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

First published: 30/07/2015

Last updated: 13/05/2024

Study Finalised

Administrative details

EU PAS number

EUPAS10446

Study ID

39254

DARWIN EU® study

No

Study countries

Denmark

Germany

Spain

Sweden

Study description

This is a large, multinational, longitudinal retrospective cohort and nested case-control study using 5 European databases aiming at comparing the risk of hospitalisation for acute liver injury (ALI) in patients initiating treatment with agomelatine and other antidepressants with the risk in patients initiating treatment with citalopram used as a common reference group.

Study status

Finalised

Research institutions and networks

Institutions

RTI Health Solutions (RTI-HS)

France
Spain
Sweden
United Kingdom
United Kingdom (Northern Ireland)
United States

First published: 21/04/2010

Last updated: 11/08/2026

Institution | Not-for-profit | ENCePP partner

EpiChron Research Group on Chronic Diseases, Aragon Health Sciences Institute (IACS)

Spain

First published: 17/02/2017

Last updated: 02/04/2024

Institution | Educational Institution | ENCePP partner

Leibniz Institute for Prevention Research and Epidemiology - BIPS

Germany

First published: 29/03/2010

Last updated: 30/03/2026

Institution | Not-for-profit | ENCePP partner

Centre for Pharmacoepidemiology, Karolinska Institutet (CPE-KI)

Sweden

First published: 24/03/2010

Last updated: 02/06/2026

Institution | Educational Institution | Laboratory/Research/Testing facility | Not-for-profit | ENCePP partner

Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina, IDIAPJGol

Spain

First published: 05/10/2012

Last updated: 09/07/2026

Institution | Educational Institution | Laboratory/Research/Testing facility | Not-for-profit | ENCePP partner

Southern Denmark University Denmark

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Manel Pladevall

Primary lead investigator

Study timelines

Date when funding contract was signed
Actual: 01/04/2015

Study start date
Planned: 29/01/2016

Actual: 18/01/2016

Date of interim report, if expected
Planned: 30/09/2016

Actual: 29/09/2016

Date of final study report
Planned: 12/12/2017

Actual: 12/12/2017

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Les Laboratoires Servier

Study protocol

PASS_Final protocol_22July2015_redacted.pdf (1.02 MB)

PASS_ Final Protocol_18May2017_redacted.pdf (1.1 MB)

Regulatory

Was the study required by a regulatory body?

Yes

Is the study required by a Risk Management Plan (RMP)?

EU RMP category 3 (required)

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Main study objective:

Primary objective: to estimate, with the nested case-control analysis, the fully adjusted odds ratio of hospitalisation for ALI comparing patients initiating treatment with agomelatine and other antidepressants with patients initiating citalopram used as a common reference group.

Study Design

Non-interventional study design

Case-control

Cohort

Other

Non-interventional study design, other

Post-Authorization Safety Study (PASS)

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code

(N06AX22) agomelatine

agomelatine

Medical condition to be studied

Major depression

Population studied

Short description of the study 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.

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

Patients with any of the listed conditions recorded at any time before the start date will be excluded from the study:

- 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
- Jaundice
- Hepatomegaly

- Other and unspecified disorders of the liver
- Non-specific elevation of levels of transaminases and lactic acid dehydrogenase (LDH)

Age groups

- Adults (18 to < 46 years)
- Adults (46 to < 65 years)
- Adults (65 to < 75 years)
- Adults (75 to < 85 years)
- Adults (85 years and over)

Special population of interest

Hepatic impaired

Estimated number of subjects

65.000

Study design details

Outcomes

Primary endpoint: hospital diagnosis for ALI identified with specific ICD-9-CM or ICD-10-CM1 diagnosis codes (common in all the study data sources). Secondary endpoint : Hospital diagnosis for ALI identified with specific and non-specific ICD-9-CM or ICD-10-CM1 diagnosis codes evaluated only in Spain/Denmark in which validation of this less specific outcome will be possible.Tertiary endpoint : 1/specific and non-specific codes identified in both hospital and ambulatory settings. 2/evaluated in all data sources but validated in Spain/Denmark

Data analysis plan

Cohort analysis 1/Crude and age- and sex-standardised incidence rates of hospitalisation for ALI for current use of agomelatine and each antidepressant.2/Kaplan-Meier to estimate crude cumulative incidence of ALI at monthly intervals after first dispensing of agomelatine and each antidepressant.3/Age- and sex-adjusted incidence rate ratios for agomelatine and each antidepressant during current use, compared with citalopram current use.Nested case-control analysis: 1/Cases and controls will be matched on age, calendar year of start date, and sex.2/Using density-based sampling, controls will have follow-up proportionate to cases and index date of case will be assigned to matched controls.3/For all endpoints, risk of ALI in current users agomelatine and current users other antidepressants will be compared with risk in current users of citalopram, adjusting for confounders using conditional logistic regression.4/Sensitivity analyses to include assessment recent/past use antidepressants

Documents

Study results

CLE-20098-094 Abstract EU-PASS Register.pdf (113.24 KB)

Study publications

Forns J, Cainzos-Achirica M, Hellfritzsch M, Morros R, Poblador-Plou B, Hallas ...

Pladevall-Vila, M., Pottegård, A., Schink, T. et al. Risk of Acute Liver Injury...

M. Pladelvall, A. Pottegard, T. Schink, J. Reutfors, R. Morros, B. Poblador-Plo...

Forns J, Pottegård A, Reinders T, Poblador-Plou B, Morros R, Brandt L, et al. A...

Pladevall M, Hallas J, Schink T, Morros R, Poblador B, Forns J, Maja H, Reinder...

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s)

Sweden National Prescribed Drugs Register / Läkemedelsregistret

The Information System for Research in Primary Care (SIDIAP)

German Pharmacoepidemiological Research Database

Data sources (types)

Administrative healthcare records (e.g., claims)

Drug dispensing/prescription data

Electronic healthcare records (EHR)

Other

Data sources (types), other

Hospital discharge data

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No