TARGET-EU: Tolvaptan and risk associated to hepatotoxicity in autosomal dominant polycystic kidney disease

First published: 20/05/2026

Last updated: 20/05/2026

Study Ongoing

Administrative details

EU PAS number

EUPAS1000001005

Study ID

1000001005

DARWIN EU® study

No

Study countries

Netherlands

Spain

United Kingdom

Study description

This case study is part of the broader TARGET EU project (EUPAS1000000539), which aims to advance the regulatory use of real-world data through the application of target trial emulation and estimand methodologies.

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a chronic, inherited systemic disorder with manifestations that occur mainly renally, but also in other organs. Tolvaptan is the only approved drug for treatment of ADPKD in adults who are at risk of a rapidly progressive phenotype. Tolvaptan is a vasopressin V2 receptor agonist that blocks vasopressin signalling, which is an important driver of kidney cyst growth in ADPKD. A potentially serious side effect of tolvaptan is hepatotoxicity. In several clinical trials the risk of hepatotoxicity has been reported, and special warnings and safety measures have been included in the label.

Objectives: The current study aims to investigate the safety of tolvaptan use through assessing the risk of hepatotoxicity associated with tolvaptan treatment in ADPKD patients compared to the risk in patients who are unexposed to tolvaptan.

Methods: We will conduct a cohort study with a prevalent new-user design using linked electronic health records from the UK (CPRD) from 2015 until the latest available data. Eligible individuals are adults (≥ 18 years) with ADPKD who, for the intervention group, initiated tolvaptan treatment since market authorisation or, for the control group, who had a time-matched visit to a physician without a tolvaptan prescription. In the primary estimand, a treatment policy strategy is used for treatment discontinuation, a hypothetical strategy is used for tolvaptan initiation in the control group or the use of medication with hepatotoxic effects, and a while alive strategy is used for all-cause mortality. The primary analysis uses a Cox proportional hazards model, with supplemental analyses using an

accelerated failure time model to estimate restricted mean survival time(RMST).

Study status

Ongoing

Research institutions and networks

Institutions

Electronic Health Records (EHR) Research Group, London School of Hygiene & Tropical Medicine (LSHTM)

United Kingdom

First published: 19/04/2010

Last updated: 30/10/2024

Institution | Educational Institution | ENCePP partner

Division of Pharmacoepidemiology & Clinical Pharmacology (PECP), Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University

Netherlands

First published: 01/03/2010

Last updated: 27/05/2026

Institution | Educational Institution | ENCePP partner

Clinical Pharmacology, Vall d'Hebron Institut de Recerca (VHIR)

Spain

First published: 18/05/2021

Last updated: 20/05/2021

Institution | Outdated | Hospital/Clinic/Other health care facility | ENCePP partner

University Medical Center Utrecht (UMCU)

Netherlands

First published: 24/11/2021

Last updated: 22/02/2024

Institution | Educational Institution | Hospital/Clinic/Other health care facility | ENCePP partner

Teamit Institute

Spain

First published: 12/03/2024

Last updated: 12/03/2024

Institution | Other | ENCePP partner

Networks

Vaccine monitoring Collaboration for Europe (VAC4EU)

- Belgium
- Denmark
- Finland
- France
- Germany
- Italy
- Netherlands
- Norway
- Spain
- United Kingdom

First published: 22/09/2020

Last updated: 22/09/2020

Network | Outdated | ENCePP partner

EU Pharmacoepidemiology and Pharmacovigilance (PE&PV) Research Network

- Netherlands

First published: 01/02/2024

Last updated: 24/09/2025

Network

Contact details

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Study timelines

Date when funding contract was signed

Actual: 19/09/2024

Study start date

Actual: 16/03/2026

Date of final study report

Planned: 10/06/2026

Sources of funding

- EMA

Study protocol

Emulation_Protocol.pdf (1.49 MB)

Regulatory

Was the study required by a regulatory body?

No

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

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

A pragmatic design with real-world data captures care as it is delivered in practice. Although the observational emulation cannot perfectly mimic randomisation in the target trial, several measures are taken to minimise bias and confounding. The prevalent new-user design avoids immortal time bias an

Main study objective:

To investigate the safety of tolvaptan use through assessing the risk of hepatotoxicity associated with tolvaptan treatment in ADPKD patients compared to the risk in patients who are unexposed to tolvaptan.

Study Design

Non-interventional study design

Cohort

Other

Non-interventional study design, other

This study will emulate a hypothetical target trial using a retrospective, prevalent new-user cohort design based on routinely collected electronic health records.

Study drug and medical condition

Medicinal product name

TOLVAPTAN ACCORD

Study drug International non-proprietary name (INN) or common name

TOLVAPTAN

Anatomical Therapeutic Chemical (ATC) code

(C03XA01) tolvaptan

tolvaptan

Medical condition to be studied

Hepatotoxicity

Additional medical condition(s)

Autosomal dominant polycystic kidney disease

Population studied

Short description of the study population

The study population will consist of adults with ADPKD, without use of medication with hepatotoxic effects, history of hepatotoxicity, liver enzyme elevation or use of diuretics.

For the intervention group, time 0 is defined as the first prescription of tolvaptan. This is when participants enter the study, which mimics initiation of tolvaptan therapy in the target randomised controlled trial. For participants in the control group, time 0 is the date of a physician visit without a tolvaptan prescription, matched on time since ADPKD diagnosis to the date of a treatment receipt in the intervention group. Additionally, the control and intervention time

0 are also matched on the calendar time scale. The matching will not be on the exact value but on the quintile. In the first stage of matching, on calendar time, matching will be done 5 : 1 for control group: intervention group. This is necessary to end up with a 1:1 control: intervention group allocation for the second matching step on propensity score. Individuals can only be eligible as matched control once and can only be assigned to either the control group or the intervention group once (at time 0).

Age groups

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

Study design details

Setting

This study is conducted using routinely collected electronic health records from 2015 to 2024, reflecting the period of tolvaptan use in routine clinical practice. The study is set primarily in primary care, drawing on longitudinal data from general practices with linkage to hospital data. Data are sourced from the United Kingdom (Clinical Practice Research Datalink [CPRD]), providing population-based and representative coverage of real-world clinical care.

Comparators

There is no alternative treatment to tolvaptan to which the risk of hepatotoxicity could be compared. Clinically it is most relevant to compare tolvaptan use to ADPKD patients unexposed to tolvaptan, who may receive symptomatic treatment, as per clinical practice. Any dose or regimen of tolvaptan is eligible for inclusion. Comparators will thus be adults with ADPKD who do not use tolvaptan, without use of medication with hepatotoxic effects, history of hepatotoxicity, liver enzyme elevation or use of diuretics.

Outcomes

Clinical trials have suggested that there is an association between tolvaptan treatment and elevations in liver enzyme levels (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) [2,6]. In these studies, hepatotoxicity is defined as increases in ALT or AST levels to more than 3 times the upper limit of normal (ULN) [2,6]. It is expected that, at least in the unexposed group, liver enzyme levels are not registered regularly. In this emulation, hepatotoxicity will be defined as the registration of ICD-10, Read, or SNOMED codes related to hepatotoxicity or increases in the following liver enzymes if data are available:

ALT > 3x ULN

AST > 3x ULN

Total bilirubin > 2x ULN

Alkaline phosphatase > 2x ULN + elevated GGT and/or 5-NT

Data analysis plan

The analyses are conducted within a target trial emulation framework to estimate the effect of tolvaptan exposure compared with non exposure on the

risk of hepatotoxicity.

For Estimand 1, the main estimand supporting decision making, the primary causal effect summary measure is the hazard ratio for time to first hepatotoxicity event, estimated using a stratified Cox proportional hazards model in the propensity score-matched sample.

Sensitivity analyses will assess robustness of the primary findings to key assumptions, including inverse probability of censoring weighting (IPCW) (assuming censoring is independent of the outcome, with all common causes of both the outcome and censoring being accounted for conditional on the treatment, time-varying covariates and survival up to the time of censoring as well as indirectly baseline covariates used to estimate the treatment weights), best/worst case scenario analysis, and outcome misclassification (details in Section 7.6.5).

Two supplemental estimands are also defined: Estimand 2, applying a while-on-treatment strategy for intercurrent events, and Estimand 3, estimating treatment effects using restricted mean survival time (RMST) derived from a Propensity score matched Weibull accelerated failure time (AFT) model. In addition, supplemental analyses (e.g., crude and PS-matching adjusted Kaplan–Meier curves, crude Cox models, event counts and incidence rates, propensity score and weight distributions, covariate balance before and after weighting, censoring and intercurrent event patterns, proportional hazards diagnostics, positivity checks, and multiple-imputation diagnostics) will be conducted to support interpretation of the main analysis.

For all estimands, conditional propensity scores will be calculated, and patients will be matched accordingly. For estimand 1 and 2, the Cox model will be used

to calculate the HR of hepatotoxicity of tolvaptan users vs. nonusers.

Summary results

Not yet available.

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)

Clinical Practice Research Datalink

Data sources (types)

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

Yes

CDM Mappings

CDM name

ConcepTION CDM

CDM website

https://www.imi-conception.eu/

CDM release frequency

6 months

CDM version

V2.2

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Yes

Data characterisation details

The feasibility assessment for this case study, detailed in the appendix of the study protocol, was conducted as part of the broader TARGET-EU feasibility assessment (EUPAS1000000791). Data source suitability was evaluated using a structured framework based on the EMA data quality framework, assessing system characteristics, data quality, and fitness for the research question.

CPRD is deemed feasible to use as a data source for studying hepatotoxicity risks involved with tolvaptan use. It is expected that the target sample size for intervention and control groups will be reached. Elements with high criticality are available and fairly reliable with sufficient recency, although dispensing data is unavailable, discontinuation must be inferred from prescription duration, and diagnostic coding may be incomplete in some emergency room settings. Some other limitations are present, but these are manageable within the study design.

Data characterisation details

Feasibility Assessment.pdf

English (423.25 KB - PDF)

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