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

**First published:** 15/11/2024

**Last updated:** 10/08/2026

Study Finalised

## Administrative details

**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**

Finalised

# 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
- Lithuania
- Netherlands
- Norway

Poland
Portugal
Spain
Sweden
United Kingdom
United States

**First published:** 01/02/2024

**Last updated:** 05/11/2026

Network

## Contact details

**Study institution contact**

Ilse Schuemie study@darwin-eu.org

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

Actual: 01/05/2025

## 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

Safety study (incl. comparative)

**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

**Medicinal product name, other**
Statins

---

**Anatomical Therapeutic Chemical (ATC) code**
(C10AA05) atorvastatin

atorvastatin

(C10AA01) simvastatin

simvastatin

(C10AA07) rosuvastatin

rosuvastatin

(C10AA04) fluvastatin

fluvastatin

(C10AA03) pravastatin

pravastatin

---

**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

---

**Outcomes**

1. Myopathy (primary)
2. Myositis (secondary)
3. Myalgia (secondary)

---

**Summary results**

This large, federated, population-based cohort study was initiated in response to regulatory interest in the role of OATP1B1 in atorvastatin-associated myopathy. Real-world evidence reported in this study may support existing clinical knowledge on the benefits of candidate genetic testing for SLCO1B1 (rs4149056, rs2306283) and ABCG2 (rs2231142) to reduce SAMS, especially when prescribing simvastatin. However, the non-significant results highlight that these genotype-statin-dose combinations may still warrant attention, and we recommend future studies with additional Biobanks, more precise phenotyping with biomarker data, together with more comprehensive characteristics of multiple genetic variations (e.g., polygenic models or allele combinations).

## Documents

**Study report**

DARWIN EU_Report_P3-C3-004_Statins and myopathy_V3.pdf (3.09 MB)

# 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)**

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