DARWIN EU® - Association between genetic polymorphisms of interest and risk of myopathy among statin users

First published: 15/11/2024

Last updated: 06/01/2025

Study Ongoing

Administrative details

PURI

https://redirect.ema.europa.eu/resource/1000000369

EU PAS number

EUPAS1000000369

Study ID

1000000369

DARWIN EU® study

Yes

Study countries

☐ Estonia

United Kingdom

Study description

Around 1% to 30% of statin users report mild muscle symptoms including pain and/or weakness, usually
without significant creatine kinase (CK) elevation. Severe myopathy (CK elevation <10 times normal) occurs
in 0.1% of cases, while rhabdomyolysis (>40 times normal CK) is even rarer (<0.01%).
There is current regulatory interest in exploring the role the OATP1B1 (SLCO1B1 c.521CC) gene
polymorphism in atorvastatin users (treated with a fixed dose combination of acetylsalicylic acid/atorvastatin/ramipril) with regards to the risk of myopathy. SLCO1B1 encodes the liver-expressed OATP1B1
protein, which clears statins like rosuvastatin, atorvastatin, simvastatin, and pravastatin from the blood.
The SLCO1B1 521T>C polymorphism (rs4149056) reduces hepatic clearance of these statins, with
simvastatin being most affected, and fluvastatin and rosuvastatin less so. Atorvastatin, a first-line lipid
lowering drug for cardiovascular disease, is widely prescribed but often discontinued due to muscle
complaints.
More broadly, the aim of this study is to inform whether genetic testing could help predict the risk of
myopathy in users of atorvastatin and other selected statins, and whether dose adjustment would help
minimise risk for carriers of known polymorphisms. In addition, this study serves as a proof-of-concept of
the capacity of DARWIN EU to generate pharmacogenomic evidence to support

regulatory decision making.

Study status

Ongoing

Research institutions and networks

Institutions

Department of Medical Informatics - Health Data Science, Erasmus Medical Center (ErasmusMC)

☐ Netherlands

First published: 03/11/2022

Last updated: 02/05/2024

Institution **Educational Institution** **ENCePP partner**

Networks

Data Analysis and Real World Interrogation Network (DARWIN EU®)

☐ Belgium
☐ Croatia
☐ Denmark
☐ Estonia
☐ Finland
☐ France

- [ ] Germany
- [ ] Greece
- [ ] Hungary
- [ ] Italy
- [ ] Netherlands
- [ ] Norway
- [ ] Portugal
- [ ] Spain
- [ ] Sweden
- [ ] United Kingdom

First published: 01/02/2024

Last updated: 30/04/2025

Network

Contact details

Study institution contact

Ilse Schuemie

Study contact

study@darwin-eu.org

Primary lead investigator

Junqing Xie

Primary lead investigator

Study timelines

Date when funding contract was signed
Planned: 06/06/2024

Actual: 06/06/2024

Study start date
Planned: 06/11/2024

Actual: 06/06/2024

Date of final study report
Planned: 17/03/2025

Sources of funding

- EMA

Study protocol

DARWIN EU_Protocol_P3-C3-004_Statins_V6.pdf(775.56 KB)

Regulatory

Was the study required by a regulatory body?

Yes

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

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

Study topic, other:

pharmacogenetics

Study type:

Non-interventional study

Scope of the study:

Other

If ‘other’, further details on the scope of the study

To estimate the association between SLCO1B1 (and additionally ABCG2) genetic variants and the risk of statin-associated myopathy

Data collection methods:

Secondary use of data

Study design:

New User Cohorts

Main study objective:

Primary objectives

1a - To estimate the risk of myopathy in new users of atorvastatin (any dose) according to genotype status

1b - To estimate the risk of myopathy in new users of lower-dose atorvastatin according to genotype status

1c - To estimate the risk of myopathy in new users of higher-dose atorvastatin according to genotype status

Secondary objectives
2a - To estimate the risk of myopathy in new users of simvastatin (separately for any dose, lower-dose and higher-dose) according to genotype status
2b - To estimate the risk of myopathy in new users of rosuvastatin (separately for any dose, lower-dose and higher-dose) according to genotype status if feasible (See Section 8.7 "Study Size" for more details on how to determine if this analysis is feasible)
2c - To estimate the risk of myopathy in new users of fluvastatin (separately for any dose, lower-dose and higher-dose) according to genotype status if feasible (See Section 8.7 "Study Size" for more details on how to determine if this analysis is feasible)
2d - To estimate the risk of myopathy in new users of pravastatin (separately for any dose, lower-dose and higher-dose) according to genotype status if feasible (See Section 8.7 "Study Size" for more details on how to determine if this analysis is feasible).

Study Design

Non-interventional study design
Cohort

Study drug and medical condition

Name of medicine, other
Statins

Medical condition to be studied
Myopathy

Population studied

Short description of the study population

The source population will comprise of all incident statin users during the study period.

Age groups

Adult and elderly population (≥18 years)

Study design details

Setting

This study will be conducted using two prospective Biobank cohorts with primarily collected genetic data linked to routinely collected electronic health records in two European countries. Except for the genetic information, all other data have been previously mapped to the OMOP CDM to allow for federated analytics, and DARWIN EU data quality controls have been completed during onboarding to the network.

1. UK Biobank (UKBB), United Kingdom
2. Estonian Biobank (EBB), Estonia

Data management

Data sources

Data source(s)

UK Biobank

Estonian Biobank

Data sources (types)

Other

Data sources (types), other

Biobank

Use of a Common Data Model (CDM)

CDM mapping

Yes

CDM Mappings

CDM name

OMOP

CDM website

https://www.ohdsi.org/Data-standardization/

CDM version

https://ohdsi.github.io/CommonDataModel/index.html

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

Unknown