, Germany, Denmark, and Sweden, where the use of agomelatine is more common than in Italy and the UK (Pladevall et al., 2013a). IRIS submitted the protocol synopsis outline to the EMA during the first quarter of 2014.

In this regulatory context and based on the positive conclusion of the feasibility study, IRIS requested that RTI-HS develop this detailed study protocol for conducting a PASS to evaluate the risk of hospitalisation for ALI associated with the use of agomelatine.

Hepatotoxic reactions also occur with other antidepressants; they seem to be more common with iproniazid, nefazodone, phenelzine, imipramine, amitriptyline, duloxetine, bupropion, trazodone, and tianeptine but less common with citalopram, escitalopram, paroxetine, and fluvoxamine (Park and Ishino, 2013; Voican et al., 2014). Paroxetine, fluoxetine, fluvoxamine, citalopram, mirtazapine, and venlafaxine are associated with reversible liver injury upon discontinuation of the agent (Park and Ishino, 2013). However, life-threatening or severe ALI has been reported for antidepressants such as monoamine oxidase (MAO) inhibitors,

tricyclic/tetracyclic antidepressants, venlafaxine, duloxetine, sertraline, bupropion, nefazodone, trazodone, and agomelatine (Voican et al., 2014).

We have identified a single study on the risk of ALI associated with the use of antidepressants using an automated health care data source, which was conducted in the Ingenix Research Data Mart in the United States (Xue et al., 2011). In that study, current use of duloxetine was associated with an increased risk of hepatic injury compared with non-use of duloxetine. In addition, initiators of duloxetine had a higher risk of hepatic events than initiators of venlafaxine or tricyclic antidepressants.

8. RESEARCH QUESTION AND OBJECTIVES

The objective is to assess the risk of hospitalisation for ALI in patients initiating treatment with agomelatine or other antidepressants compared to patients initiating citalopram.

8.1. Specific Aims

The primary objective of the study is to estimate, using the nested case-control-analysis, the fully adjusted odds ratio of hospitalisation for ALI comparing new users of agomelatine, fluoxetine, paroxetine, sertraline, escitalopram, mirtazapine, venlafaxine, duloxetine, and amitriptyline with new users of citalopram used as a common reference group.

The secondary objective of the study is to estimate the following values from the cohort analysis:

- The age- and sex-adjusted incidence rate ratios of hospitalisation for ALI comparing new users of agomelatine, fluoxetine, paroxetine, sertraline, escitalopram, mirtazapine, venlafaxine, duloxetine, and amitriptyline with new users of citalopram.
- To estimate, from the full cohort analysis, the age- and sex-standardised incidence rates of hospitalisation for ALI among new users of agomelatine and the other study antidepressants.

For the primary and secondary endpoints, ALI will be identified using hospital discharge codes. For the additional exploratory tertiary endpoint, ALI will be identified using both hospitalisation and outpatient codes. In the data sources with available information, cases (either outpatient or hospitalised) will be validated by clinical review of medical records and/or results of liver enzyme and function tests.

9. RESEARCH METHODS

9.1. Study Design

This is a large, European multinational database, longitudinal retrospective cohort and nested case-control study of new users of agomelatine (main exposure of interest) and new users of citalopram (common reference group), fluoxetine, paroxetine, sertraline, escitalopram, mirtazapine, venlafaxine, duloxetine, and amitriptyline.

- In the cohort study, crude incidence rates and age- and sex-standardised incidence rates of ALI will be calculated in new users of each of the study antidepressants. Moreover, age- and sex-adjusted incidence rate ratios will be estimated for agomelatine and each of the study antidepressants versus citalopram (common reference group).

- In the nested case-control study, the risk of hospitalisation for ALI in new users of agomelatine and each of the other study antidepressants will be compared with the risk in new users of citalopram, adjusting for all known or suspected confounding factors.

The study is proposed to be conducted in the following countries and data sources:

- Spain, the EpiChron database
- Spain, the Information System for the Advancement of Research in Primary Care (Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària [SIDIAP]) database in Catalonia
- Germany, the German Pharmacoepidemiological Research Database (GePaRD)
- Denmark, the Danish national and regional registries
- Sweden, the Swedish national registers

A detailed description of these data sources is included in Section 9.4.

Study Participation

The investigators at EpiChron and SIDIAP (Spain), the GePaRD (Leibniz Institute for Prevention Research and Epidemiology [BIPS GmbH], Germany), The Karolinska Institutet (Sweden), and the University of Southern Denmark (Institute of Public Health) have reviewed the protocol version 1.0 and confirmed interest in participating in the study.

The full cohort, comprising all antidepressant-specific cohorts, will be used to identify the ALI endpoint. Patients will be followed for the occurrence of ALI from the date of first dispensing of a prescription for any of the study antidepressants. The medical history of each patient prior to entry in the study cohorts will be ascertained using all available diagnoses recorded in the data sources. This information will be used to establish eligibility for cohort entry and to generate indicator variables for comorbidities, comedications, health care resource use, and clinical conditions that could act as potential confounders of the association between antidepressant use and ALI. If appropriate, these variables will be used for adjustment purposes in the nested case-control analysis.

Hospitalisations for ALI will be identified according to specific hospital discharge diagnoses in all databases (primary endpoint). In the study data sources with adequate information, specific and non-specific hospitalisation diagnoses of ALI will be confirmed (secondary endpoint) through the review of hospital medical records and/or results of liver enzymes and function tests, according to international criteria for the definition of ALI (Section 9.3.1.1). Cases of ALI identified either by hospitalisation or outpatient specific and non-specific codes will be identified in all databases (tertiary endpoint).

The study will start in 2015 after the study protocol is endorsed. The study period in each data source will begin at the launch date of agomelatine in each country (2009) and end with the most recent data available in each data source (2012 to 2014). See Table (9.2.2) 1.
This study protocol is a common protocol that will be adapted to the specifications of each of the participating data sources. The analysis will be conducted separately in each data source, and overall estimates of effect will be obtained using meta-analytic techniques.

9.2. Setting

9.2.1. Source Population

The source population includes all individuals aged 18 years or older registered in each study data source since the date of the first-recorded prescription of agomelatine or any of the other study antidepressants.

9.2.2. Study Period

The study period is defined in each data source as the time between the date of first-recorded prescription for agomelatine and the latest date of data availability (see Table (9.2.2) 1). Data availability in each data source depends on the frequency with which data are updated at each data source and on the approvals for obtaining the data (e.g., 6 to 9 months for the GePaRD, Germany).

Table (9.2.2) 1 - Estimated Study Period in Each Study Data Source

Event	EpiChron, Spain	SIDIAP, Spain	GePaRD, Germany	National and Primary Care Registries, Denmark	National Registers, Sweden
Agomelatine launch in country[a]	Nov 2009	Nov 2009	Mar 2009	Jun 2009	Jun 2009
Study period (based on agomelatine launch date in each country and data availability in each data source)	2010 – 2013[b]	2010 – 2014	Mar 2009 – 2012[c]	Mar 2009 – 2013	Mar 2009 – 2013

EpiChron = EpiChron Research Group on Chronic Diseases; GePaRD = German Pharmacoepidemiological Research Database; SIDIAP = Information System for the Advancement of Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària) database, Catalonia, Spain.

[a] *Provided by IRIS.*

[b] *Data for 2014 can be available during the second half of 2015.*

[c] *Data for 2013 are available for two of the SHIs contributing to the GePaRD. Data for 2013 from other SHI databases may become available at a later time.*

9.2.3. Study Cohort

The study cohort comprises all individuals from the source population who have a first-recorded prescription (new users) of agomelatine or one of the other study antidepressants during the study period and have been continuously enrolled or registered in the data source for at least 12 months prior to this first-recorded prescription.

9.2.3.1. Study Antidepressants

The selected study antidepressants and corresponding Anatomical Therapeutic Chemical (ATC) codes are presented in Table (9.2.3.1) 1.

Table (9.2.3.1) 1 - Study Antidepressants

Antidepressant	Class	ATC Code
Citalopram (common comparator)	Selective serotonin reuptake inhibitors	N06AB04
Agomelatine (main exposure of interest)	Other antidepressants	N06AX22
Fluoxetine	Selective serotonin reuptake inhibitors	N06AB03
Paroxetine	Selective serotonin reuptake inhibitors	N06AB05
Sertraline	Selective serotonin reuptake inhibitors	N06AB06
Escitalopram	Selective serotonin reuptake inhibitors	N06AB10
Mirtazapine	Other antidepressants	N06AX11
Venlafaxine	Other antidepressants	N06AX16
Duloxetine	Other antidepressants	N06AX21
Amitriptyline	Non-selective monoamine reuptake inhibitors	N06AA09

ATC = Anatomical Therapeutic Chemical (classification system).

The study antidepressants other than agomelatine were selected based on sales data provided by IRIS (Germany, Spain) and on number of antidepressant users publicly available (Denmark, Sweden) (Table (9.2.3.1) 2). The selected antidepressants are those commonly used across all countries. Citalopram is the most commonly used antidepressant in three of the four countries (Table (9.2.3.1) 2), and according to clinical reviews is among the antidepressants with the least potential for hepatotoxicity (Park and Ishino, 2013; Voican et al., 2014). Moreover, although escitalopram use in Spain is much more common than citalopram use (ranked number 1 and 7, respectively, in Table (9.2.3.1) 2, in SIDIAP and according to data provided by database custodians, citalopram use is more common than escitalopram use. The selected study antidepressants are prescribed for the treatment of major depressive episodes (e.g., agomelatine) and also for other psychiatric indications (Appendix 14.4; Table (14.4) 1). The ATC codes for the study antidepressants are listed in Table (9.2.3.1) 1.

Table (9.2.3.1) 2 - Rank of Study Antidepressants According to the Frequency of Use in the Four Countries

N06A Antidepressants	Spain[a]	Germany[a]	Denmark[b]	Sweden[b]
Agomelatine	13	15	14	19
Selective serotonin reuptake inhibitors				
Citalopram	7	1	1	1
Fluoxetine	3	11	12	8
Paroxetine	2	13	10	10
Sertraline	6	9	3	2
Escitalopram	1	14	6	6
Other antidepressants				
Mirtazapine	10	2	2	3
Venlafaxine	4	5	4	5
Duloxetine	8	10	9	9
Non-selective monoamine reuptake inhibitors				
Amitriptyline	9	3	5	4

NA = ranking not available.

[a] *Ranking based on sales information provided by IRIS.*

[b] *Denmark, Sweden: ranking based on number of users in prescription registries. Sources: http://medstat.dk/ and http://192.137.163.49/sdb/lak/val.aspx; accessed 2 June 2013.*

9.2.3.2. New Users

A new user is defined as any member of the study cohort who has a first-recorded dispensing of a prescription for agomelatine or for one of the other study antidepressants during the study period and who has not had a previous recorded dispensing for the same study antidepressant during the prior 12 months. Inclusion in the study cohort as a new user of agomelatine or one of the other study antidepressants does not preclude the patient from being included as a new user of another antidepressant if the criteria for inclusion in the study cohort are met.

9.2.3.3. Start Date

The date of cohort entry is defined as the date of receiving a first prescription for agomelatine or one of the study antidepressants that qualifies the user as a new user.

9.2.3.4. Eligibility Criteria

All persons meeting the following criteria during the study period are eligible for study inclusion:

- First prescription or dispensing of one of the study antidepressants with no prescription of this medication during the prior 12 months (new users)
- Aged 18 years or older
- Continuous registration or enrolment in the study data source for at least 12 months prior to the start date

9.2.3.5. Exclusion Criteria

To control for potential confounding factors, the study cohort will be restricted to patients without a history of liver disease or risk factors for liver disease. Therefore, patients with any of the listed conditions recorded at any time before the start date will be excluded from the study (see Appendix 14.5 for detailed list of conditions and ICD-9 and ICD-10 codes):

- Acute and subacute liver disease including viral and other infectious or toxic hepatitis
- Chronic liver diseases, such as cirrhosis or fibrosis of the liver, alcoholic liver disease, chronic toxic liver disease, hemochromatosis, Wilson disease, deficit of alpha-1-antitrypsin, and Budd-Chiari syndrome
- Disorders of bilirubin excretion such as Gilbert's syndrome and Crigler Najjar syndrome
- Chronic biliary or pancreatic disease
- Risk factors for liver disease: alcohol use disorder, heart failure
- Malignancy
- Human immunodeficiency virus (HIV) infection
- Organ transplant
- Drug abuse and dependence
- History of paracetamol intoxication

In addition, person-time of women during pregnancy from the start date and during follow-up will be excluded. Thus all women will be included in the study, but person-time during pregnancy will be excluded from the analysis.

The reasons for excluding patients with the conditions listed above are several. Primarily, we will exclude patients with a history of liver diseases because these conditions are potential confounders as they may be associated with the choice of antidepressants and the occurrence

of ALI. Restricting the study population to subjects without potential confounding factors is an effective way of preventing confounding (Rothman and Ray, 2002).

Potential differential exposure or endpoint ascertainment can occur in patients using health care resources whose data are not included in the routine data collection of the study automated health data source. For example, this problem could occur in patients with HIV infection, transplantation, or cancer who might be treated and monitored in health care facilitates external to the data source system.

We decided to exclude person-time of pregnancy because pregnancy can be associated with an increased risk of hepatic injury. Specific liver disorders associated with pregnancy include preeclampsia, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, and hyperemesis gravidarum (Hay, 2008). Person-time during pregnancy will be excluded. Pregnancy will be identified through diagnosis codes compatible with initiation and/or termination of pregnancy, and duration of pregnancy will be estimated through specific time windows set up around the date of diagnosis.

Patients with a history of infectious liver injury or HIV/AIDS (who have a higher risk of viral hepatitis than the general population) will be excluded from the study cohort because the focus of this study is non-infectious ALI (Rothman and Ray, 2002).

We do not exclude patients with non-alcoholic fatty liver disease, but adjustment on factors of metabolic syndrome will be done in the analysis.

9.2.3.6. Follow-up

Each member of the study cohort will be followed from the start date to the earliest of the following dates: (1) diagnosis of ALI, (2) occurrence of an exclusion criteria, (3) end of study period, (4) disenrolment from the health plan or removal from the data source registry, or (5) death. Follow-up will not be censored when an episode of current use of an index antidepressant is ended or when a patient switches to or adds another index antidepressant.

9.2.4. Nested Case-Control Study

A case-control study nested in the study cohort of users of antidepressants will be conducted to estimate and compare the risk of hospitalisation for ALI associated with use of agomelatine and the other study antidepressants with the risk of hospitalisation for ALI associated with use of citalopram, adjusting for confounding factors.

9.2.4.1. Selection of Cases

All cases identified in the study cohort will be included in the nested case-control study (see Section 9.3.1 for case definition, ascertainment, and validation).

9.2.4.2. Selection of Controls

Controls will be selected from the study cohort using density sampling. In density-sampled case-control studies, controls are sampled from the unique set of subjects in the study cohort who are at risk of becoming a case at the time a case is diagnosed. Using density sampling, the probability of any person from the study cohort being selected as control is proportional to the contribution of that person to the person-time at risk (Rothman et al., 2008). If the sampling of controls is conducted independently of exposure, the odds ratio estimated from the case-control study is a valid estimate of the incidence rate ratio (Rothman, 2002).

Up to 20 controls per case will be randomly selected from the risk set of each case (see sample size calculations). Controls will be matched to cases on index date (see Section 9.2.4.3), age, calendar year of start date, and sex. The same year of birth will be used to match by age. Matching for start date will be implemented so potential cohort effects related to changes in drugs indications or coding or prescription practices are controlled in the analysis. By using density-based sampling, controls will have a duration of follow-up proportionate to that of cases, and the index date of the case will be assigned to the matched control. Given that controls will be selected using incidence density sampling, matched at the index date within the data source only by age and sex, and that it is expected that there will be many new users of study medications other than agomelatine in the study cohort, it is expected that the target of up to 20 controls per case will be met. However, if for a specific case the number of available controls is below 20, the analysis will be conducted with the available controls with a minimum of one control per case. Cases with no available controls will be reviewed for consideration of whether specific matching criteria can be relaxed, such as matching with a control 1 year older or younger, or alternatively if the case should be excluded from the analyses. In that situation, the case will be fully described.

Subjects selected as controls will continue to be eligible to become a case if they develop ALI. Similarly, subjects selected as controls will continue to be eligible for selection as a control if they did not develop ALI.

9.2.4.3. Index Date

The index date for cases is the date of hospitalisation for ALI. The index date for controls is the same as the index date of the corresponding matched case.

9.3. Variables

9.3.1. Endpoint Definition and Ascertainment

Acute liver injury (ALI) refers to a sudden appearance of liver test abnormalities and encompasses a spectrum of clinical diseases ranging from mild biochemical abnormalities to acute liver failure (Hussaini and Farrington, 2007; Hussaini and Farrington, 2014). Elevations of serum enzyme levels (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase [ALP]) are indicators of liver injury, whereas increases in total and conjugated bilirubin levels measure overall liver function. Severe hepatotoxicity involves impaired liver function. Acute liver failure refers to the development of severe ALI with encephalopathy and impaired synthetic function (international normalised ratio ≥ 1.5) in a patient without cirrhosis or preexisting liver disease (Lee et al., 2012).

Operational definitions of ALI used in previous pharmacoepidemiological studies are based on diagnosis and/or procedural codes or liver function test results (Garcia Rodriguez et al., 1999; Kaye et al., 2014; Perez Gutthann and Garcia Rodriguez, 1993; Shin et al., 2013; Traversa et al., 2003; Xue et al., 2011), and standardised definitions for use in epidemiologic studies have been proposed (Aithal et al., 2011; Kachroo et al., 2009).

Drug-induced liver injury is an adverse hepatic reaction that is unexpected on the basis of the pharmacological action of the drug administered and differs from drug overdose. Drug-induced liver injury, excluding injury caused by acetaminophen overdose, accounts for 7% to 15% of the cases of acute liver failure in Europe and the United States each year (Aithal et al., 2011; Hussaini and Farrington, 2014).

9.3.1.1. Endpoint Definition

The primary and secondary study endpoints will include only hospitalised cases of ALI. The tertiary endpoint will include both outpatient and hospitalised cases.

- The primary endpoint will be assessed in all the study data sources according to specific hospital discharge diagnoses related to ALI.
- The secondary endpoint will be based on specific and non-specific hospital discharge diagnosis codes and validation of potential cases by clinical review of hospital medical charts and/or results from outpatient liver enzymes and function tests. The secondary endpoint will be evaluated in those study data sources that have access to medical records or liver test results. This information is available in the data sources of EpiChron and SIDIAP in Spain and Denmark.
- The tertiary endpoint will be assessed using specific and non-specific codes identified in both hospital and ambulatory settings, and the endpoint will be evaluated in all data sources whether or not validation is feasible.

In Table (9.3.1.1) 1, we present a summary of the implementation and validation of all endpoints across all study databases.

Table (9.3.1.1) 1 – Summary of Endpoint Implementation and Validation Across All Study Databases

Data Source	Hospital-Based Endpoints (Primary and Secondary Endpoints)				Hospital- and Outpatient-Based Endpoint (Tertiary Endpoint)	
	Primary Endpoint Evaluated	Primary Endpoint Validated	Secondary Endpoint Evaluated	Secondary Endpoint Validated	Tertiary Endpoint Evaluated	Tertiary Endpoint Validated
EpiChron, Spain	Yes	No	Yes	Yes (hospital records)	Yes	Yes (hospital records, primary care free text – if available – and liver test results)[a]
SIDIAP, Spain	Yes	No	Yes	Partially (primary care liver test results)[b]	Yes	Partially (primary care liver test results and primary care free text if available)
GePaRD, Germany	Yes	No	No	No	Yes	No
National Registries, Denmark	Yes	No	Yes	Yes (hospital records)	Yes[c]	Yes (hospital records)
National Registries, Sweden	Yes	No	No	No	Yes[c]	No

[a] *EpiChron in Spain; outpatient and inpatient laboratory values available since 2010, Intralab system.*
[b] *SIDIAP in Spain; outpatient laboratory values available, but liver test results only available for 27% of the ALI cases with an outpatient diagnosis (according to SIDIAP feasibility).*
[c] *Denmark and Sweden; ambulatory data limited to outpatient hospital clinics.*

The primary endpoint will be ascertained in all data sources and is based on hospital cases using the most specific codes, the ones that have showed the highest positive predictive value in previous studies (Lo Re et al., 2013). The second and the third endpoints both use less specific codes. However, the secondary endpoint is based on hospital cases and will be ascertained only in those data sources where validation is feasible within the study time frame

(i.e., databases in Spain and Denmark). In SIDIAP, where only partial validation is possible, and for analysis purposes, cases that cannot be validated will not be evaluated. The tertiary endpoint will be ascertained in all data sources and includes both hospitalised and outpatient cases. This tertiary endpoint is the endpoint most prone to misclassification and surveillance biases.

Using the three different endpoints allows inclusion of all potential cases while at the same time ranking the endpoints by their degree of specificity. Partial validation (in those data sources where it is feasible) will allow estimation of positive predictive values of the different codes (outpatient and hospitalised) and will help in the interpretation of the study results for the three different endpoints.

9.3.1.1.1. Primary Endpoint (All Countries and Databases)

For all countries and databases, the primary study endpoint is defined as any patient with a hospital discharge diagnosis for ALI. Potential cases of ALI will be identified in all the study data sources by using specific ICD-9-CM and ICD-10-CM/-GM‡ diagnosis codes associated with ALI (Table (9.3.1.1.1) 1). These codes were selected after reviewing the literature on their positive predictive values (Bui et al., 2014; Kachroo et al., 2009; Lo Re et al., 2013; Maggini et al., 1999; Shin et al., 2013; Traversa et al., 2003).

Table (9.3.1.1.1) 1 - Primary Endpoint: Specific Hospital Discharge Codes for Acute Liver Injury

Code	Description
ICD-9-CM code	
570.x	Acute and subacute necrosis of liver
572.2	Hepatic coma
573.3	Hepatitis unspecified
ICD-10-CM code	
K71.0	Toxic liver disease with cholestasis
K71.1	Toxic liver disease with hepatic necrosis
K.71.2	Toxic liver disease with acute hepatitis
K71.6	Toxic liver disease with hepatitis, not elsewhere classified
K71.9	Toxic liver disease, unspecified
K72.0	Acute and subacute hepatic failure
K72.9	Hepatic failure, unspecified
K75.9	Inflammatory liver disease, unspecified
K76.2	Central haemorrhagic necrosis of liver

ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification;* ICD-10-CM = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification*.

9.3.1.1.2. Secondary Endpoint (Selected Databases)

In databases with available information, the secondary endpoint is defined as any patient admitted to a hospital for confirmed ALI. Only validated cases will be analysed. Therefore, the secondary endpoint of confirmed ALI will be evaluated in the data sources of Spain and Denmark, which have access to clinical information that can be used to confirm cases of ALI. The impact of this validation will be described in the validation report and the study report. Potential cases of ALI will be identified using specific and non-specific ICD-9-CM and ICD-10-CM hospital discharge codes and procedures potentially associated with ALI (see Table (9.3.1.1.2) 1).

‡ The ICD-10-GM (German Modification) codes will be listed in the SAP adaptation to the GePaRD.

Table (9.3.1.1.2) 1 - Secondary Endpoint: Specific and Non-Specific Hospital Discharge Codes for Acute Liver Injury

Code	Description
Specific codes	Same codes as those for primary endpoint (Table (9.3.1.1.1) 1)
ICD-9-CM code	
570.x	Acute and subacute necrosis of liver
572.2	Hepatic coma
573.3	Hepatitis unspecified
ICD-10-CM code	
K71.0	Toxic liver disease with cholestasis
K71.1	Toxic liver disease with hepatic necrosis
K71.2	Toxic liver disease with acute hepatitis
K71.6	Toxic liver disease with hepatitis, not elsewhere classified
K71.9	Toxic liver disease, unspecified
K72.0	Acute and subacute hepatic failure
K72.9	Hepatic failure, unspecified
K75.9	Inflammatory liver disease, unspecified
K76.2	Central haemorrhagic necrosis of liver
Non-specific codes	
ICD-9-CM code	
573.8	Other specified disorders of liver
573.9	Unspecified disorders of liver
782.4	Jaundice, unspecified, not of newborn
V42.7	Liver transplant
790.4	Non-specific elevation of levels of transaminase or lactic acid dehydrogenase
789.1	Hepatomegaly
ICD-10-CM code	
K76.8	Other specified diseases of liver
K76.9	Liver disease, unspecified
R17	Unspecified jaundice, excludes neonatal
R16.0	Hepatomegaly, not elsewhere classified
R16.2	Hepatomegaly with splenomegaly, not elsewhere classified
R74.0	Non-specific elevation of levels of transaminase and lactic acid dehydrogenase [LDH]
Z94.4	Liver transplant

ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10-CM = International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification. The ICD-10-GM (German Modification) codes will be listed in statistical analysis plan adapted to the GePaRD.

9.3.1.1.3. Tertiary Endpoint (All Databases)

This endpoint will be evaluated in all databases using the specific and non-specific codes listed in Table (9.3.1.1.2) 1 but without restriction to the hospital setting. Thus, both ambulatory and hospitalised codes will be used for case identification of this endpoint. Validation of potential tertiary endpoint cases, which will include outpatient cases, will be implemented in the data sources of Spain and Denmark, if feasible. The impact of the validation on the study results for this endpoint will be also assessed in those same data sources.

9.3.1.1.4. Validation of Secondary and Tertiary Endpoints

Potential cases of ALI identified with specific and non-specific codes will be confirmed according to the definition criteria established by an international Expert Working Group on drug-induced liver injury (see Table (9.3.3.2.3.1) 1) (Aithal et al., 2011). The definition criteria are based on increases in the levels of alanine aminotransferase (ALT), alkaline phosphatase (ALP), and bilirubin with less than 1 year of persistence. According to the Working Group, increases of these parameters for more than 1 year are compatible with chronic liver injury. This is based on a prospective multicentre study in which about 42% of patients with drug-

induced liver injury had persistent elevation of liver enzymes at 3 months of follow-up, and 17% had persistent elevations at 1 year of follow-up (Borraz et al., 2010). Because the rate of resolution fell considerably after 1 year, the Working Group suggested that 1 year could be a reasonable cut-off point to define chronicity.

The validation of cases will be based on biological results. However, other information such as admission and discharge diagnoses and dates, clinical findings, and results from diagnostic procedures will be collected and studied. This will allow a better understanding of the identified cases but could also allow assessment of surveillance bias.

In Denmark, validation of hospitalised cases and ambulatory cases (identified only through outpatient hospital clinic diagnosis codes) will be implemented based on hospital medical records chart review. Liver function test results available in the medical records will be used for validation purposes..

In EpiChron, validation of cases will be based on biological results from inpatient and outpatient data (Intralab system), hospital medical record chart review, and review of computer-generated patient profiles (including anonymised free-text data, if available) for outpatient cases.

In SIDIAP, validation will be accomplished only in outpatient data, using laboratory results on liver enzymes and function tests and review of computer-generated patient profiles (including anonymised free-text data, if available).

The validation process will allow determination of the positive predictive value, defined as the proportion of identified cases that are true cases according to the validation. A differential validation between antidepressant drugs or between SIDIAP/EpiChron (where ambulatory laboratory data are available) and the other data sources could be due to systematic biological monitoring limited to agomelatine because the validation is based only on results of biological testing.

For the review of hospital medical records, specific outcome information will be abstracted from hospital medical charts and evaluated to confirm the diagnosis of ALI according to the secondary endpoint definition criteria based on levels of ALT, ALP, and bilirubin (see Table (9.3.3.2.3.1) 1. Data abstraction will be conducted by trained personal using a standardised abstraction form and will not include identifiable data. As data are available, information to be abstracted will include admission and discharge diagnoses and dates, clinical findings, results from diagnostic procedures (liver tests, histology), and in-hospital death. For the review of outpatient records, information available in electronic records (including free-text data, if available) will be reviewed.

Final confirmation of cases will be conducted independently by physicians who will be blinded to exposure to medications. Difficult cases will be categorised by consensus between the validation physicians. The date of occurrence of ALI will be assigned as the date on which the symptoms initiated or the patient had a first-recorded code or procedure associated with any of the diagnoses used to screen the data source for potential cases.

The results of outpatient liver enzymes and function tests will be manually reviewed by physicians to confirm the levels of ALT, ALP, and bilirubin, and dates.

Table (9.3.3.2.3.1) 1 - Secondary and Tertiary Endpoint Validation Criteria

Endpoint	Definition
Acute liver injury[a]	Any one of the following increases in ALT, ALP, and bilirubin with less than 1 year of persistence: ≥ 5 x ULN ALT ≥ 2 x ULN ALP ≥ 3 x ULN ALT and > 2 x ULN bilirubin

ALP = alkaline phosphatase; ALT = alanine aminotransferase; ULN = upper limit of normal range.
Source: International DILI Expert Working Group (Aithal et al., 2011).

Results and impact of the validation process will be studied in depth and presented in a validation report that will be appended to the final report. The main conclusions will be summarised in the final report.

9.3.2. Exposure Assessment

In the different data sources, exposures will be assessed using prescriptions written by physicians or dispensed prescriptions by community pharmacies. Note that information on the in-hospital use of antidepressants is not available in the study data sources. The clinical indication (see Appendix 14.4; Table (14.4) 1) and guideline recommendations (see Appendix 14.4; Table (14.4) 2) in the four countries for each of the study antidepressants are not consistent.

For most indications, the recommended duration of treatment with agomelatine and the other antidepressants is at least 6 months. In most epidemiologic studies involving antidepressants, the majority of cases of liver injury occur during the interval between several days and 6 months after treatment initiation, but ALI might happen from 5 days to 3 years after starting therapy (Park and Ishino, 2013; Voican et al., 2014). In some studies, most cases have been detected within the first 45 days following the start of therapy, but ALI can occur up to 30 days after stopping treatment (Bénichou, 1990). Overall, this timing of events is compatible with an elevated risk from the beginning of treatment that is maintained during the whole course of therapy, and which may continue during the few weeks following the stop of treatment. After that period, the risk presumably reaches the background level seen among non-users of antidepressants.

Based on these findings, **time at risk** will be defined in the cohort study and in the nested case-control study according to the days of supply of each prescription plus a period of 40 days. Days of supply is defined as the intended number of days of treatment associated with each dispensing/written prescription. The period of 40 days is added to allow detection of cases with onset of ALI after stopping treatment (Bénichou, 1990). Since the exact start date of medication use cannot be ascertained from the data, we will assume that exposure starts accumulating on the day of the dispensed/written prescription.

9.3.2.1. Exposure and Time at Risk in the Cohort Study

In the cohort study, incidence rates of ALI will be calculated during current use of each of the study medications.

- Current use will comprise the sum of all the episodes of continuous treatment plus 40 days occurring during the cohort follow-up time.

- Consecutive prescriptions are those prescriptions following the first one separated by gaps of 40 days or less. For consecutive prescriptions of the index medication separated by gaps of 40 days or less, time at risk from current use will include the gaps between prescriptions.
- Overlapping time at risk from current use for consecutive prescriptions of the index medication will be concatenated, with the overlapping time counted only once.

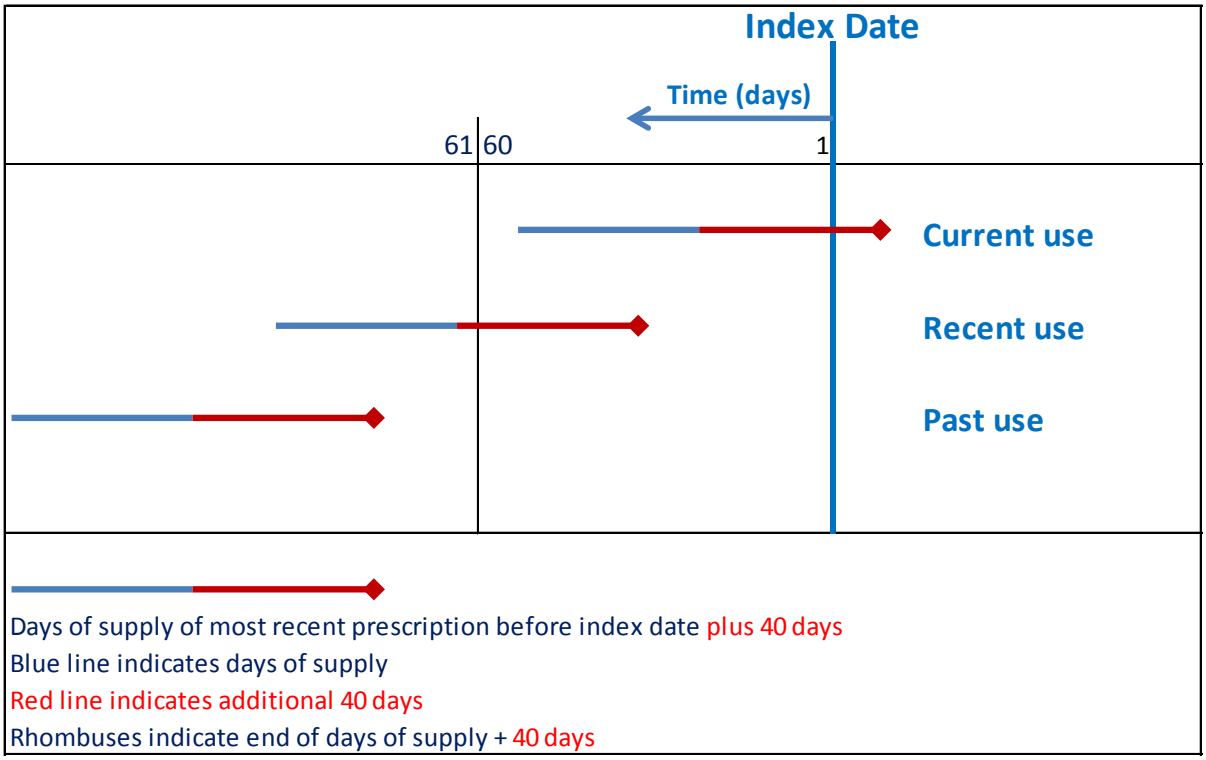
If a gap of 40 days is inconsistent with the usual duration of antidepressant drug supply in a given data source, the gap between prescriptions used in analyses could be adjusted in the statistical analysis plan adapted to the data source.

9.3.2.2. Exposure and Time at Risk in the Nested Case-Control Study

In the nested case-control study, time at risk will be categorised for each patient and each antidepressant into three mutually exclusive categories of exposure according to the days of supply of the most recent prescription received on or before the index date (see Figure (9.3.2.2) 1).

- Current use: when the period of days of supply of the most recent prescription plus 40 days overlaps the index date
- Recent use: when the period of days of supply of the most recent prescription plus 40 days ends within 60 days before the index date
- Past use: when the period of days of supply of the most recent prescription plus 40 ends more than 60 days before the index date

Figure (9.3.2.2) 1 - Exposure Definition

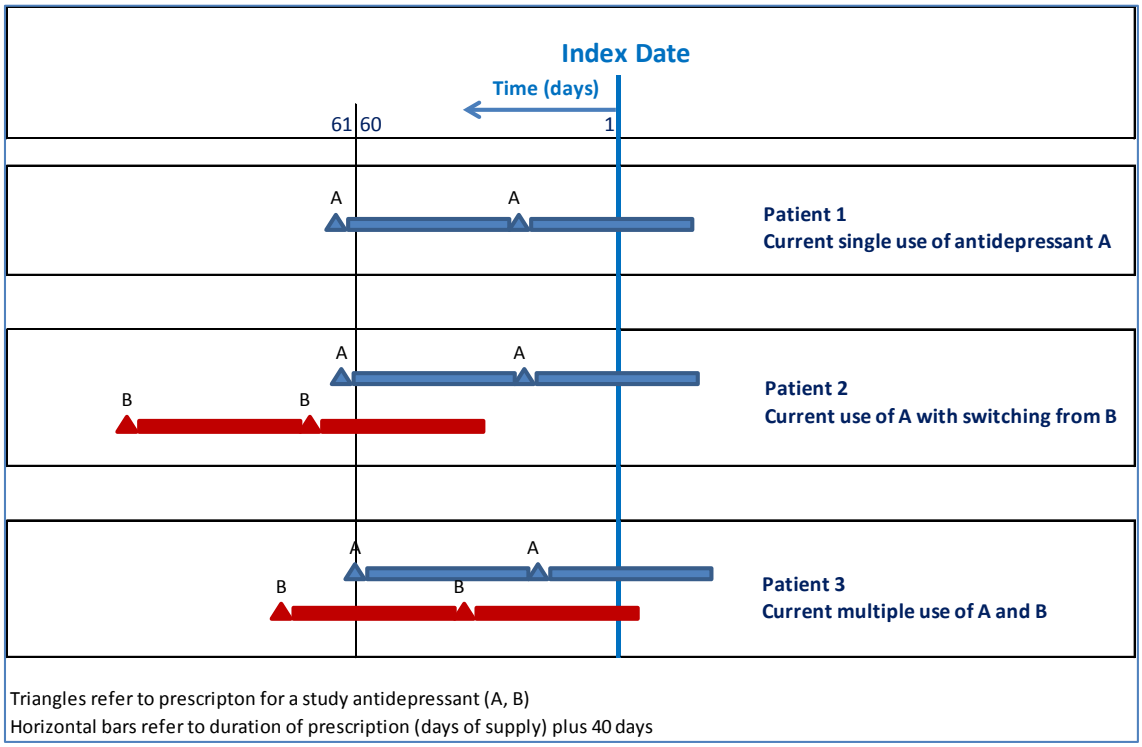


Exposure classification (current, recent, or past use) will be assessed independently for each study antidepressant, as described above. Tapering and cross-tapering are recommended by clinical guidelines when stopping and switching antidepressants (Anderson et al., 2000; van Geffen et al., 2005). Therefore, concurrent use of two antidepressants is expected to occur

commonly when switching from one antidepressant to the other. Therefore, for each antidepressant, person-time of current use will be further categorised in the following mutually exclusive categories (see Figure (9.3.2.2) 2).

- Current single use: is defined as periods of current use of a single study antidepressant without current or recent use of any of the other study antidepressants.
- Switching: is defined as periods of current use of a single study antidepressant with recent use of any of the other study antidepressants.
- Multiple use: will be defined as periods of current use of more than one study antidepressant, with or without recent use of one or more of the study antidepressants.

Figure (9.3.2.2) 2 - Exposure and Time at Risk in the Nested Case-Control Study, Classification of Current Users



9.3.2.3. Assessment of Dose and Duration

Estimation of the effect of dose will not be conducted since information on dosage instructions is not available in the study databases and daily dose cannot be calculated.

Duration of use of agomelatine and the other antidepressants will be estimated as the person-time of consecutive prescriptions, defined as those issued within a specific period of time. Calculations of consecutive use will allow for a maximum gap in treatment (e.g., 60 days) between the estimated end of use of one prescription and the dispensing date of the following prescription; the length of the gap could be determined by the pattern of use as a first component of the study.

9.3.3. Risk Factors and Confounding

The main risk factors for ALI include age, sex, alcohol use disorder, overweight/obesity/metabolic syndrome, concurrent use of other hepatotoxic medications, and severe comorbidity. Other diseases that can be associated with increase of liver enzymes or bilirubin, such as prior liver or chronic biliary or pancreatic disease, must be also considered as confounding factors. To control for these and other potential confounders, we use restriction and censoring in the study cohorts and matching and adjustment in the analysis in the nested case-control study. Adjustment will allow taking into account the effect of events related to these predefined disorders occurring during follow-up. Also patients will be censored at the date of occurrence of an exclusion criteria during follow-up. If feasible and information related to the variables can be obtained in the data sources, the definition of these variables will be based on both outpatient and inpatient data. If additional variables are identified as potential confounders when comparing the different cohorts of study antidepressants at baseline, they will be included in the adjusted analyses.

In Table (9.3.3) 1, we list the risk factors and confounding factors and the method of adjustment: restriction and censoring, matching, and control in the analysis. Potential confounders are described in detail in the following sections.

Table (9.3.3) 1 - Potential Confounders and Method of Control

	Cohort Study		Nested Case-Control Study	
Risk Factor/Confounder	**Exclusion/Censoring**	**Control in Analysis**	**Matching**	**Control in Analysis**
Age	—	Yes	Yes	—
Sex	—	Yes	Yes	—
Index date (date of event)	—	—	Yes	—
Liver diseases				
Liver disease, study endpoints (see Table (9.3.1.1.1) 1)	Yes	—	NA	NA
Liver disease, all liver disease other than study endpoints	Yes	—	—	—
Haemochromatosis	Yes	—	—	—
Wilson's disease	Yes	—	—	—
Deficit of alpha-1-antitrypsin	Yes	—	—	—
Budd-Chiari syndrome	Yes	—	—	—
Disorders of bilirubin excretion (e.g., Gilbert's syndrome)	Yes	—	—	—
Acute biliary and pancreatic disease	—	No[a]	—	Yes
Chronic biliary and pancreatic disease	Yes	—	—	—
Risk factors for liver disease				
Acute alcohol intoxication	—	No[a]	—	Yes
Alcohol use disorder	Yes	—	—	—
Drug abuse and dependence	Yes	—	—	—
Heart failure	Yes	—	—	—
Obesity, overweight	—	No[a]	—	Yes
Hyperlipidaemia and hypertriglyceridaemia	—	No[a]	—	Yes
Diabetes	—	No[a]	—	Yes
Hypertension	—	No[a]	—	Yes
Occupational exposure[b]	—	No[a]	—	Yes
Malignancy	Yes	—	—	—
Human immunodeficiency virus/AIDS	Yes	—	—	—
Organ transplant	Yes	—	—	—
Time during pregnancy	Yes[c]	—	—	Yes[b]

	Cohort Study		Nested Case-Control Study	
Risk Factor/Confounder	**Exclusion/Censoring**	**Control in Analysis**	**Matching**	**Control in Analysis**
Severe comorbidity: selected Charlson comorbidity index components[d]	—	No[a]	—	Yes
History of rheumatic diseases	—	No[a]	—	Yes
History of peptic ulcer disease	—	No[a]	—	Yes
Concurrent use of hepatotoxic drugs	—	No[a]	—	Yes
Concurrent use of other antidepressants	—	No[a]	—	Yes
Number of other antidepressants used	—	No[a]		Yes
Indication of treatment with antidepressants	—	No[a]	—	Yes
Time since first antidepressant prescription	—	No[a]	—	Yes
Number of liver tests performed[e]	—	No[a]	—	Yes
Health care resource utilisation	—	No[a]	—	Yes

NA = not applicable.
[a] *Variable will not be controlled in the analysis but will be included in the cohort description at start date*
[b] *Difficult to obtain in data sources.*
[c] *Only person-time during follow-up will be excluded.*
[d] *Most components addressed in through restriction and censoring.*
[e] *Only available in SIDIAP and EpiChron, Spain, and in GePaRD*

9.3.3.1. Cohort Study

By design, patients with prior liver disease, chronic biliary or pancreatic disease, alcohol use disorder, and life-threatening disease are excluded from the study cohort or censored at the time of occurrence of any of these conditions during follow-up.

9.3.3.2. Nested Case-Control Study

By design, cases and controls are matched on age, sex, and calendar year of start date, and the index date of the case will be assigned to the matched controls. The occurrence of the following risk factors and potential confounders will be adjusted for in the analysis and will be evaluated both before the start date (using all historical available information) and during follow-up before the index date:

- Acute biliary and pancreatic diseases
- Acute alcohol intoxication
- Obesity, overweight
- Hyperlipidaemia
- Hypertriglyceridaemia
- Diabetes
- Hypertension
- Severe comorbidity: components of the Charlson comorbidity index not addressed in exclusion/censoring factors
- Concurrent use of other hepatotoxic drugs
- Concurrent use of other antidepressants
- Indication of treatment with antidepressants
- Time since first antidepressant prescription
- Number of liver tests performed (available only in SIDIAP and EpiChron, Spain)
- Utilisation of health care resources

These factors are described in detail below.

9.3.3.2.1. Age and Sex

By design, in the nested case-control study cases and controls are matched on age and sex. Increasing age may be related to an increased risk of drug-induced ALI, and there is evidence that drug-induced hepatotoxicity affects women more commonly than men (Navarro and Senior, 2006). The same year of birth will be used to match on age. If for a specific age the number of controls is insufficient (< 20), an extended age period will be used (i.e., ± 1 year or ± 2 years).

9.3.3.2.2. Socioeconomic Status

Socioeconomic status can be associated with use of unreimbursed drugs and also with lifestyle conditions that might be a risk factor for ALI. However, the extent to which socioeconomic status can be measured (and the method used) will vary by data source. Therefore, the exact variables and coding used will be described in detail in the statistical analysis plan adapted to each data source.

9.3.3.2.3. Liver Disease and Risk Factors

Liver disease is one of the main risk factors for ALI. Patients with a history of liver disease, alcohol use disorder, and other risk factors for liver disease such as occupational exposures are excluded from the study cohorts or censored during follow-up (see Appendix 14.5). The effect of other risk factors for ALI such as obesity and overweight, hyperlipidemia, and hypertension will be adjusted in the analysis. The ICD-9-CM and ICD-10-CM codes for these risk factors are presented in Table (9.3.3.2.3) 1.

Table (9.3.3.2.3) 1 - Liver Disease and Risk Factors Not Included in the Exclusion Criteria to be Adjusted in the Analysis

ICD-9-CM/ICD-10-CM Descriptions	ICD-9-CM Code	ICD-10-CM Code
Acute alcohol intoxication	305.0, 303.0, 980	T51, F10.0
Obesity and overweight	278.0, V85.2 to V85.4, 649.1	E66.x, Z68.25 to Z68.29, Z68.3, Z68.4,
Hyperlipidaemia and hypertriglyceridaemia	272.x	E78.x
Diabetes	249.x, 250.x, 366.41, 362.0, 357.2	E08.x to E13.x, E14.x
Hypertension	401.x to 405.x, 362.11, 437.2	I10.x to I15.x, H35.03, I67.4

ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10-CM = International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification.

9.3.3.2.3.1. Specifications for Risk Factors for Liver Injury

- Overweight and obesity
  - Body mass index can be recorded in databases based on primary care diagnoses, such as occurs in EpiChron and SIDIAP in Spain. In these databases, body mass index will be included in the analysis to further adjust for obesity and overweight.
- Hyperlipidemia, hypertriglyceridemia, diabetes, and hypertension
  - These diseases will be further ascertained according to the concurrent use of medications at the index date (see Table (9.3.3.2.3.1) 1).

Table (9.3.3.2.3.1) 1 - Medications to Assess Specific Risk Factors for Liver Disease

Disease Description	ATC Code(s)
Hyperlipidaemia, hypertriglyceridaemia	
Lipid-modifying agents	C10
Diabetes	
Insulins	A10A
Blood glucose–lowering drugs	A10B, A10X
Hypertension	
Antihypertensives	C02
Diuretics	C03
Beta-blocking agents	C07
Calcium channel blockers	C08
Agents acting on the renin-angiotensin system	C09

ATC = Anatomical Therapeutic Chemical (classification system).

9.3.3.2.4. Disease of the Biliary Tract or Pancreas

Diseases of the biliary tract or pancreas can affect the liver and may be related to the treatment with antidepressants. Patients with chronic biliary and/or pancreatic disease are excluded from cohort entry or censored during follow-up. The effect of acute biliary and/or pancreatic disease before the index date will be controlled in the analysis. A list of acute biliary and pancreatic diseases and ICD-9-CM/ICD-10-CM codes is presented in Table (9.3.3.2.4) 1.

Table (9.3.3.2.4) 1 - Acute Diseases of the Biliary Tract and Pancreas

ICD-9-CM Description/ICD-10-CM Description	ICD-9-CM Code	ICD-10-CM Code
Disease of gallbladder and biliary tract		
Cholelithiasis	574.x	K80.x
Other disorders of gallbladder	575.0, 575.10, 575.2-575.9	K81.0, K81.9, K82.x
Other disorders of biliary tract	576.x	K83.x
Disease of pancreas	577.0, 577.2-577.9x	K85.0, K85.1, K85.3-K85.9, K86.2-K86.9
Disorders of gallbladder, biliary tract, and pancreas in diseases classified elsewhere	—	K87.x

ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10-CM = International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification.

9.3.3.2.5. Pregnancy

All person-time of women during pregnancy involving the start date and/or follow-up will be excluded. Thus all women will be included in the study but person-time during pregnancy will be excluded from the analysis. Pregnancy will be identified through diagnoses codes compatible with initiation and/or termination of pregnancy, and duration of pregnancy will be estimated through specific time windows set up around the date of diagnosis.
ICD-9-CM/ICD-10-CM codes for pregnancy are presented in Appendix 14.5; Table (14.5) 4.

9.3.3.2.6. Severe Comorbidity

Severe comorbidity may be related to the risk of liver injury and to the treatment with antidepressants. Severe comorbidity at any time before the index date will be evaluated through the components of the Charlson comorbidity index not addressed in the exclusion/censoring criteria (Charlson et al., 1987; Deyo et al., 1992). The weights for the comorbidity index in this study will be taken from the update made by Quan et al. (2011). The index components, conditions, and corresponding ICD-9-CM/ICD-10-CM codes are presented in Table (9.3.3.2.6) 1.

Table (9.3.3.2.6) 1 - Charlson Comorbidity Index

Comorbidities	Enhanced ICD-9-CM	ICD-10
Myocardial infarction	410.x, 412.x	I21.x, I22.x, I25.2
Peripheral vascular disease	093.0, 437.3, 440.x, 441.x, 443.1–443.9, 447.1, 557.1, 557.9, V43.4	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular disease	362.34, 430.x–438.x	G45.x, G46.x, H34.0, I60.x–I69.x
Dementia	290.x, 294.1, 331.2	F01.x–F03.x, F05.1, G30.x, G31.1
Chronic pulmonary disease	416.8, 416.9, 490.x–505.x, 506.4, 508.1, 508.8	I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3
Rheumatic disease	446.5, 710.0–710.4, 714.0– 714.2, 714.8, 725.x	M05.x, M06.x, M31.5, M32.x–M34.x, M35.1, M35.3, M36.0
Peptic ulcer disease	531.x–534.x	K25.x–K28.x
Diabetes without chronic complication	250.0–250.3, 250.8, 250.9	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Diabetes with chronic complication	250.4–250.7, 366.41, 362.0, 357.2	E10.2–E10.5, E10.7, E11.2–E11.5, E11.7, E12.2–E12.5, E12.7, E13.2–E13.5, E13.7, E14.2–E14.5, E14.7
Hemiplegia or paraplegia	334.1, 342.x, 343.x, 344.0–344.6, 344.9	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0–G83.4, G83.9
Renal disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0–583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x	I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2

HIV = human immunodeficiency virus; ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th Revision.
Adapted from Quan et al. (2005) and Charlson et al. (1987).

9.3.3.2.7. Concurrent Use of Other Hepatotoxic Drugs

The effect of concurrent use of other hepatotoxic medications will be adjusted in the analysis. Concurrent use of hepatotoxic drugs at the index date will be ascertained through the identification of prescriptions issued from the start date up to but not including the index date. In addition, we will adjust by the number of hepatotoxic medications used at the index date. A multilevel variable (e.g., no concurrent use of hepatotoxic drugs, concurrent use of one hepatotoxic drug, and concurrent use of two or more hepatotoxic drugs) will be created to account for the number of concurrent hepatotoxic drugs used. A list of potential hepatotoxic medications, according to the type of liver injury, is presented in Table (9.3.3.2.7) 1, (Navarro and Senior, 2006).

Table (9.3.3.2.7) 1 - Drugs Associated With Liver Injury, by Predominant Injury Pattern

Medication, by Type of Liver Injury	ATC Code
Hepatocellular (elevated ALT)	
Acarbose	A10BF01
Acetaminophen	N02BE01, N02BE51, N02BE71
Allopurinol	M04AA01, M04AA51
Amiodarone	C01BD01
Baclofen	M03BX01
Bupropion	N06AX12
Ciprofloxacin[a]	J01MA02, S01AE03, S02AA15, J01RA10 (with metronidazole), J01RA12 (with ornidazole), J01RA11 (with tinidazole)
Highly active antiretroviral drugs	J05A

Medication, by Type of Liver Injury	ATC Code
Isoniazid	J04AM03, J04AC01, J04AC51, J04AM02, J04AM05, J04AM06, J04AM01, J04AM04
Interferon beta 1a/1b[a,b]	L03AB02, L03AB07, L03AB08
Ketoconazole	J02AB02
Lisinopril	C09AA03, C09BB03, C09BA03
Lamotrigine[a]	N03AX09
Levofloxacin[a,b]	J01MA12, J01RA05 (with ornidazole), S01AE05, A02BD10 (with lansoprazole and amoxicillin)
Losartan	C09CA01, C09DB06, C09DA01
Methotrexate	L01BA01, L04AX03
NSAIDs	M01A
Omeprazole	A02BC01, A02BD05, A02BD01
Pyrazinamide	J04AK01, J04AM05, J04AM06
Rifampicin	J04AB02, J04AM02, J04AM05, J04AM06
Risperidone	N05AX08
Statins	C10AA
Tetracyclines	J01A
Telithromycin[b]	J01FA15
Trazodone	N06AX05
Trovafloxacin	J01MA13
Valproic acid	N03AG01
Cholestatic (elevated ALP and elevated TB)	
Amlodipine[b]	C08CA01
Anabolic steroids	A14A
Chlorpromazine	N05AA01
Clopidogrel	B01AC04
Oral contraceptives	G03A
Oxacillin[b]	J01CF04
Erythromycins	J01FA01
Estrogens	G03C, G03F
Irbesartan	C09CA04, C09DB05, C09DA04
Phenothiazines	N05AA, N05AB, N05AC
Terbinafine	C01BA02
Tricyclics	N06AA01-N06AA16, N06A18, N06AA19, N06AA23
Amoxicillin/clavulanic acid	J01RA01
Mixed (elevated AST and elevated ALT)	
Azathioprine	L04AX01
Aripiprazole[a,c]	N05AX12
Captopril	C09AA01, C09BA01
Carbamazepine	C03AF01
Clindamycin	J01FF01, G01AA10, D10AF01, D10AF51 in combination
Cyproheptadine	R06AX02
Enalapril	C09AA02, C09BA02, C09BB02, C09BB06
Flutamide	L02BB01
Nitrofurantoin	J01XE01
Phenobarbital	N03AA02
Phenytoin	N03AB02
Sulfonamides	J01EA, J01EB, J01EC, J01ED, J01EE02 to J01EE07
Trazodone	N06AX05
Trimethoprim-sulfamethoxazole	J01EE01
Verapamil	L08DA01, L08DA51, C09BB10

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATC = Anatomical Therapeutic Chemical (classification system); NSAIDs = non-steroidal anti-inflammatory drugs; TB = total bilirubin.
Sources: No superscript: Navarro and Senior (2006); [a] Shin et al. (2013); [b] Chalasani et al. (2008);
[c] US Food and Drug Administration (2009).

9.3.3.2.8. Concurrent Use of Other Antidepressants

Concurrent use of other antidepressants can be related to the indication of treatment and severity of underlying disease, which may be associated with the risk of ALI. The list of other antidepressants and their ATC codes is provided in Table (9.3.3.2.8) 1.

Table (9.3.3.2.8) 1 - Other Antidepressants

Antidepressant	ATC Code	Antidepressant	ATC Code
Non-selective monoamine reuptake inhibitors			
Desipramine	N06AA01	Doxepin	N06AA12
Imipramine	N06AA02	Iprindole	N06AA13
Imipramine oxide	N06AA03	Melitracen	N06AA14
Clomipramine	N06AA04	Butriptyline	N06AA15
Opipramol	N06AA05	Dosulepin	N06AA16
Trimipramine	N06AA06	Amoxapine	N06AA17
Lofepramine	N06AA07	Dimetacrine	N06AA18
Dibenzepin	N06AA08	Amineptine	N06AA19
Nortriptyline	N06AA10	Maprotiline	N06AA21
Protriptyline	N06AA11	Quinupramine	N06AA23
Selective serotonin reuptake inhibitors			
Zimelidine	N06AB02	Fluvoxamine	N06AB08
Alaproclate	N06AB07	Etoperidone	N06AB09
Monoamine oxidase inhibitors, non-selective			
Isocarboxazid	N06AF01	Tranylcypromine	N06AF04
Nialamide	N06AF02	Iproniazid	N06AF05
Phenelzine	N06AF03	Iproclozide	N06AF06
Monoamine oxidase A inhibitors			
Moclobemide	N06AG02	Toloxatone	N06AG03
Other antidepressants			
Oxitriptan	N06AX01	Medifoxamine	N06AX13
Tryptophan	N06AX02	Tianeptine	N06AX14
Mianserin	N06AX03	Pivagabine	N06AX15
Nomifensine	N06AX04	Milnacipran	N06AX17
Trazodone	N06AX05	Reboxetine	N06AX18
Nefazodone	N06AX06	Gepirone	N06AX19
Minaprine	N06AX07	Desvenlafaxine	N06AX23
Bifemelane	N06AX08	Vilazodone	N06AX24
Viloxazine	N06AX09	Hyperici herba	N06AX25
Oxaflozane	N06AX10	Vortioxetine	N06AX26
Bupropion	N06AX12		

ATC = Anatomical Therapeutic Chemical (classification system).

9.3.3.2.9. Indication for Treatment With Antidepressants and Other Mental and Behavioural Disorders

The indication for which an antidepressant is prescribed may be related to treatment and to ALI through an association with lifestyle habits (e.g., sedentariness leading to obesity, alcohol abuse). Therefore, analysis will be adjusted by history, before the start date, of diseases that are potential indications for treatment. In addition, the analysis will include other mental and behavioural disorders that could be treated with the study antidepressants (Table (9.3.3.2.9) 1).

Table (9.3.3.2.9) 1 - Indications for Treatment With the Study Antidepressants

Indication and Other Mental and Behavioural Disorders	ICD-9-CM Code	ICD-10 Code
Indication		
Major depression	296.2, 296.3, 311.x	F32.x, F33.x, F34.1
Panic disorders	300.01, 300.21	F40.01, F41.0
Generalised anxiety disorder	300.02	F41.1
Obsessive compulsory disorder	300.3	F42.0
Social anxiety disorder	300.23	F40.1
Posttraumatic stress disorder	309.81	F43.1
Bulimia nervosa	307.51	F50.2
Nocturnal enuresis	307.6	F98.0
Bipolar disorder	296.0, 296.4 to 296.7, 296.80, 296.89	F31.x
Neuropathic pain	357.2, 249.xa, 250.x[a], 729.2b, 337.1b, 355.9[b]	E08.40 to E08.43, E09.40 to E09.43, E10.40 to E10.43, E11.40 to E11.43, E12.40 to E12.43, E13.40 to E13.43 E08.1x[c] to E08.3x[c], E08.44[c], E08.49[c], E08.5[c] to E08.9[c] E09.1x[c] to E09.3x[c], E09. 44[c], E09.49[c], E09.5[c] to E09.9[c] E10.1x[c] to E10.3x[c], E10.44[c], E10.49[c], E10.5x[c] to E10.9x[c] E11.1x[c] to E11.3x[c], E11.44[c], E11.49[c], E11.5x[c] to E11.9x[c] E12.1x[c] to E12.3x[c], E12.44[c], E12.49[c], E12.5x[c] to E12.9x[c] E13.1x[c] to E13.3x[c], E13.44[c], E13.49[c], E13.5x[c] to E13.9x[c] M54.1[d], M79.2[d] G99.0[d], G58.9[d]
Other mental and behavioural disorders		
Dysthymia	300.4	F34.1
Schizoaffective disorders	295.7	F25.x
Phobias	300.2	F40
Acute stress disorder	308.x	F43.0
Adjustment disorders	309.x	F43.2

ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

[a] *Combined with code 337.1 Peripheral autonomic neuropathy in disorders classified elsewhere or 355.9 Mononeuritis of unspecified site.*

[b] *Combined with code 338.2 Chronic pain.*

[c] *Combined with code G99.0 Autonomic neuropathy in diseases classified elsewhere or G58.9 Mononeuropathy, unspecified.*

[d] *Combined with R52.1 Chronic intractable pain, or R52.2 Other chronic pain, or R52.9 Pain, unspecified.*

9.3.3.2.10. Time Since First Antidepressant Prescription

Time since the date of the first prescription for any antidepressant will be included in the analysis, as duration of disease may be related to treatment and risk factors for liver injury. All available historical data will be used.

9.3.3.2.11. Number of Liver Tests Performed

To adjust for potential surveillance bias, analyses will be adjusted by the number of liver tests performed within 12 months prior to the index date. This variable is available only in SIDIAP and EpiChron in Spain, and GePaRD in Germany.

9.3.3.2.12. Health Care Utilisation

Measures of health care utilisation, such as number of outpatient visits and number of hospitalisations, from the study start date and up to but not including the index date will be used as an additional adjustment for preexisting illnesses not specifically captured otherwise.

9.4. Data Sources

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

Based on the results of the feasibility evaluation of European data sources conducted by RTI-HS (Pladevall et al., 2013a), to allow for an adequate precision of the risk estimates, a study using multiple data sources is required. Therefore, we plan to conduct the study in population-based automated health databases from four European countries:

- Spain, the database of the EpiChron Research Group on Chronic Diseases at the Aragón Institute of Health Sciences (Instituto Aragonés de Ciencias de la Salud [IACS])
- Spain, the Information System for the Advancement of Research in Primary Care (Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària [SIDIAP]) database in Catalonia
- Germany, the German Pharmacoepidemiological Research Database (GePaRD)
- Denmark, the national registries
- Sweden, the national registers

9.4.1. Status of Contacts With the Study Data Sources

Contacts with the researchers at each data source to explore interest in and availability to conduct this study are ongoing. The status in each data source is listed in Table (9.4.1) 1.

Table (9.4.1) 1 - Status in Each Data Source

Data Source	Shared Study Protocol Synopsis	Interest in Participating
EpiChron, Spain	Yes	Confirmed
SIDIAP, Spain	Yes	Confirmed
National Registries, Denmark	Yes	Confirmed
GePaRD, Germany	Yes	Confirmed[a]
National Registers, Sweden	Yes	Confirmed

[a] *Pending approval by the statutory health insurance providers.*

9.4.2. Description of the Data Sources

Key characteristics of the study data sources are described in Table (9.4.2) 1. A brief description of each study data sources follows the table.

Table (9.4.2) 1 - Key Features of Databases

Database Feature	EpiChron (Aragón Institute of Health Sciences)	SIDIAP (Information System for the Advancement of Research in Primary Care)	German Pharmacoepidemiological Research Database	Danish National Patient and Prescription Registries	Swedish Prescription and Inpatient National Databases
Population of country[a]	Spain: 46,512,199	Spain: 46,512,199	Germany: 80,767,463	Denmark: 5,627,235	Sweden: 9,644,864
Database type	Primary health care electronic medical record database; link to hospital discharge data and pharmacy data	Primary health care electronic medical record database, link to hospital discharge data, pharmacy data, and mortality data	Claims database, four Statutory Health Insurance (SHI) plans	National health record databases, link to other national databases through a unique personal identification number (The Danish National Civil Registration System)	National health record databases, link with other national databases through the unique civil personal registration number
Data on medications and type of prescriptions	Reimbursed pharmacy-dispensed prescriptions	Reimbursed pharmacy-dispensed prescriptions and electronically prescribed drugs	Reimbursed pharmacy-dispensed prescriptions	All (reimbursed and non-reimbursed) pharmacy-dispensed prescriptions; in regional databases, only reimbursed prescriptions	All (reimbursed and non-reimbursed) pharmacy-dispensed prescriptions
Drug dictionary codes/therapeutic classification	ATC	ATC	ATC	ATC	ATC
Disease and procedure coding system(s)	Primary health care, ICPC; hospital, ICD-9-CM	ICD-10-CM	ICD-10-GM for diagnoses; OPS for surgical and diagnostic procedures; EBM for types of treatments and diagnostic procedures	ICD-10-CM	ICD-10-CM
Laboratory (requests, results)	Yes	Yes	Lab requests, but not results	No	No
Data availability	Partial since 2005; complete 2010 through 2013	2006 to Dec 2014	Since 2004	Since 1994	Since July 2005 (patient register data available since 1987)
Approximate time lag (updates per year)	1 year (1 per year)	1 year (2 per year)	1.5-1.8 year (at least 1 per year)	1 year (1 per year)	12 months (monthly updates for the Prescribed Drugs Register)
Access to medical records	Yes	No	No	Yes	No

ATC=Anatomical Therapeutic Chemical (ATC) Classification System; EBM = Einheitlicher Bewertungsmaßstab codes; ICD-10-CM = International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification; ICD-10-GM = International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; ICPC=International Classification of Primary Care; OPS = Operationen- und Prozedurenschlüssel.

[a] *Population data from (Eurostat, 2014).*

9.4.2.1. Spanish Databases

9.4.2.1.1. Aragón Institute of Health Sciences Database

The EpiChron Research Group on Chronic Diseases at the Aragón Institute of Health Sciences (Instituto Aragonés de Ciencias de la Salud [IACS]) has linked the electronic medical and administrative databases in the region to create the EpiChron database. These source databases contain administrative and clinical information from outpatient clinics (primary care centres), emergency departments, hospitals, and pharmacies. From 2010 onwards, data are available for 1.3 million patients covered by all outpatient practices in Aragón. The following types of data are available: administrative and clinical information from outpatient clinics (primary care centres), emergency department diagnoses and care, hospital procedures and discharge diagnoses, and pharmacy prescription data. Studies are conducted in collaboration with the Institute of Public Health and Health Services Research; ethics committee approval is needed for the study.

9.4.2.1.2. SIDIAP Database

The Information System for the Advancement of Research in Primary Care (Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària [SIDIAP]) in Catalonia, Spain, is a primary-care database set up by the Institute of Research in Primary Care (Institut D'Investigació en Atenció Primària) and Catalan Institute of Health (Institut Català de la Salut). The database collects information from 279 primary health care centres and includes more than 5.8 million patients, about 78% of the Catalan population covered by the Catalan Institute of Health (SIDIAP, 2014). Data from health care visits are recorded in the electronic medical records. See Appendix 14.6; Table (14.6) 2, for key features of the database.

Linkage by an individual's national security number provides the potential to access information from different data sources, including demographic information from the Catalan Health Services database, electronic primary care clinical and laboratory test records, drugs dispensed in community pharmacies, hospital discharge codes from an external database of hospital admissions (CMBD-AH), and other available disease or procedural registries.

Information on pharmacy-dispensed drugs is available since 2005. Additional data available are the date and value of clinical variables, prescriptions issued, dispensed prescriptions (since 2005), and laboratory results (since 2006). The database can be linked to the Catalonian death registry, which includes date and cause of death of all residents (Bolíbar et al., 2012).

All research projects applying to use SIDIAP data are assessed by an institutional review board (IRB) and the SIDIAP scientific review committee.

9.4.2.1.3. Strengths and Limitations of the Databases Available in Spain for This Study

- Broad coverage and representation of the general population covered by the Catalan Health System. The database in Aragón covers the whole population in the region.
- Spain is the country with the highest number of agomelatine users per 1,000 inhabitants.
- The Catalan and Aragón health systems have universal coverage of drugs and other health care of the population assigned to the primary health care centre.
- Linkage to hospital discharge codes and the mortality registry is possible.
- Access to pharmacy-dispensed prescriptions. Only those prescriptions dispensed in a hospital setting or purchased over the counter will be missed.

- Information on relevant confounders is captured in both databases.
- Laboratory ambulatory test results are available in SIDIAP and EpiChron.
- Access to medical records for validation of events is available in EpiChron, although the process of obtaining access involves intensive effort and requires special approvals.
- Fewer studies have been published using or evaluating the validity of SIDIAP or EpiChron compared with the other study data sources.

9.4.2.2. Germany, GePaRD

The German Pharmacoepidemiological Research Database (GePaRD) is a population-based database that consists of claims data obtained from four statutory health insurance agencies (SHIs) in Germany (Jobski et al., 2012; Kraut et al., 2010; Pigeot and Ahrens, 2008). Ninety-one percent of the population in Germany is insured with the SHIs. The database covers over 17 million SHI members from all regions of Germany, approximately 21% of the 81 million German population in 2014 (Eurostat, 2014). Membership in SHIs is fairly stable over time. Available data contain demographic information and information on hospitalisations, outpatient physician visits, and outpatient dispensing of prescribed medications in the pharmacies (see Appendix 14.6; Table (14.6) 1).

Prescription drug information is recorded for all outpatient dispensings that are reimbursable by SHIs and includes the date of prescription, date of dispensing, central pharmaceutical number (CPN), and information on the prescribing physician with the physician specialty. Via linkage of the CPN to a pharmaceutical reference database, information is available on the prescribed quantity, strength, formulation, generic and trade names, ATC code, and defined daily dose.

The study will be conducted in collaboration with the Leibniz Institute for Prevention Research and Epidemiology (BIPS GmbH); approval from SHIs and their respective governing authorities (e.g., the Federal Insurance Office for national SHI providers) is needed for the study.

9.4.2.2.1. Strengths and Limitations of the GePaRD for this Study

- This data source has the largest population of users in Europe, although it also has the longest lag time for data availability.
- Prescriptions of agomelatine and indication can be identified using validated methods.
- Most relevant potential confounders are available.
- Lack of availability of laboratory results and access to medical records will not allow ascertainment of cases of ALI according to some of the standard approaches for validation of cases.

9.4.2.3. Danish Databases

The Danish health care system provides universal coverage to all Danish residents (5.6 million inhabitants; http://international.ucl.dk/life-in-denmark/the-danish-health-care-system). Health care coverage includes visits to general practitioners and specialists, hospital admissions, and outpatient visits. The costs of medicines are partially covered by the Danish health system. The centralised Civil Registration System in Denmark allows for personal identification of each person in the entire Danish population and for the possibility of linkage to all Danish registries containing civil registration numbers, such as the Danish National Patient Register, Danish

National Prescription Registry, and the Danish Register of Causes of Death. Data collected in these registries are available for research purposes. The process requires collaboration with a local university or investigator affiliated with a research institute to access the data and ethics committee notification or approval to handle data (Danish Data Protection Agency, 2013; Danish Health and Medicines Authority, 2014). All applications have to be submitted in Danish.

Denmark's primary health care sector, which includes general practitioners, specialists, and dentists, generates about 96% of the prescription sales, most of which are reimbursable and are dispensed by community pharmacies. Each dispensing record contains information on the patient, drug, and prescriber. Dispensing records retain the patient's universal personal identifier, allowing for individual-level linkage to all Danish registries and medical databases.

Two national registries (Danish National Patient Register and Danish National Prescription Registry) and the Danish National Database of Reimbursed Prescriptions will be of particular interest for implementation of the agomelatine PASS. Key features of the Danish databases may be found in Appendix 14.6; Table (14.6) 3. Moreover, the Danish National Civil Registration System will be used to obtain information on death and migration status.

9.4.2.3.1. Danish National Patient Register

The register includes data on all hospital admissions since 1 January 1977 and on outpatient clinic and emergency department visits since 1995 (Danish Health and Medicines Authority, 2012; Lynge et al., 2011). Hospital discharge diagnoses and information on surgical procedures, in-hospital deaths, and some selected drugs are recorded. After 1993, hospital discharge diagnoses are coded using ICD-10 codes.

9.4.2.3.2. Danish National Prescription Registry

The registry provides patient-level data on drug prescriptions dispensed by pharmacies since 1994 (Kildemoes et al., 2011). The National Prescription Registry collects data on reimbursed and unreimbursed drugs.

9.4.2.3.3. The Danish National Database of Reimbursed Prescriptions

This data source encompasses the reimbursement records of all reimbursed drugs sold in community pharmacies and hospital-based outpatient pharmacies in Denmark since 2004 (Johannesdottir et al., 2012). On average, approximately 3.5 million users are recorded in the database each year. Individuals are identified by the unique central personal registration (CPR) number assigned to all persons born in or immigrating to Denmark. This new data source avoids restrictions imposed on data use at the Danish National Prescription Registry. Most importantly, CPR numbers are reversibly encrypted, which allows re-identification of drug users. These features are very important for validation purposes; for this study we plan to use this database instead of the Danish National Prescription Registry.

9.4.2.4. Swedish National Databases

In Sweden, the national health care system provides universal coverage to all residents—9.6 million inhabitants (Eurostat, 2014). Health care coverage includes visits to general practitioners (GPs) and specialists, hospital admissions, and hospital outpatient visits; drug costs are either partially or completely covered. A centralised civil registration system has been in place for many years, enabling personal identification of each person in the entire population

and linkage to all national registers containing civil registration numbers, e.g., patient register, cancer register, prescription databases, register of causes of death, and population registers (Furu et al., 2010). Information on the national databases in Sweden is summarised in Appendix 14.6; Table (14.6) 4.

The National Patient Register covers all inpatient care in Sweden from 1987 and includes information on diagnoses, surgical procedures, and in-hospital deaths. Since 2001, it also includes outpatient hospital care data. The register includes about 1.5 million discharges annually. Whereas coverage of the inpatient register is currently almost 100%, coverage of hospital-based outpatient care is considerably lower (about 80%) (Ludvigsson et al., 2011). Visits to GPs and specialists outside the hospitals are not included in the registers.

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

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

9.4.2.5. Strengths and Limitations of the Danish and Swedish Databases for This Study

- Data from national registers include all age ranges in the population.
- At the national level, all dispensed prescriptions, regardless of reimbursement, are available.
- As is true for most databases, determination of indication must be based on proxies. Cause of death is available through linkage to mortality registries.
- Source medical records can be accessed for selected projects and with special approvals for studies conducted in the Danish data sources and in the Swedish regional databases (but not for studies initiated in the national prescription databases). Validation of all hospitalised cases, and in one region for ambulatory cases, can be performed in Denmark, and validation of a subset of identified cases could potentially be performed in the regional databases in Sweden.
- General practice and other outpatient diagnoses and information can be obtained through the Swedish or Danish regional databases. However, given the study timelines and that the whole population of Denmark and Sweden is required for study size purposes, use of the regional databases in either country is neither feasible nor applicable. For both data sources, the only outpatient data available will be data from outpatient hospital clinics.
- With the exception of detailed information on alcohol use, which could be captured only at the regional level, data on most potential confounders can be obtained from the national databases, although only hospital-based diagnosis are available.

9.5. Study Size

The study size is driven by the uptake of agomelatine in the populations from which the automated data sources obtain data. For each data source, we will identify all new users of agomelatine and the other study antidepressants since the drug became available in the country.

Table (9.5) 1 displays data on users of agomelatine in the Spanish databases, GePaRD, Denmark, and Sweden. For the Aragón database, only prescription counts were available, so those counts were used to estimate the potential number of users based on the average number of prescriptions per user found in the Swedish Prescribed Drug Register, which had information available on both number of prescriptions and number of users. In the GePaRD, user counts were not available, and we estimated the number of potential users in the database from published data on defined daily doses of agomelatine available in Germany (Schwabe and Paffrath, 2011; Schwabe and Paffrath, 2012; Schwabe and Paffrath, 2013; Schwabe and Paffrath, 2014). It should be noted that for the purpose of efficiency, we may select a random sample of new users of the study antidepressants other than agomelatine if the number of users is very high. However, all new users of agomelatine will be included in the study.

Table (9.5) 1 - Numbers of Users of Agomelatine in the Different Study Data Sources Reviewed, by Year From 2009-2013

Data Source	Period Covered by User Counts or Estimated Number of Users	Number of Users or Estimated Number of Users
Germany (GePaRD)	2010	12,345[a]
		23,044[b]
	2011	18,619[a]
		34,756[b]
	2012	24,994[a]
		46,656[b]
	2013	25,095[a]
		46,844[b]
Denmark[c]	2009	2,662
	2010	6,346
	2011	8,806
	2012	8,341
	2013	7,200
Sweden[d]	2009	927
	2010	1,963
	2011	5,592
	2012	7,095
	2013	6,725
Spain (EpiChron)[e]	2010-2111	7,000
Spain (SIDIAP)[f]	2010-2013	14,655

GePaRD = German Pharmacoepidemiological Research Database; SIDIAP = Information System for the Advancement of Research in Primary Care, Spain.
[a] Estimated from defined daily doses (Schwabe and Paffrath, 2011; Schwabe and Paffrath, 2012; Schwabe and Paffrath, 2013; Schwabe and Paffrath, 2014), assuming the recommended minimal duration of treatment, 168 days.
[b] Estimated from defined daily doses (Schwabe and Paffrath, 2011; Schwabe and Paffrath, 2012; Schwabe and Paffrath, 2013; Schwabe and Paffrath, 2014), assuming a 90 days mean duration of treatment.
[c] Source: http://medstat.dk/.
[d] Source: http://192.137.163.49/sdb/lak/val.aspx.
[e] Source: Aragón database custodians. Estimated from 28,000 prescriptions during the period and assuming a mean of four prescriptions per user based on data obtained from the Swedish Prescribed Drug Register.
[f] Source: SIDIAP database custodians.

With 65,000 patients in agomelatine cohort, the incidence rate can be estimated with an absolute precision of ± 2 per 100,000 if the expected incidence rate is 1 case per 100,000 person-years and ± 9 per 100,000 if the incidence rate is 14 cases per 100,000 person-years. Even in the case with the lowest hypothesised incidence rate, the incidence rate can be reliably estimated not to be above 3 per 100,000 person-years (based on 95% confidence interval).

For the nested case-control study, we calculated the number of cases and controls that would be needed for the following assumptions:

- Prevalence of exposure calculated as the percentage of users of agomelatine among all users of agomelatine and citalopram in the study data sources. According to these calculations, four scenarios of prevalence were used in the calculations: 2%, 5%, 10%, and 20%
- Four scenarios of the ratio of number of controls to number of cases: 1:1, 4:1, 10:1, and 20:1
- Power of 80%
- Alpha-level of 0.05
- Odds ratios to be detected of 1.5, 2.0, 3.0, 4.0, 5.0, and 10.0

Assuming an intermediate prevalence of use of 5% and a control-to-case ratio of 20:1, the number of cases needed for a power of 80% range from 825 cases for detecting an odds ratio of at least 1.5 to 10 cases for detecting an odds ratio of at least 10.0 (see Appendix 14.7).

We also estimated the number of cases that would be detected assuming a 5% prevalence of agomelatine use and using different scenarios of the published incidence of ALI in the general population and the expected number of users of agomelatine in the study populations.

- Published incidences of ALI range from 1 case per 100,000 person-years (Ibanez et al., 2002) to 14 cases per 100,000 person-years (Sgro et al., 2002).
- The number of users of agomelatine in the study data sources was estimated by using the number of users in the most recent year in each data source and adding 20% of the number of users in prior years, which assumes that 20% of the prior users are users by one of the definitions of this study. We assumed a low and high scenario of the number of users across the data sources according to low and high estimates from Germany (65,000 and 92,000).

These calculations are presented in Table (9.5) 2 and Figure (9.5) 1. Combining all new users across the study data sources assuming the scenario with the lowest number of users of agomelatine (65,000) and a ratio of 20 controls per case, the minimum odds ratios to be detected are 6.8 for an incidence of ALI of 1 case per 100,000 person-years, 3.7 for an incidence of 3.4 cases per 100,000, and 2.1 for an incidence of 14 cases per 100,000.

For the scenario with the highest number of users of agomelatine (92,000) the minimum odds ratios to be detected for the same incidences are 5.6, 3.1, and 1.9, respectively.

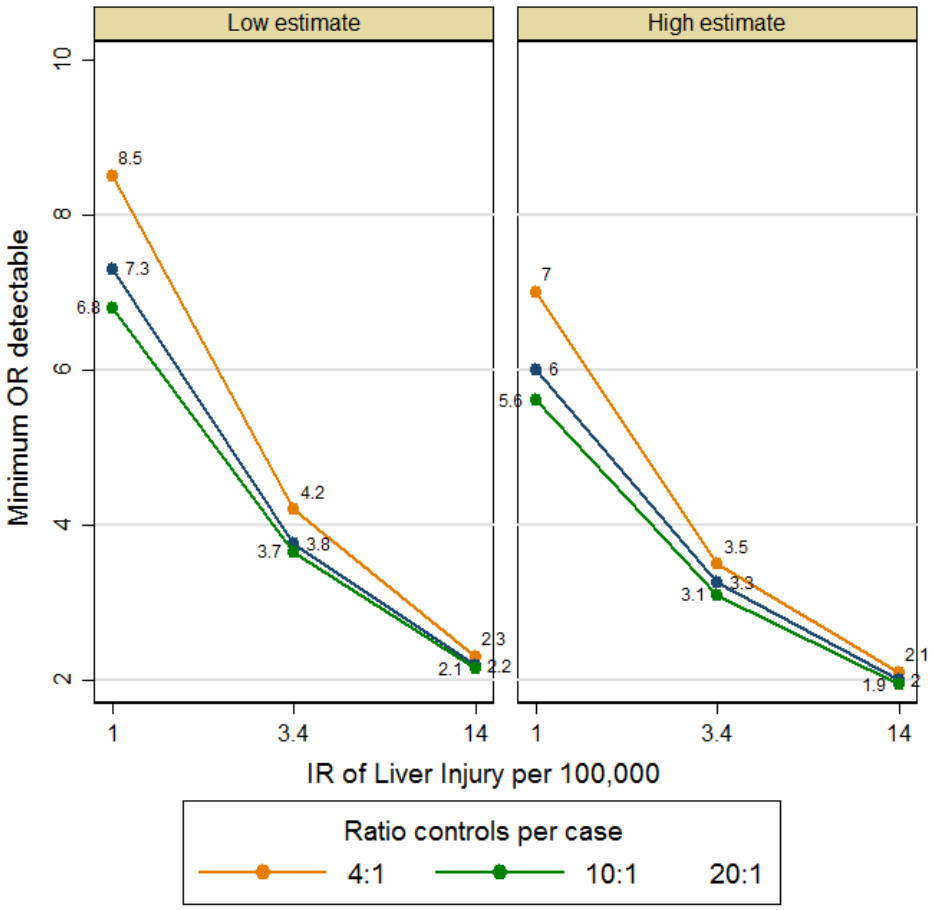
In this study, incidence rates of ALI will be estimated with a good precision. In the nested case-control study, the precision will be lower. However, the loss of precision from the sampling of controls is small if the number of controls per case is large (Rothman and Greenland, 1998).

Table (9.5) 2 - Odds Ratios That Could be Detected With 80% Power Under Different Scenarios for Number of Agomelatine Users and Varying Incidences of Liver Injury

Estimated Number of Users of Agomelatine	Incidence Rate of ALI × 100,000 in Unexposed (Citalopram)	Ratio Controls/Cases	Number of Cases Unexposed	Minimum Odds Ratio to be Detected	Number of Cases Exposed	Total Number of Cases
65,000	1.0	1	12	13.4	9	21
Lowest estimate	1.0	4	12	8.5	6	18
	1.0	10	12	7.3	5	17
	1.0	20	12	6.8	4	16
	3.4	1	42	5.9	13	55
	3.4	4	42	4.2	9	51
	3.4	10	42	3.8	8	50
	3.4	20	42	3.7	8	50
	14.0	1	173	2.9	26	199
	14.0	4	173	2.3	21	194
	14.0	10	173	2.2	20	193
	14.0	20	173	2.1	19	192
92,000	1.0	1	17	10.4	10	27
Highest estimate	1.0	4	17	7.0	6	24
	1.0	10	17	6.0	6	23
	1.0	20	17	5.6	5	22
	3.4	1	59	4.8	15	74
	3.4	4	59	3.5	11	70
	3.4	10	59	3.3	10	70
	3.4	20	59	3.1	10	69
	14.0	1	245	2.5	32	277
	14.0	4	245	2.1	27	272
	14.0	10	245	2.0	26	270
	14.0	20	245	1.9	25	270

ALI = acute liver injury.

Figure (9.5) 1 – Odds Ratios That Could Be Detected With 80% Power Under Different Scenarios for Number of Agomelatine Users and Varying Incidences of Liver Injury



IR = incidence rate; OR = odds ratio.

9.6. Data Collection and Management

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

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff. Appropriate data storage and archiving procedures will be followed (i.e., storage on CD-ROM or DVD), with periodic backup of files to tape. Standard procedures will be in place at each research centre to restore files in the event of a hardware or software failure.

9.7. Data Analysis

The software to be used for data management and statistics will be SAS and Stata. A description analysis of the reasons for exclusion, the cohort (such as number of new users of each medication and the baseline characteristics (including potential confounders before start date at baseline), the cases and the controls, and the covariates of interest will be performed.
The analysis of the primary objective of the study will be performed in the nested case-control analysis. The analysis of the secondary objectives will be performed in the full cohort.

9.7.1. Cohort Analysis (Secondary Analysis)

9.7.1.1. Cohort Description

Baseline characteristics of study population at the time of cohort entry will be presented.

The study inclusion/exclusion criteria will be applied to select the study population. For each data source, the impact on the study size at each step of applying the study criteria in a stepwise fashion will be presented. Once the study population is identified, each study antidepressant cohort will be described at the time of cohort entry. The study cohorts will be characterised according to age, sex, calendar year of the start date, duration of follow-up, medical history, use of medications in the year prior to the start date, and risk factors and confounders at any time before the start date. Duration of treatment and potential indications for starting each antidepressant drug will be also described. Categorical data will be presented as counts and proportions. Continuous data will be presented as number of observations, number of patients with missing information (if applicable), mean, standard deviation, and median and inter-quartile range when appropriate.

9.7.1.2. Estimation of Crude Incidence Rates and Age- and Sex-Standardised Incidence Rates

Crude incidence rates and age- and sex- standardised incidence rates of ALI per patient-time (all endpoints), and 95% confidence intervals (CIs), will be estimated for agomelatine and each study antidepressant during current use, which will comprise the sum of all the episodes of continuous treatment occurring during the cohort follow-up time.

9.7.1.3. Estimation of Cumulative Incidences

We will use the Kaplan-Meier method to estimate the cumulative incidence rate of ALI (with 95% CI) (all endpoints) at monthly intervals after the first dispensing of agomelatine and each study antidepressant during the first episode of continuous current use for each patient. The first episode of continuous current use will be defined as the person-time from the date of the first prescription of a study antidepressant to the end of supply for the last consecutive prescription plus a period of 40 days, allowing for treatment gaps of 40 days between prescriptions. The allowed gap duration might need to be adapted in some of the data sources.

9.7.1.4. Estimation of Age- and Sex-Adjusted Incidence Rate Ratios

Age- and sex-adjusted incidence rate ratios of ALI and 95% CIs (all endpoints) will be estimated using the Mantel-Haenszel method for agomelatine and each study antidepressant during current use (which will comprise the sum of all the episodes of continuous treatment occurring during the cohort follow-up time), compared with citalopram current use.

9.7.2. Case-Control Analysis (Primary Analysis)

9.7.2.1. Description of the cases and controls

Characteristics of cases and controls, including age, sex, calendar year, and potential confounders with their respective crude odds ratios (ORs) and mutually adjusted ORs from logistic regression models, will be described. Additional variables of interest such as those that are data source–specific or those that may be collected at the time of the endpoint validation may also be described in the study report or in the validation report, as applicable.

9.7.2.2. Estimation of Odds Ratio Adjusted for Additional Confounders

Conditional logistic regression will be used to estimate and compare the risk of hospitalisation for ALI associated with the use of agomelatine and the other study depressants with the risk associated with the use of citalopram, adjusting for potential confounders listed in Section 9.3.3. In the context of a nested case-control study, the estimated odds ratios give the same results as the incidence rate ratios estimated from the study population if sampling is independent of exposure (Rothman and Greenland, 1998). In the next sections, we describe the analyses to be conducted, classified as follows: main analysis, secondary analysis, sensitivity analyses. All analyses will be conducted separately for all endpoints, taking into account the limitations inherent to the tertiary endpoint (see Section 9.9).

9.7.2.2.1. Main Analysis

For all study endpoints, the *main comparison of interest* will be current use of agomelatine and current use of each of the other study antidepressants versus current use of citalopram (see Table (9.7.2.2.1) 1).

Table (9.7.2.2.1) 1 - Shell Table for the Estimation of Crude and Adjusted Odds Ratio of Acute Liver Injury for Current, Use of Each Study Medication Compared With Current Use of Citalopram

Current Use	Number of Cases (%)	Number of Controls (%)	Age- and Sex-Matched Odds Ratio (95% CI)	Adjusted Odds Ratio[a] (95% CI)
Citalopram	**xx (%)**	**xx (%)**	**1.0 (Reference Category)**	**1.0 (Reference Category)**
Agomelatine	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)
Fluoxetine	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)
Paroxetine	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)
Sertraline	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)
Mirtazapine	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)
Venlafaxine	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)
Duloxetine	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)
Amitriptyline	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)

CI = confidence interval.
[a] *Adjusted for all confounding factors.*

9.7.2.2.2. Secondary Nested Case-Control Analysis

In addition, for all study endpoints, the risk associated with current single use of agomelatine and current single use of each of the other study antidepressants will be compared with the risk associated with current single use of citalopram (see Table (9.7.2.2.2) 1).

Table (9.7.2.2.2) 1 - Shell Table for the Estimation of Crude and Adjusted Odds Ratio of Acute Liver Injury for Current Single Use of Each Study Medication Compared With Current Single Use of Citalopram

Current Single Use	Number of Cases (%)	Number of Controls (%)	Age- and Sex-Matched Odds Ratio (95% CI)	Adjusted Odds Ratio[a] (95% CI)
Citalopram	**xx (%)**	**xx (%)**	**1.0 (Reference Category)**	**1.0 (Reference Category)**
Agomelatine	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)
Fluoxetine	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)
Paroxetine	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)
Sertraline	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)
Escitalopram	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)
Mirtazapine	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)
Venlafaxine	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)
Duloxetine	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)
Amitriptyline	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)

CI = confidence interval.
[a] *Adjusted for all confounding factors including age and sex.*

9.7.3. Interim Analysis

For the interim analysis, case validation results will not be available and therefore the analysis will be restricted to the primary endpoint. This analysis will include both main and secondary nested case-control analyses, as well as the cohort analysis of the primary endpoint. Results of the main analysis from each data source will be combined using meta-analytic techniques (see Section 9.7.5).

9.7.4. Sensitivity Analyses

Various sensitivity analyses will be performed for the nested case-control analysis, the main and secondary analyses for the primary and secondary endpoints, with the exception of the case validation sensitivity analysis. The impact of validation will be assessed in both the cohort and case-control analyses for the tertiary endpoints.

9.7.4.1. Impact of Exposure Definition

The impact of the exposure definition on current use will be assessed in a sensitivity analysis adding 15 days and 60 days (instead of 40 days) to the days of supply of the most recent prescription before the index date. The sensitivity analysis will be applied to the current use and current single use for the primary and secondary endpoints.

9.7.4.2. Recent and Past Use of Antidepressants

For the primary and secondary study endpoints, recent and past use of each antidepressant will be compared with current use of citalopram. This will allow estimation of the effect of each antidepressant after stopping treatment. Using current use of citalopram as the reference category, as used in the main analysis, will allow evaluation and comparison of the effect of current, recent, and past use for each study antidepressant.

9.7.4.3. Switching and Multiple Current Use

Switching and multiple current use will be compared to current single use of citalopram. Switching and multiple use will be considered together.

9.7.4.4. Effect of Duration of Use

The effect of duration of use will be estimated for current single use of each antidepressant separately. Current single use of citalopram will be used as the reference category.

9.7.4.5. Confirmed Cases Versus Unconfirmed Cases

A sensitivity analysis including only confirmed (validated) cases will be implemented for the tertiary end-point. This analysis in the cohort and the nested case-control components will enable evaluation of the impact on the risk estimates of including only validated cases. If after validation of the secondary endpoint, the results indicate that the positive predictive value of the specific codes used to identify the primary endpoint is not adequate, an additional sensitivity analysis restricted to validated cases of the primary endpoint could be performed in all data sources.

9.7.5. Meta-analysis

All analyses described previously for both the cohort study and the nested case-control study will be conducted in each data source. Meta-analytic techniques will be used to combine the odds ratio estimates obtained from the nested case-control study in the different data sources. Meta-analyses for all endpoints will be conducted for the main analysis and, if there are relevant differences between the main and the sensitivity analyses, for the sensitivity analyses. Summary odds ratios and 95% CIs for ALI will be produced first using random effect models. If results are homogeneous across databases, fixed-effect models will be presented (Higgins and Green, 2011).

9.7.6. Missing Values

The extent of missing data will be evaluated and described. Covariates will be ascertained on the start date or on the index date, and the number of subjects with missing data will be reported. Variables known to be recorded only partially or inconsistently in a specific database will not be included in the analysis in that database. Detailed information on how missing data will be handled in the analysis will be included in the statistical analysis plan.

9.8. Quality Control

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

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

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

9.9. Limitations of the Research Methods

The design of this study allows assessment of the risk of hospitalisation for ALI associated with periods of use of agomelatine and the other study antidepressants compared with periods of use of citalopram. The study will be conducted using health information recorded in population-based databases that collect and record data on a regular basis, thereby minimising bias related to differential reporting of the exposures and outcomes of interest.

One of the challenges of studying antidepressants is to address the potential confounding introduced by the different types of indication and use patterns across the different antidepressants even among those that are related pharmacologically. We have attempted to select antidepressants with similar indications; however, as shown in Appendix 14.4; Table (14.4) 1, there is some variability in the indication across the different study antidepressants. Also, reimbursement policies vary by antidepressant, although agomelatine should be used in most of the countries in the study when treatment with other generic drugs (mainly selective serotonin reuptake inhibitors [SSRIs]) is unsuccessful. Indication of antidepressants may be also related to ALI through the association with lifestyle habits (e.g., sedentariness leading to obesity, alcohol abuse) and use of other hepatotoxic medications. To minimise potential confounding by indication, we will control in the analysis for history of diseases that are potential indications of treatment, risk factors for ALI, and previous and concurrent use of antidepressant drugs and other hepatotoxic medications. Information on some risk factors such as obesity, overweight, and alcohol use are not available in some databases (Denmark, Sweden, GePaRD) and may be partially recorded in some others (SIDIAP, EpiChron). Therefore, residual confounding may remain. An analysis on recent and past use will allow assessment of potential remaining confounding.

The heterogeneity of data across data sources will require adaptation to address case ascertainment and validation and to obtain complete information on the availability of relevant confounders in each data source. There is heterogeneity between data sources regarding exposure information (prescribed vs. dispensed medications) and ascertainment of risk factors and confounders. Some of the data sources might have limited data availability for some comorbidities and potential confounders. Three of the study data sources (GePaRD, Denmark, Sweden) are mainly based on diagnoses upon discharge from the hospital or in connection with a hospital outpatient clinic visit, whereas the databases in Spain are mainly based on information from GPs (in Sweden, data from primary care have also recently become available). The publication of studies conducted in the Spanish databases is limited, but the databases include a high number of users and validation of cases is feasible. Ascertainment of covariates using hospital discharge diagnoses might result in the identification of individuals with more severe comorbidity. Nevertheless, differential misclassification of covariates across the study antidepressants is not expected.

This study will not be able to evaluate the effect of daily dose of the study antidepressants, because adequate data to calculate dose are not available in the study databases. However, the effect of duration of use of the study antidepressant will be evaluated, as duration will be estimated from the time between consecutive prescriptions.

We considered the use of disease risk scores to control for confounding using a single parameter that summarises the effect of several variables. However, we withdrew this option because most of the predictive factors for ALI were included as exclusion criteria for cohort

entry, and also because the expected low number of ALI events would largely restrict the total number of variables that could be used in the predicting models used to calculate the scores.

A limitation of databases is the uncertain validity of the recorded information for some diagnoses, including the diagnosis of ALI. The definitive diagnosis of ALI requires results from blood tests that will be available in some but not all of the study data sources; thus, cases in this study would require validation. However, validation of cases of ALI within the study time frame will not be feasible in Germany and Sweden. Therefore, we defined the primary endpoint according to specific diagnoses for ALI that have shown a high positive predictive value. However, residual misclassification is possible. This misclassification will most probably be non-differential with respect to the exposure and can bias the effect estimates towards the null, potentially underestimating a real increase in liver injury risk associated with the use of agomelatine.

Since the start of pregnancy will be estimated in most data sources form birth dates, and abortion data will not be available in all data sources, exclusion of pregnancy time among women might also be susceptible to misclassification. However, this misclassification will most probably be non-differential with respect to the exposure.

According to the label for agomelatine, the liver enzymes of agomelatine users need to be monitored periodically by blood tests; therefore, a potential detection bias could occur. The likelihood of this bias is large for the tertiary outcome that will include non-hospitalised cases. Mild cases of liver injury that do not require hospitalisation or mild elevations of liver tests are more likely to be detected among users of agomelatine than among users of other antidepressants that are not required to have routine liver test monitoring. Moreover, validation of all cases within the study time frame will be feasible in only some of the study data sources, and validation of outpatient cases will be possible only in those databases that have data available on liver tests results. Therefore, caution will be necessary when interpreting the results of the tertiary outcome.

On the other hand, the impact of this potential detection bias in the identification of potential cases of liver injury is expected to be minimal for the primary and secondary outcomes because the identification of cases is based on hospitalised clinical diagnoses related to liver injury and because it is expected that liver enzyme and bilirubin values will be available for these patients regardless of recommended monitoring practices. Moreover, in the analysis, we will try to control for the number of serum liver chemistry tests performed, although this information is available only in SIDIAP, EpiChron, and the GePaRD. It should be taken into account that the endpoint of ALI will be evaluated for the first time in the Spanish databases (SIDIAP and EpiChron). However, potential cases of ALI will be validated by examining the results of outpatient liver tests in SIDIAP and by reviewing the hospital medical records of potential cases in EpiChron. In SIDIAP, there is uncertainty about the extent of the availability of liver test results as these are available only for outpatients; thus, if availability is low, a potential identification bias could impact the number of cases that, after identification, can be validated in SIDIAP. The impact of a potential detection bias is expected to be minimal in the validation of potential cases of liver injury in EpiChron, in which validation will be based on review of medical records.

Estimation of incidence rates of ALI using only specific diagnoses to identify cases will result in underestimation of incidence rates. However, incidence rates estimated using specific and non-specific diagnoses with additional validation of potential cases will provide valid rates in

current users of agomelatine and the other study antidepressants. These incidence rates will be available only for Spain and Denmark because case validation within the study time frame is not feasible in Germany and Sweden. Also, since we used restriction for control of confounding factors, incidence rates will refer to the population of users of the study antidepressants without history of liver disease and risk factors for ALI.

Another limitation has to do with the limited number of agomelatine users that will be available during the study period, even combining all available data sources. Therefore, the power to detect a relevant increase in the risk of ALI associated with agomelatine will be limited, especially if the incidence of ALI in the study data sources is below 14 cases per 100,000 person-years.

In spite of these limitations, this study will be the first evaluation of the incidence of hospitalisation for ALI in users of agomelatine from several European countries involving a large population of users.

10. PROTECTION OF HUMAN SUBJECTS

This is a retrospective, non-interventional study and does not pose any risks for patients. All data collected in the study will be either de-identified (electronic data in databases and registries) or specially protected (hospital charts) with no breach of confidentiality with regard to personal identifiers or health information. Each data source research partner will apply for an independent ethics committee review according to local regulations; in addition, as the coordinating centre, RTI-HS will obtain approval from the RTI International* IRB.

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

10.1. RTI International

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

10.2. EpiChron, Aragon, Spain

The final study protocol will be submitted to the local ethics committee and to the Spanish Medicines Agency.

10.3. SIDIAP, Catalonia, Spain

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

** RTI Health Solutions is a business unit of RTI International, a private, not-for-profit research organization.*

10.4. GePaRD, Germany

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

10.5. National Databases, Sweden

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

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

10.6. National and Regional Databases, Denmark

For the Danish national databases, approval will be requested from the Danish National Board.

10.7. Other Good Research Practice

This study adheres to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)* of the International Society for Pharmacoepidemiology (ISPE, 2007) and has been designed in line with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP, 2014b). The *ENCePP Checklist for Study Protocols* (ENCePP, 2013) is included in Appendix 14.2.

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 tripartite guideline *Pharmacovigilance Planning E2E* (ICH, 2004) and provided in the EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies* (EMA, 2013b), and with the 2012 European Union pharmacovigilance legislation, adopted June 19, 2012 (European Commission, 2012). The study will comply with the study reporting requirements specified in Module VIII Section VIII.B.6.3.2. “Final Study Report” of the *Guideline on Good Pharmacovigilance Practices (GVP)* (EMA, 2013b).

The study will be registered in the EU PAS Register (ENCePP, 2014a) before the study implementation commences. IRIS has agreed to grant the research team independent publication rights in line with the ENCePP Code of Conduct (ENCePP, 2011).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Based on current guidelines from the International Society for Pharmacoepidemiology (ISPE, 2007) and the EMA (2012b), non-interventional studies such as the one described in this protocol, conducted using medical chart reviews or electronic claims and health care records, do not require expedited reporting of suspected adverse events/reactions. Because of the data sources used for this study, no suspected adverse events/reactions are expected.

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 Safety Update Reports, and other regulatory milestones and requirements. Study reports will be prepared using a template following *Guideline on Good Pharmacovigilance Practices (GVP)*, Module VIII, Section B.6.3 (EMA, 2013b).

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

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

The marketing authorisation holder and the principal investigators (e.g., the principal investigators at the study coordinating centre and at the data source research centres) will agree upon a publication policy allowing the principal investigators to independently prepare publications based on the study results, irrespective of data ownership. The marketing authorisation holder will be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication (EMA, 2013b).

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14. APPENDIX

14.1. List of Stand-Alone Documents

None.

14.2. 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:
Post-Authorisation Safety Study of Agomelatine and the Risk of Hospitalisation for Acute Liver Injury

Study reference number:
The study will be registered in the EU PAS Register following European Medicines Agency endorsement and prior to start of data collection.

Section 1: Milestones	Yes	No	N/A	Page Number(s)
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection1	☒	☐	☐	22
1.1.2 End of data collection2	☒	☐	☐	22
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	22
1.1.5 Registration in the EU PAS Register	☒	☐	☐	22
1.1.6 Final report of study results	☒	☐	☐	22

Comments:

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)	☒	☐	☐	15,23-24
2.1.2 The objectives of the study?	☒	☐	☐	15,24-24
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	15,26
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:

The study compares the risk of acute live injury of agomelatine and other antidepressants with the risk of citalopram. There is no prior hypothesis.

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)	☒	☐	☐	15,24-26
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	15-17,30-35
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)	☒	☐	☐	15-17,56-59

Comments:

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

Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	☒	☐	☐	15-17, 46-51
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	26
4.2.2 Age and sex?	☒	☐	☐	28-30
4.2.3 Country of origin?	☒	☐	☐	15-17, 46-51
4.2.4 Disease/indication?	☒	☐	☐	44-45
4.2.5 Co-morbidity?	☒	☐	☐	38-41
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)	☒	☐	☐	28-29

Comments:

Seasonality is not applicable because this is not of relevance to the study.

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	15-17, 35-38
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)	☒	☐	☐	15-17, 35-38
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	35-38
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?	☒	☐	☐	37

Comments:

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	15-17, 31-33
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)	☒	☐	☐	31-35, 60-62

Comments:

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)	☒	☐	☐	38-45
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☒	☐	

Comments:

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.)	☒	☐	☐	46-51
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.)	☒	☐	☐	46-51
8.1.3 Covariates?	☒	☐	☐	46-51
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)	☒	☐	☐	Annex 14.6: 104-111
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	Annex 14. 6: 104-111
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	Annex 14. 6: 104-111
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	40-42,46-48
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☒	☐	☐	32-33,46-48
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	27,41-44, 46-48
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	46-51

Comments:

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	51-55 Annex 14.7: 111

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?	☒	☐	☐	15-17, 56-59
10.3 Are descriptive analyses included?	☒	☐	☐	56,56-56
10.4 Are stratified analyses included?	☒	☐	☐	56-57
10.5 Does the plan describe the methods for adjusting for confounding?	☒	☐	☐	38-46
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	

Comments:

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?	☒	☐	☐	59
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	59,55
11.3 Are methods of quality assurance described?	☒	☐	☐	59
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	46-51, 60-62
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	59-62

Comments:

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss: 12.1.1 Selection biases?	☒	☐	☐	44, 45
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)	☒	☐	☐	31, 35
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	23-24, 46
12.3 Does the protocol address other limitations?	☒	☐	☐	60-62

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?	☒	☐	☐	62-63 Annex 14.6: 104-111

Section 13: Ethical issues	Yes	No	N/A	Page Number(s)
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	62

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?	☒	☐	☐	17

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)?	☒	☐	☐	64
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	64

Comments:

Name of the main author of the protocol: Manel Pladevall

Date: 22/July/2015

Signature: [redacted]